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Studies On Enone Photocycloaddition Part One: The Orientation Determining Factors In Enone Photocycloaddition Part Two: Attempted Syntheses Of Biradical Precursors In Enone Photocycloaddition

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STUDIES ON ENONE PHOTOCYCLOADDITION

PART ONE

THE ORIENTATION DETERMINING FACTORS IN ENONE PHOTOCYCLOADDITION

PART TWO

ATTEMPTED SYNTHESES OF BIRADICAL PRECURSORS IN ENONE PHOTOCYCLOADDITION

by

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Submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy

Faculty of Graduate Studies
The University of Western Ontario
London, Canada
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To "MURPHY" Who established The Great Laws:

1. In Any Field Of Scientific Endeavor, Anything That Can Go Wrong, Will Go Wrong.
2. Left To Themselves, Things Always Go From Bad To Worse
3. If There Is A Possibility Of Several Things Going Wrong, The One That Will Go Wrong, Is The One That Will Do The Most Damage.
4. Nature Always Sides With The Hidden Flaw.
5. If Everything Seems To Be Going Well, You Have Obviously Overlooked Something.
6. Mother Nature Is A Bitch.

ABSTRACT

PART ONE

The syntheses of 3,3-di(trifluoromethyl)-2,3-dihydrofuran (6) and 3,3-dimethyl-2,3-dihydrofuran (9) are described.

The photochemical cycloaddition of 2-acetoxycyclopent-2-en-1-one (7) to the dihydrofurans (6) and (9), and to 2,3-dihydrofuran (8) are investigated.

With either dihydrofuran 8 or 9, the cycloaddition proceeds smoothly to give, in each case, two 1:1 adducts. On the other hand with dihydrofuran 6 no such adduct is formed.

The stereochemistry of the 1:1 adducts is shown to be anti, head-to-tail and syn, head-to-tail in the case of 8, and anti, head-to-tail and anti, head-to-head in the case of 9.

These results are discussed in terms of three factors: the dipole-dipole interactions, steric and electronic effects. The importance of the dipole-dipole interaction is shown in the observed solvent-dependency of the product ratio in these cycloadditions.

The failure of the cycloaddition in case of 6 is

proposed to be due to both steric and dipole-dipole interaction effects.

PART TWO

The stereochemical aspect of the photochemical cycloaddition of cyclohexenones to olefins is discussed assuming triplet 1,4-biradicals to be the reaction intermediates. It is proposed that trans-fused products are formed only from those biradicals which are generated by the reaction at C_2 of the enones.

In order to justify this view, syntheses of the triplet biradicals by a route other than the photocycloaddition are planned.

In particular the biradicals which are assumed to be intermediates in the addition of cyclohex-2-en-1-one to isobutylene are chosen as the synthetic targets. As their immediate precursors, the corresponding six-membered ring azo compounds are chosen, and the attempted syntheses of these substances are described.

ACKNOWLEDGEMENT

To try to acknowledge all those who were a part of my life in London, both inside and outside the lab, could not be done without omission. Nevertheless, I will make an attempt.

To Dr. Paul de Mayo, I must extend my heartiest congratulations for his ultimate success in "kicking me out" of his group after numerous attempts over so many years. He has been quite effective over these years in caging me in the lab so that I have had little chance of following my natural tendencies; wandering in the woods and upon the mountains. Without his gentle encouragement, I would surely have had to continue my chemical work a few more years. He also instructed me in the intricacies of Canadian chemical education through the organization of his lab and students.

I must extend my thanks and appreciation to the other faculty members for their unlimited availability and helpfulness, to the graduate students for their friendship and support ("through adversity, united"), to the postdocs for their comradeship, laboratory know-how and general knowledge, to the supporting staff for their warm hospitality and assistance, and to the janitors who rescued me each evening from beneath a mountain of cigarette ashes.

To the "McKibben Boys" and "Homesteaders" who introduced me to life in London - its language, culture, customs, male-female relationships etc. - I extend the sincerest form of flattery - attempted imitation.

TABLE OF CONTENTS

PART ONE

THE ORIENTATION DETERMINING FACTORS IN ENONE PHOTOCYCLOADDITION

PART ONE

THE ORIENTATION DETERMINING FACTORS IN ENONE PHOTOCYCLOADDITION

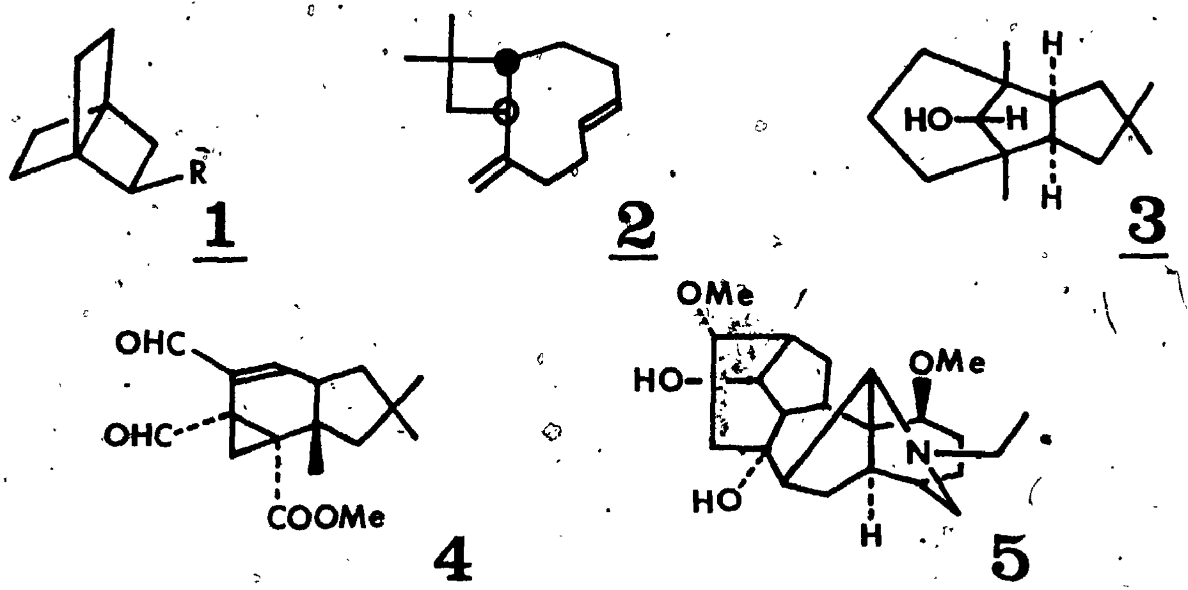
INTRODUCTION

The potential synthetic usefulness of the photochemical cycloaddition of cyclic enones to olefins has been exemplified several times. Amongst application so far made have been successful syntheses of strained molecules, e.g., a [2,2,2] propellane (1) (1), of natural products, e.g., caryophyllene (2) (2), α-caryophyllene alcohol (3) (3), methyl isomarasmate (4) (4) and talatisamine (5) (5) (Figure 1). (Other synthetic applications have been summarized in references 6 and 7).

When using an unsymmetrical olefin, the problem of the orientation (regiospecificity) of the reaction is one of the most difficult problems the synthetic organic chemist has to face (7). It is therefore very important to achieve an understanding of the mechanistic factors which control this regiospecificity.

Two orientational factors have been proposed in

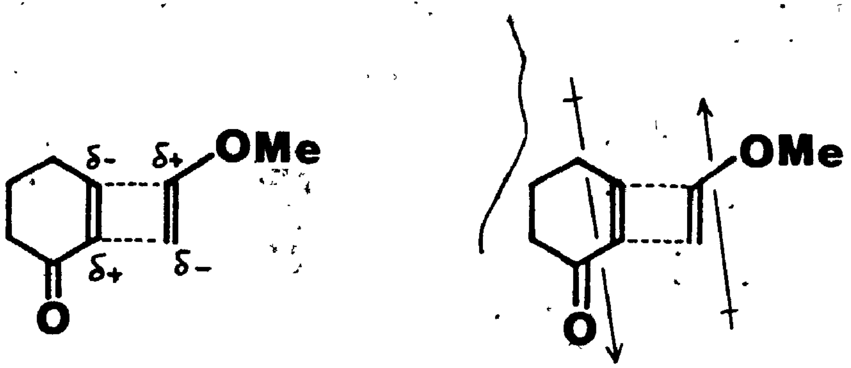
FIGURE 1



the literature. Corey observed high orientational specificity in his study on cyclohexenone photocycloadditions: when unsymmetric olefins having electron donating substituent(s) on the double bond were used, head-to-tail (HT) oriented products were formed predominantly (8). In order to rationalize this specificity, he proposed the formation of a HT-oriented complex as the first step of the reaction. He found that, with assumptions with regards the electron distributions in the excited enone and the known polarization of substituted olefins, he could predict the observed regiospecificity. The assumptions were that the state involved was the nπ* state, and that the electron distribution derived from calculation of the Frank - Condon state were plausible. These indicated that C_3 was rather more electron-rich than C_2.

An example of the application of the view is shown in Figure 2.

FIGURE 2

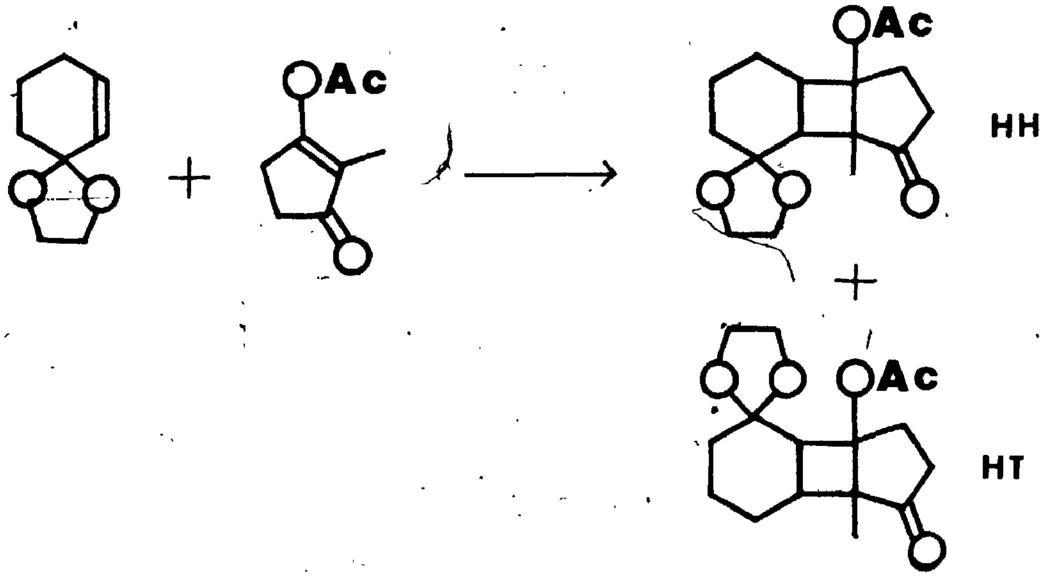


Corey's Oriented Complex

Dipole-dipole Interaction

Corey's analysis has been accepted widely in the literature (6, 9, 10) and has been termed the "oriented complex rule" (9).

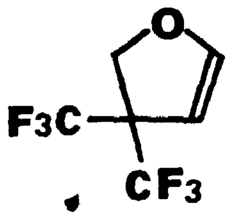
A second orientational factor which has been proposed in the literature is a dipole-dipole interaction between the triplet enone and ground state olefin (7, 11, 12, 13). This interaction is believed to be operative because of solvent effects on regiospecificity which are linearly related to a dipole-dipole interaction of the Kirkwood-Onsager type (14). This was first reported (for a ground state reaction) by Benson as being operative in Diels-Alder reactions (15). Later, de Mayo reported a drastic solvent effect on reaction 1. In hydrocarbon solvents the head-to-head (HH) adduct was formed in 98% while in methanol, this adduct was formed only in rather less than 50% (16). Since there is little polarization of the olefinic double bond in this olefin (7), the formation of specifically oriented complex which requires polarized double bonds can not be expected. Thus, the dipole-dipole interaction is clearly important in this reaction.



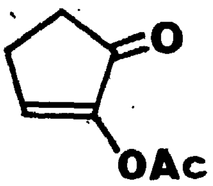
(1)

For reactions using unsymmetric electron-rich olefins (e.g., methoxyethylene), the predicted orientation is the same on the basis of either the dipole-dipole interaction or the electronic effect (Corey's oriented complex effect). An example is shown in Figure 2. Therefore, it remains to be determined which of the two orientational factors is the more important in the reactions with electron-rich olefins. In order to investigate this, it is necessary to choose a suitably substituted electron-rich olefin in which the overall dipole moment could be varied by appropriate substitution.

For this purpose, 3,3-di(trifluoromethyl)-2,3-dihydrofuran (6) was chosen as the olefin in the present research. This substance has supposedly an electron-rich polarized double bond (required for the electronic effect), and a relatively large dipole moment (required for the dipole-dipole interaction). Since the direction of the dipole moment is expected to be roughly opposite to those of simple electron-rich olefins (e.g., methoxyethylene), preferential formation of HH-oriented products is predicted if the dipole-dipole interaction be the stronger influence. If the electronic effect be the stronger, then the normal 'Corey'-oriented products will be obtained, because the direction of the bond polarization in 6 is same as those of simple electron-rich olefins.

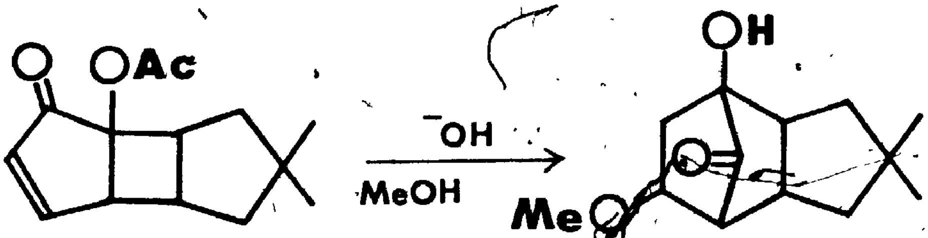


6



7

As for the reaction partner of 6, 2-acetoxyclopent-2-en-1-one (7) was chosen on the basis of the following considerations. First, the choice of a cyclopentenone rather than a cyclohexenone was made to decrease the number of possible products; that is, by using a five-membered enone the formation of trans-fused products would be avoided (*). Second, to obtain a larger dipole-dipole interaction, it seemed better to introduce a suitable substituent on C_2 of cyclopentenone. The choice of acetoxyl group as the substituent was considered to have a two-fold effect: it would increase the dipole movement of cyclopentenone without affecting its direction greatly; and the determination of product-orientations would be simplified by applying the known facile base-catalysed rearrangement of such adducts to the 2,2,1-bicycloheptane system as shown in reaction 2 (4).



(2)

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* To our knowledge no trans-fused product to a cyclopentenone has ever been reported.

Finally, the presence of an extra substituent would simplify the pmr spectra.

Although the introduction of this substituent into the cyclopentenone skeleton could cause steric problems as well as some perturbation in the electronic nature of the excited states of the enone, it was believed that these factors would not alter the orientational mode of the reaction.

For comparison, photocycloadditions of enone 7 with 2,3-dihydrofuran (8) and 3,3-dimethyl-2,3-dihydrofuran (9) were also investigated.

In the following section, the syntheses of the unknown dihydrofurans (6 and 9) and the photochemical cycloadditions of enone 7 with these dihydrofurans (6, 8 and 9) will be described.

RESULTS

SYNTHESES OF DIHYRDOFURANS

2,3-Dihydrofuran (8) was prepared by the method of R. Paul et al (17). The substance showed signals for the olefinic protons which were analyzed as an AX spectrum with $\nu_A = 6.31$ and $\nu_B = 4.93$ ppm with $J_{AX} = 2.4$ Hz (18).

In the cmr spectrum the sp_2 carbons appeared at 145.95 and 99.29 ppm (*).

3,3-Di(trifluoromethyl)-2,3-dihydrofuran (6) and 3,3-dimethyl-2,3-dihydrofuran (9) were synthesized according to Scheme 1.

i) 3,3-DIMETHYL-2,3-DIHYDROFURAN (9)

3,3-Dimethylpent-4-en-1-al (13) was prepared following the general method of P. Cresson (19), that is, via Cope rearrangement of the allyl vinyl ether 12. Ozonolysis of the corresponding dimethyl acetal 14 in methanol at -78° and subsequent reduction using sodium borohydride gave the cyclic acetal 16 in 75% yield. The acetal 16 was passed entrained by nitrogen through a heated (240°) column packed with finely powdered sodium bisulphate (20) to give a mixture of the dihydrofuran (9), methanol and unreacted acetal 16 in the ratio of 1.7 : 1.7 : 1.0 (estimated yield of 9 = 54%). Lithium aluminum hydride was added to the mixture to destroy the methanol and subsequent distillation of the mixture yielded 9 of 97% purity (glc). This substance after purification by glc had a molecular ion peak at m/e 98 and showed the expected pmr pattern; the methyl groups and the methylene group

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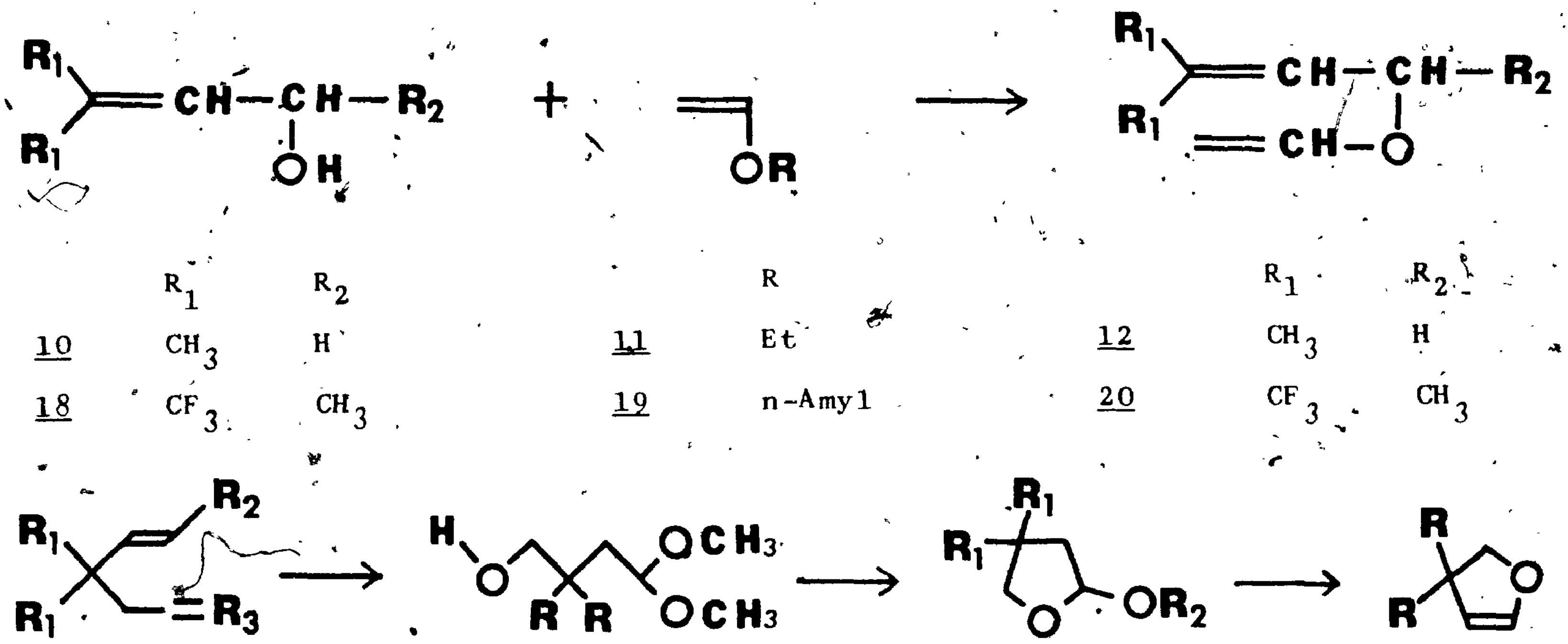
* We would like to express our thanks to Dr. Stothers for his kindness in obtaining the cmr spectra.

SCHEME 1



	R_1	R_2
10	CH_3	H
18	CF_3	CH_3

	R
11	Et
19	n-Amyl

	R_1	R_2
12	CH_3	H
20	CF_3	CH_3

	R_1	R_2	R_3
13	CH_3	H	O
14	CH_3	H	$(OMe)_2$
21	CF_3	CH_3	O
22	CF_3	CH_3	$(OMe)_2$

	R
15	CH_3
23	CF_3

	R_1	R_2
16	CH_3	CH_3
17	CH_3	H
24	CF_3	CH_3
25	CF_3	H

	R
8	H
9	CH_3
6	CF_3

appeared as singlets at 1.13 and 3.95 ppm, respectively, and the olefinic protons showed an AX pattern at 4.86 and 6.24 ppm with J_{AX} = 1.3 Hz. The cmr showed the sp_2 carbons at 111.59 and 144.05 ppm.

An attempt to generate the dihydrofuran 9 by dehydration of the hemiacetal 17 was rather unsuccessful. This was prepared by hydrolysis of 16 using 10% aqueous sulfuric acid in a sealed tube at 65-70°. Upon treatment with catalytic amounts of concentrated sulfuric acid or p-toluenesulfonic acid (21), or of activated sodium bisulphate (all under nitrogen), 17 gave the dihydrofuran 9 but in a poor yield and with the predominant formation of tars.

ii) 3,3,-DI(TRIFULUOROMETHYL)-2,3-DIHYDROFURAN (6)

The allylic alcohol 18 (22, 23) was prepared by the Meerwein-Pondorf reduction (*) of the corresponding ketone, based on the reported procedure of Plakhova and Gambaryan (22). The substance, isolated by a spinning band column distillation, showed a single peak on glc and boiled at 124-126°, although an azeotropic mixture of 18 and diethylether of bp 125-126° was reported to be obtained by the authors (22).

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* In our experiments, the reported method (22) using lithium aluminium hydride did not yield 18 cleanly; instead the major product was $CF_2 = C(CF_3)\ CH_2CH\ (OH)\ CH_3$. At least three minor products were observed on glc. The results are similar to those reported in reference 23.

Vinylation of the alcohol 18 was performed by modification of the method A of W. H. Watanabe et al (24), using n-amyl vinyl ether (19) and mercuric acetate (*). The reaction was only successful at bath temperatures below 75° and thus reduced pressure was necessary to distil the product from the reaction pot as it was formed. The yield of the allyl vinyl ether (20) was ca. 45%. When the reaction was conducted at higher temperatures (with the total exclusion of acidic impurities) (⁑), 20 was not formed at all, but unidentified decompositions took place.

Cope rearrangement (19, 25) of 20 at 200° in a nitrogen atmosphere led to the formation of the alkenal 21, bp 146-148°, in 66% yield. Oxonolysis of the corresponding dimethyl acetal 22 at -78° and subsequent reduction with sodium borohydride gave the hydroxy dimethyl acetal 23 in 93% yield. Hydrolysis of 23 (5% aqueous sulfuric acid) in a sealed tube at 110-115° yielded the cyclic acetal 24 as the predominant product

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* The purification of mercuric acetate was not necessary in our experiment. However see reference 25 .

⁑ When the apparatus had not been treated with base, several products were formed, one, the di-n-amyl acetal of acetoaldehyde predominating. The latter was identified (pmr, ir and mass) by comparison with an authentic sample (see Experimental).

when the reaction was stopped after ca. five hours. However, when the reaction was heated for a longer time (34 hours), the cyclic hemiacetal 25 was isolated in 93% yield.

Attempts to convert 24 to the dihydrofuran 6 by elimination of methanol using various acids (21) or sodium bisulphate (20) were all unsuccessful. The generation of 6 was achieved by dehydration of 25 using a catalytic amount of concentrated sulfuric acid (21) at 120-125°. The yield was 72%. Activated sodium bisulphate also catalysed the dehydration. The dihydrofuran 6 showed a molecular ion peak at m/e 206. The olefinic protons appeared at 6.61 and 4.96 ppm as an AX pattern with J_{AX} = 3.0 H_z. The methylene protons appeared as a singlet at 4.52 ppm. The cmr showed the sp_2 carbons at 153.57 and 93.25 ppm.

STRUCTURE AND STEREOCHEMISTRY OF THE ADDUCTS

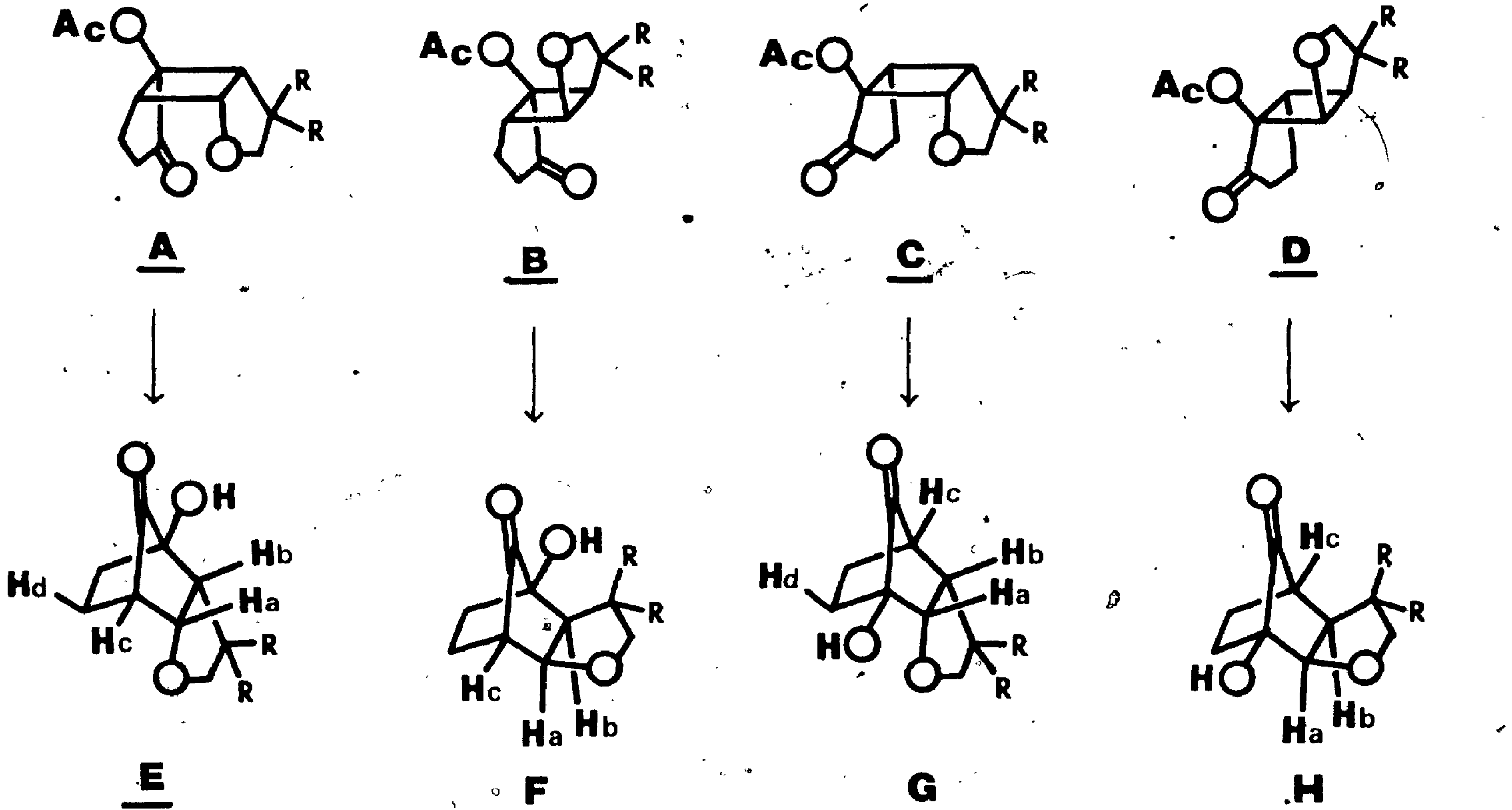
i) with 2,3-DIHYDROFURAN (8)

2-Acetoxycyclopent-2-en-1-one (7) was irradiated in the presence of 2,3-dihydrofuran (8) (solvent: a mixture of ether and cyclohexane) to give two crystalline adducts 26, mp 64.0-64.5°, and 27, mp 79.5-80.0°. Both adducts showed the strong absorption band at ca. 1735 cm^{-1} expected for this kind of adduct (4). The pmr confirmed the 1:1

nature of the adducts since the acetyl methyl and the partial structure $-CHOCH_2CH_2-$ were readily discernible. The former appeared at 2.05 in 26 and 2.07 ppm in 27. The methylene protons on carbon bearing oxygen appeared as an AB part of an ABXY system in both adducts at 3.98 and 3.76 in 26 and 4.15 and 3.78 ppm in 27. The corresponding methine proton appeared at 4.63 in 26 and 4.26 ppm in 27. The general nature of the adducts has established analogy (4).

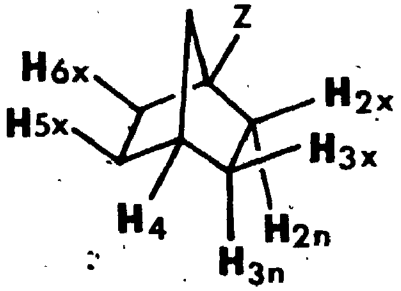
Four structures, A-D (R=H), are possible for these adducts (see Figure 3). However, structural assignment in such systems is complicated when using pmr data because of the well-known variation in J_{cis} and J_{trans} with the comformational variations of the cyclobutane ring and because of the occurence of diagonal coupling (26). We, therefore, took advantage of the known facile rearrangement (4) which leads to the bicyclo [2,2,1] cycloheptane system. Treatment of 26 and 27 with mild base led to the expected acyloin rearrangement. Both products 28 and 29, liquids, showed absorptions due to a hydroxyl group (ca. 3550 and 3400 cm^{-1}), a bridged carbonyl group (1782-1785 cm^{-1}) (27) and the partial structure $-CHOCH_2CH_2-$. Again, four structures, E-H (R = H), corresponding to the previous four, are possible for these two substances, 28 and 29 (see Figure 3).

FIGURE 3



The basis for structure allocation in the dihydro and dimethyldihydrofuran adducts lies in observations established in the literature for the magnitude of coupling constants in the bicycloheptane system. The only large couplings (bearing in mind the cis adduct fusion) which can occur in such systems are H_{2X}/H_{3X}; H_{2N}/H_{3N} which may be of the order of 6-11.4 Hz, the exo-exo being larger than the endo-endo (28) (see Figure 4 for the specific protons). Of intermediate size is the H_{3X}/H_4

FIGURE 4



coupling (3.0-5.0 Hz) which is distinctly larger than the corresponding endo coupli[illegible]H_{3N}/H_4) ($\leq$ 1.3 Hz) (28, 29). A small long range coupling ($\leq$ 1.9 Hz) occurs between H_{2X}/H_{6X} (H_{3X}/H_{5X}) (28, 29).

The methine proton (Ha) on carbon bearing oxygen in compound 28 appears at 4.36 ppm as a doublet of doublets with J = 9.5 and 4.9 Hz. Structure E (R = H) necessarily follows for this substance. The W coupling with Hd was not resolvable, but appeared as line broadening ($\Delta 1/2$ = 2.4 Hz).

The equivalent proton in compound 29 appears at 4.23 ppm as a broad doublet (Δ 1/2 = 2.6 Hz) with J = 8.0 Hz. This broadening is clearly due to a small coupling with Hc (a broad doublet at 2.21 ppm with J = 4.2 Hz), since Ha gives rise to a sharp doublet (Δ1/2 = 1.5 Hz) upon double irradiation at 2.21 ppm. The small coupling (~1.1 Hz) between Ha/Hc must arise from a vicinal coupling in structure F, because sizable long range couplings of type Ha/Hc in G and H, to our knowledge, have never been observed (28,29). Structure F (R = H) necessarily follows for substance 29.

The following experimental observations confirm the conclusions. First, when 28 and 29 were exposed to moist air, 28 rapidly formed a hydrate (30), whereas 29 did not. This behaviour is characteristic of such bridgehead carbonyl compounds (30). Since all other factors are identical we conclude that steric hindrance must be responsible for the absence of hydrate formation in 29, i.e., that the ethereal ring has the exo stereochemistry. Secondly, we have studied the effect of the europium shift reagent, Eu(fod)$_3$ (31). With compound 29 the shift reagent produced much the same displacement of Ha, Hb and Hc (See Table 1). We interpret this to mean that the ethereal function is on the opposite side from the hydroxyl group. In an instance (see below) where we believe both oxygen functions to be on the same side only

Ha is affected by the reagent.

Thirdly, the Ha/Hb coupling constant in 28 (J = 9.5 Hz) is larger than that of 29 (J = 8.0 Hz). This is as would be expected for an exo/endo relationship (28).

TABLE 1

Eu(fod)3 EFFECT (Δppm)* ON

KETO-ALCOHOLS 29, 34 and 35

substance	Ha	Hb	Hc	Me	Me	OH
29	0.61	0.68	0.63	----	----	2.50
34	0.86	0.78	0.75	0.56	0.35	2.50
35	1.38	0.52	0.46	0.20	0.18	2.50

* The values for 29 and 34 were obtained by extrapolating to those corresponding to Δ = 2.50 ppm for their hydroxyl protons (in $CDCl_3$ at 30°).

Since the structures of the rearranged products are thus assigned, the photoadducts, 26 and 27, must have structures syn-HT (A R = H) and anti-HT (B R = H) respectively.

ii) with 3,3-DIMETHYL-2,3-DIHYDROFURAN (9)

Irradiation of 2-acetoxycyclopent-2-en-1-one (7) in the presence of 3,3-dimethyl-2,3-dihydrofuran (9) gave three adducts, 31, mp 224.0-225.0°, 32, mp 87.5-88.0°, and 33, a liquid. Adduct 31 had strong absorption at 1740 cm^{-1} and showed a mass ion peak at m/e 280: the latter corresponds to that expected for a dimer of the enone. In fact, the substance was formed upon irradiation of the enone in acetonitrile in the absence of olefin, confirming the interpretation.

Adducts 32 and 33 showed absorption at 1740 and 1735 cm^{-1}, respectively (4). The pmr confirmed the 1:1 nature of the adducts, because the acetyl methyl and the geminal methyls were observed as three singlets at 2.06, 1.33 and 0.98 in 32 and 2.09, 1.10 and 1.03 ppm in 33, respectively. Four structures A-D (R = Me), are possible for these adducts (see Figure 3). Upon treatment with base 32 and 33 were transformed to the corresponding keto-alcohols, 34, mp 76.5-77.0°, and 35, mp 91.5-92.0°, respectively. Both showed the expected infrared spectral change, i.e., appearance of bands indicative of hydroxyl and bridged carbonyl; 3560 and 1777 in 34 and 3560 and 1780 cm^{-1} in 35. Again four structures, E-H (R = Me), are possible for these two substances (34 and 35). Ha and Hb protons in 34 appeared as AX doublets (J_{ab} = 8.0 Hz) centered at 4.46 and 2.29 ppm, respectively. The equivalent protons in 35 appeared also as AX doublets (J_{ab} = 7.3 Hz) at 4.27 and 2.29 ppm, respectively. These couplings (*)

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* The size of these coupling constants is rather closer

were confirmed by double irradiation experiments. The absence of an additional large coupling with Hc (3.0-5.0 Hz) (28, 29) clearly shows that both 34 and 35 have endo-oriented Ha and Hb. This conclusion is supported by the fact that the substances resisted the formation of hydrates, probably because of the steric crowding caused by the exo-ethereal ring.

Further structural distinction, between F and H, by pmr data could be achieved by careful analyses of the expected small vicinal coupling ($\leq$ 1.3 Hz) (28,29) between Ha/Hc in F and Hb/Hc in H. Unfortunately, Ha and Hb in both 34 and 35 do not show the small splitting, but clearly exhibit a difference in their line width. Namely, Ha ($\Delta 1/2$ = 2.5) is broader than Hb ($\Delta 1/2$ = 2.0) in 34, whereas Hb ($\Delta 1/2$ = 2.0) is broader than Ha ($\Delta 1/2$ = 1.2 Hz) in 35. This implies the small coupling between Ha/Hc in 34 and Hb/Hc in 35, hence, structures F (R = Me) and H (R = Me) are assigned for 34 and 35, respectively.

In order to confirm the conclusion, Eu(fod)3 effects on 34 and 35 were investigated. In structure F, Ha, Hb and Hc are all in rather close vicinity to either the ether oxygen or the hydroxyl group, whereas in H, only Ha is close to both groups. Similarly, the methyl

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to that (J_{ab} = 8.0Hz) of 29 than that (J_{ab} = 9.5 Hz) of 28, indicating that both 34 and 35 have the same stereochemistry as that of 29 (i.e. Ha and Hb are both endo-oriented).

groups are very much closer to the hydroxyl group in F than they are in H. We, therefore, expect a reasonable europium effect on Ha, Hb, Hc as well as the methyl groups for F and a large effect only on Ha for H.

Upon addition of the reagent, Ha, Hb, Hc and the methyl groups of 34 shifted downfield, while only Ha of 35 was affected to any major extent in agreement with prediction (see Table 1).

Accordingly, the structures B (R = Me) and D (R = Me) for the adducts 32 and 33 necessarily follow (*). Again, the europium effect on these substances is confirmatory of their structures. Thus only 32 has methyl groups close to the ketone and acetoxy groups which are capable of complexing with the reagent. Experimentally the methyl groups in 32 are considerably displaced by the reagent, whereas those in 33 are barely affected (see Table 2).

iii) with 3,3-DI(TRIFLUOROMETHYL)-2,3-DIHYDROFURAN (6)

2-Acetoxyclopent-2-en-1-one (7) was irradiated

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* The methine proton on carbon bearing the ethereal oxygen in 32 appears at 4.22 ppm as a doublet of doublets with J = 5.0 and 1.5 Hz. The equivalent proton in 27 also appears as a doublet of doublets with similar coupling constants (J = 5.4 and 1.6 Hz). This similarity in their chemical shifts and coupling constants is indicative of their similar stereochemistry.

TABLE 2

Eu(fod)3 EFFECT (Δppm)*

ON ADDUCTS 32 and 33

substance	Ac	Me	Me
32	0.39	0.39	0.30
33	0.42	0.99	0.74

* Samples consisted of 20 mg adduct and 18.56 mg Eu(fod)3 in 0.25 ml $CDCl_3$ (at 30°)

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with excess dihydrofuran 6 in a variety of solvents, i.e., n-hexane, cyclohexane, ether, acetonitrile and a mixture of methanol and water (9 : 1), and in the absence of solvent. In all cases, none of the expected adducts were detected by tlc and glc other than a dimer of the enone. The latter was identified as 31 by mp and ir. In one case when a mixture of water and methanol was used as solvent, two new peaks were observed on glc, but they were not photoadducts of the enone and 6. This was established because the same peaks were observed by irradiation in the mixed solvent in the absence of 6. The structures of these compounds have not been investigated further.

SOLVENT EFFECTS ON PRODUCT RATIO

In order to test the solvent effects on product ratio, 2-acetoxyclopent-2-en-1-one (7) was irradiated with

2,3-dihydrofuran (8) and 3,3-dimethyl-2,3-dihydrofuran (9) in three solvents with different dielectric constants; isooctane, ether and acetonitrile. The product ratios (at <20% conversion) were measured by glc (using suitable calibration compounds) and extrapolated to zero concentration of the substrates in each solvent (see Table 3). The latter is necessary because the enone and olefins are themselves polar compounds and at high concentrations they contribute to the polarity of the solvent. This is more important in less polar solvents (32).

TABLE 3

PHOTOLYSES OF 2-ACETOXYCYCLOPENTENONE AND DIHYDROFURANS 8 AND 9

(product ratios in %)*

olefin	8		9	
product	26	27	32	33
isooctane	47.7	52.3	39.3	60.7
ether	35.7	64.3	41.7	58.3
acetonitrile	10.9	89.1	52.6	47.4

*% of total mixed adducts, error limits ±0.6 for 8 and ±1.2 for 9.

As the solvent polarity decreases, using dihydrofuran 8 as a substrate, the yield of syn-HT adduct 26 increases, while anti-HT adduct 27 decreases. On the other hand, in the case of dihydrofuran 9, the yield of anti-HT adduct 32 decreases, while anti-HH adduct 33 increases. In both cases, the logarithm of the product ratio is linearly related to solvent polarity in terms of $E_T(30)$ (33) (*), Ω (15), or the Kirkwood-Onsager parameter for the solvent (14).

The relative importance of the solvent effects may be estimated as follows: The logarithm of the product ratio reflects the energy difference between the transition states which lead to the different products (⁑). Therefore, any difference in product ratio which is caused by solvent should be proportional to the change in this energy difference. The change in the energy difference may thus be used as a measure of the solvent effect. This is because the proportionality factor (34) for a given reaction (the portion of the reversible intermediate that cyclizes to give adducts) (see below) is probably independent of the solvent used. For example, the quantum yield of

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* $E_T(30)$ value (an analogue of Z value (33)) for isooctane is not reported in reference 33. Therefore the value of n-hexane was assumed.

⁑ Under kinetically controlled conditions, product ratio A/B can be expressed in terms of the energy difference between the two transition states, $\Delta\Delta G_{AB}^{\ddagger} = \Delta G_A^{\ddagger} - \Delta G_B^{\ddagger}$: $\Delta\Delta G_{AB}^{\ddagger} = -RT \ln (A/B)$.

cycloaddition between cyclopentenone (0.1 - 0.2 M) and cyclohexene (2.0 M) is reported to be constant (0.42 - 0.48) over a wide range of solvent polarity (cyclohexane, ether, acetonitrile, t-butanol and acetic acid) (12).

In isooctane, the energy difference corresponding to log(26/27) is 54 cal and it rises to 1246 cal in acetonitrile, when using 8 as olefin. On the other hand, when 9 is used, the energy difference corresponding to log(32/33) is 259 cal in isooctane and -61 cal in acetonitrile (the values are at 25°). The energy differences caused by the solvent change (from isooctane to acetonitrile) are 1192 cal in the former case and 320 cal in the latter, i.e., about four times more with 8 than with 9.

DISCUSSION

First of all, it was very unfortunate that the most relevant reaction in the present study, the cycloaddition between 2-acetoxycyclopent-2-en-1-one (7) and 3,3-di(trifluoromethyl)-2,3-dihydrofuran (6), did not occur, the only product isolated being a dimer (31) of the enone. This is in strong contrast to the cycloaddition of the analogous dihydrofurans (8 and 9) which proceeded smoothly. To learn the reason for this failure, one can attempt to analyse the reactivity of both the enone (7) and the olefin (6). It appears well-established that the reactive species in the photocycloaddition of cyclic enones are triplets having energies in the 70-kcal/mole region (7, 12, 35) (*). It seems reasonable, therefore, to assume that the reactive species in the cycloaddition of 2-acetoxycyclopent-2-en-1-one (7) is also its lowest triplet.

There are two low-energy spectroscopic states in the enone triplet manifold. They are $n\pi^*$ and $\pi\pi^*$ states. According to recent calculations (38), the $\pi\pi^*$ state prefers a twisted geometry around C_2-C_3 bond (as well as out-of-plane deformation of C_2-hydrogen). The $n\pi^*$ state prefers to stay in a planar form when relaxed. Since the former distortion is very much dependent upon the flexibility of the molecule, the relative energies of these two states depend largely on molecular flexibility. That is, the $\pi\pi^*$ state is relatively more stabilized in more flexible enones than is the $n\pi^*$ state.

It appears, on the basis of recent emission studies on constrained polycyclic cyclopentenones (39), that in these substances the two states are energetically very close. In more flexible cyclopentenones (such as 7), the $\pi\pi^*$ state may become the lowest triplet state. It is also known, on the basis of phosphorescence exitation

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* Cyclohexenones having a conjugative substituent at C3 (such as a vinyl (36) or phenyl group (37) have, however, been reported to react in their singlet excited states toward olefins.

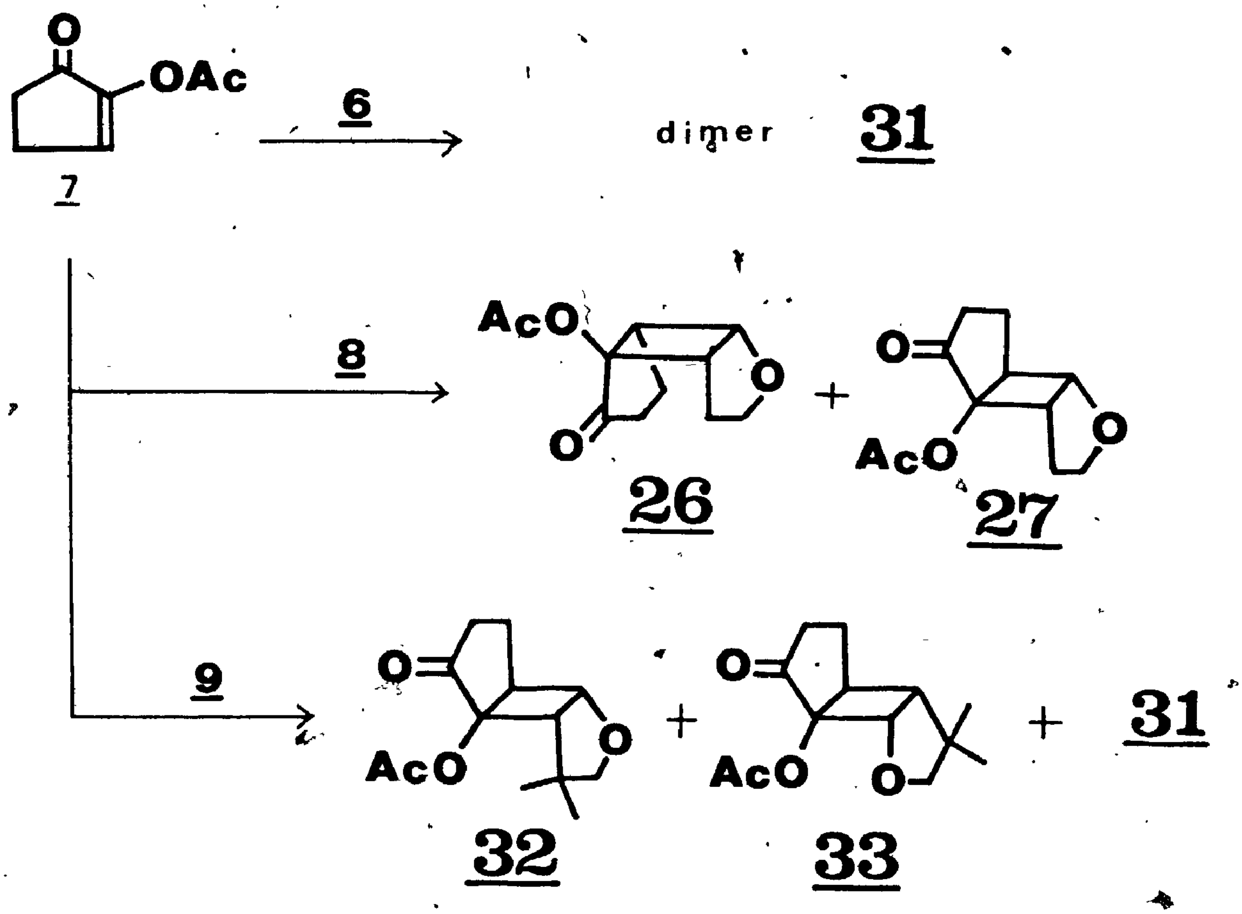
spectroscopy studies on the steroidal 4-en-3-one system (40), that the introduction of an acetoxyl group at C_2 stabilizes the ππ* state and destabilizes the nπ* state. Thus, the ππ* state of enone 7 is most probably the lowest triplet state, and is probably the species responsible for the cycloaddition to olefins.

The triplet state of the enone (7) is evidently reactive toward the usual olefins, since it was reported to react with cyclopentene and spiro-[2, 4]-hept-5-ene (4), and did react with the dihydrofurans (8 and 9). The enone also appears to behave normally in terms of regiospecificity (see below). The inertness of the enone to dihydrofuran 6, therefore, must be due to some special property of the olefin. It is thus necessary, first, to analyse the positive results with the analogous dihydrofurans (8 and 9) in order to understand the reason for the negative result with 6.

"NORMAL" ORIENTATION: THE ELECTRONIC AND DIPOLE-DIPOLE EFFECTS

With 2,3-dihydrofuran (8), the acetoxy-enone (7) yielded two products, syn-HT- and anti-HT- adducts (26 and 27) (Scheme 2). The orientational specificy was expected on the basis of either the dipole-dipole interaction effect or the electronic effect: The magnitude of dipole moments of ππ* triplet states of cyclic enones is experimentally unknown. However, on the basis of recent

SCHEME 2



calculations (38), it can be estimated to be a slightly larger than that of the ground state enones ($\mu \sim 3.5$). The direction of the dipole moment is presumably the same as in the ground state. The dipole-dipole interaction may orient the approaching molecules in a HT-manner, so that C_2 and C_3 of the triplet enone are in close vicinity to C_4 and C_5, respectively, of the dihydrofuran (see Figure 2 as a reference).

With the assumption that the charge distribution on the double bond (C_2-C_3) of the $\pi\pi^*$ triplet enone (7) is similar to that recently calculated for unsubstituted enones (38), the C_2 is slightly electrophilic, while the C_3 is rather neutral, which is basically in agreement with Corey's assumption (8). Therefore, the C_2 of the triplet enone may prefer to interact, either directly, or indirectly via "oriented exciplex" as proposed by Corey (8), with the negative end of the dihydrofuran double bond (see Figure 2 as a reference).

Thus, either based on the dipole-dipole interaction effect or based on the electronic effect, the predominant formation of HT-oriented products was expected.

The same predictions should be applicable to the reaction with 3,3-dimethyl-2,3-dihydrofuran (9), since the polarization of its double bond, and both the magnitude and direction of its dipole moment should be similar to those of 8. However, with this dihydrofuran (9), the acetoxy-enone (7) gave not only the expected HT-product (32) but also the unexpected HH-product (33) (together with the dimer (31) of the enone) (Scheme 2). The difference in behavior of these dihydrofurans (8 and 9) must, therefore, be due to sterio reasons.

"ABNORMAL" ORIENTATION: THE STERIC EFFECT

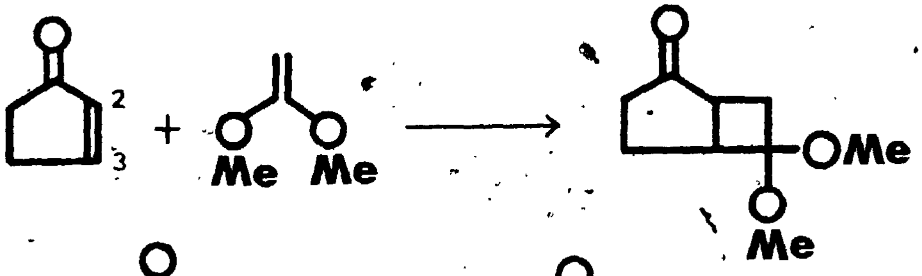
The steric effect in enone cycloaddition has been discussed on several occasions in terms of syn- versus anti-stereochemistry (6) as well as in the readiness of dimerization of substituted cyclopentenones (41): Eaton stressed the importance of the steric effect in order to rationalize the exclusive formation of anti-products in the cycloaddition of cyclopentenone to cyclopentene (42) and in the dimerization of cyclopentenone (43) (see below). Schaffner has also pointed out the importance of steric effects in explaining the absence of photodimerization of 3-t-butylcyclopentenone (41).

However, the orientational effects of steric hindrance have not been discussed in the literature. This is because, in the use of electron-rich polarized olefins (such as methoxyethylene and 1,1-dimethoxyethylene), there is no example of HH-product formation reported.

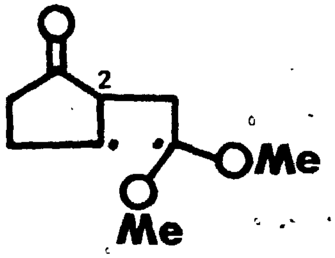
It is reasonable to assume, on the basis of presently known facts (8, 34, 44), that triplet 1,4-biradicals are intermediates in enone cycloadditions. The triplet biradicals are believed to form either directly from a triplet enone and an olefin, or indirectly via exciplexes (7, 8). In either case, the biradical formation step (the formation of the first bond) must determine the orientational as well as stereochemical outcome.

Both C_2 and C_3 of triplet enones are known to have radical-like characters and be reactive toward non-polarized olefinic bonds, such as that of norbornadiene (45). However, toward polarized bonds due to conjugation with electron-donating substituents, such as those of methoxyethylene and 1,1-dimethoxyethylene, the C_2 appears to be more reactive than the C_3. This is for the following reasons.

With the electron-rich polarized olefins, enones generally give only HT-products (6, 8) (an example is shown in reaction 3 (8)). The HT-product(reaction 3) is most probably produced by cyclization of the biradical (36) rather than of the isomeric biradical (37). This is because the unsubstituted end of the olefin has the



(3)



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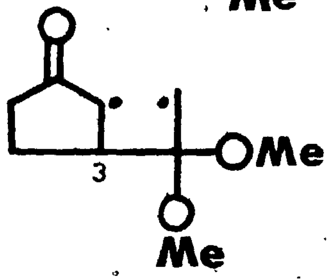

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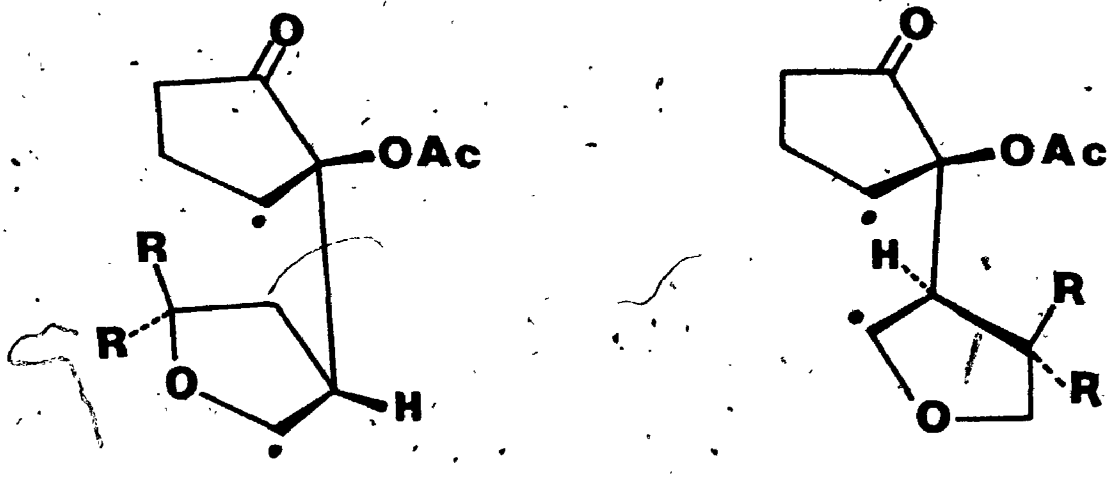
highest free valence (and so is the most reactive toward radical species) and because the same position is sterically less crowded (and thus more susceptible to radical addition (46)). Furthermore, the elecrophilic C_2 of the triplet enone prefers to react with the relatively negative end of the double bond, yielding the biradical (36), which is more stable than 37.

Therefore, with dihydrofuran 8, the first bond formation probably proceeds also predominantly at C_2 of the acetoxy-enone (7), giving the two HT-biradicals (38 and 39, R = H in Figure 5). The latter, upon ring-closure, would give the observed products (26 and 27).

FIGURE 5



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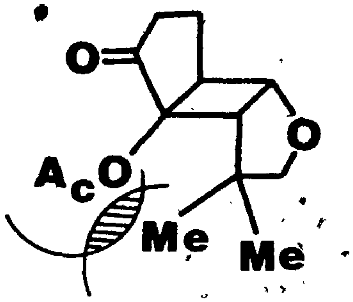
With dihydrofuran 9, the formation of the equivalent biradicals (38 and 39, R = Me) would be expected for the same reasons. However, of these expected products, only the anti-HT-product (32) was obtained. Furthermore, as we have seen, unexpected products — the anti-HH-product (33) and the dimer (31) of the enone — were also produced. The competitive formation of the dimer (31), which was not formed using olefin 8, suggested that the cycloadditions were (following the introduction of the methyl groups in 9) occuring at a slower rate.

The formation of the syn-product with the expected orientation was apparently excluded because of the large steric interaction introduced, although, that the corresponding biradical might have been formed can not be excluded.

The formation of the "abnormally" oriented product (33) indicated that this route be less subject to steric interference by the methyl groups than that of the "normally" oriented product (32). The steric interaction in the latter pathway must be between the OAc and Me groups, as indicated in Figure 6. This particular interaction is evidently lacking in the former process, which gave 33.

Although the electronic or/and the dipole-dipole effects are important in the absence of steric hindrance,

FIGURE 6



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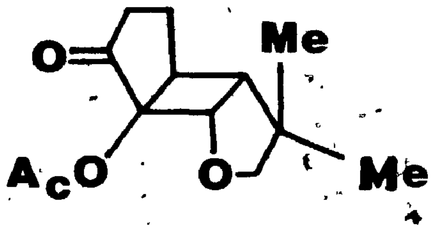

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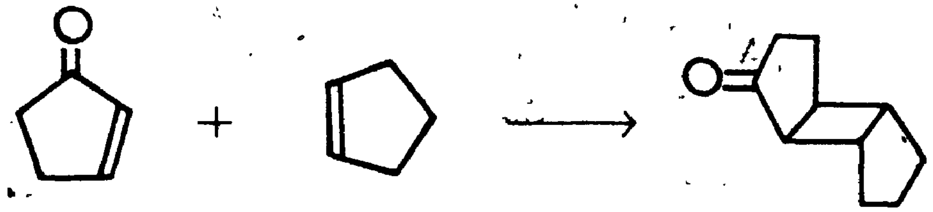
(case 8), these effects, in the presence of the steric interaction, (case 9), play a minor role.

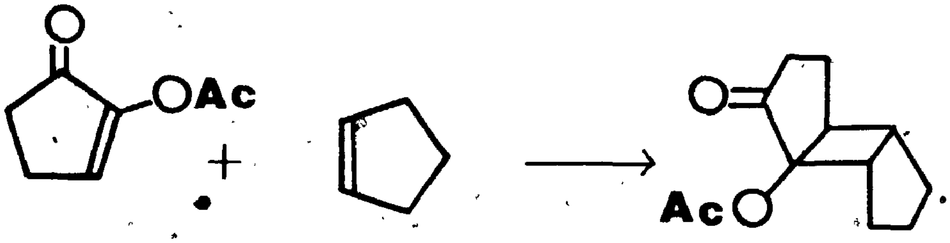
THE SYN-PRODUCT: IMPORTANCE OF THE DIPOLE-DIPOLE EFFECT

It is evident on the basis of the foregoing discussions that steric effect is important in deciding syn- and anti-stereochemistry (as well as orientation) of products. When using olefins, which have negligible dipole moments (such as cyclopentene, 0.20 D (47)), cyclopentenones are known to give exclusively anti-products regardless of the solvent used. Examples are shown in reactions 4 (42) and 5 (4).

However, in the present reaction using dihydrofuran 8, the sterically less favored syn-product (26) was formed in as high as 48% yield (in isooctane). Since the steric



(4)



(5)

effects are expected to be of similar order in both cyclopentene and the dihydrofuran, the high yield of the syn-product (26) must be due to the dipole-dipole interaction effect: the dihydrofuran has a relatively large dipole moment (calcd. $\sim$ 1.58 D) (*). The operation of the rather large dipole-dipole effect is evident in that the syn-product is largely assisted in less polar solvent (see Table 3).

However, in the presence of steric interactions, as that in the reaction with 9, the effect, as we have seen, appears to become less important (as evidenced by the appearance of the abnormally oriented product). This

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* The dipole moment of 8, which is not known experimentally,

decline in importance is also reflected in the relatively small solvent effect on product ratio observed with 4.

THE "NEGATIVE" CYCLOADDITION

With enone 7, dihydrofuran 6 did not give any adduct at all: the only product was the dimer (31) of the enone.

This inertness of the olefin does not seem to be restricted to the acetoxy-enone, but may be general, since the olefin did not yield any product with cyclopentenone itself: again, only the dimers (43) of the enone were obtained. The inertness must therefore be due either to the fact that the olefin is not reactive enough to compete with the photodimerization of the enones, or that an efficient energy transfer from the excited enones to the olefin may have taken place.

To test the latter possibility, the effect of the olefin (6) on the cycloaddition of 7 and 8 (in acetonitrile) was investigated. Parallel experiments showed that, in the presence of 6 (0.24 Ml^{-1}), the reaction ([7] = 0.011 and [8] = 0.29 Ml^{-1}), was approximately 73% as effective as in the absence of 6. The efficiency of 6 in quenching the excited enone was thus rather low (27%).

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was calculated (assuming a planar model) using the values of tetrahydrofuran ($\mu = 1.63$) (47) and cyclopentene ($\mu = 0.20$) (47).

Thus, the question is: Is the partial quenching due to the rather slow energy transfer, or due to some unproductive chemical process(es)? Though a definite answer is presently not available, it seems likely that the latter is responsible for the observed quenching. This is because the trifluoromethyl group does not appear to lower the triplet energy (E_T) of $\pi\pi^*$ states to any great extent, as may be seen from the E_T values (kcal/mole) of benzene (84.3), thrifluoromethyl benzene (83.4) and methyl benzene (82.5) (48).

A possible interpretation is as follows: With olefin 6, certain triplet biradicals are formed. These biradicals, however, effectively dissociate into the ground state molecules (after spin inversion). If this view is correct, the biradicals are most probably syn-biradicals, since the geminal trifluoromethyl groups are approximately 1.5-2.0 times bulkier than the corresponding ~~methyl~~ groups (*) and olefin 8 did not yield syn-products at all.

Why are these sterically less favored biradicals formed predominantly over anti-biradicals? This can not be

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* The relative bulkiness of the substituents is relative to hydrogen and estimated on the basis of the Taft Es values (49) (1.24 for H, 0.00 for Me and -1.16 for CF_3) and of the calculated values (A°) using covalent radii and van der Waal's radii (50) (2.25 for H, 3.79 for Me and 4.43 for CF_3).

answered on the basis of the electronic effect, since the Corey-type interaction, if important, presumably takes place in a sterically least hindered manner, i.e., in an anti-mode. It seems, thus, likely that the formation of the syn-biradicals might have been favored by the dipole-dipole interaction effect.

The calculated dipole moment of 6 is ~ 1.5 D (*), which is in a range similar to those of 8 and 9 (~ 1.6 D). Therefore, the dipole-dipole interaction (with a given enone) should, as far as magnitude is concerned, be similar within these dihydrofurans. However, the alignment of olefin 6 with the triplet enone (because of this interaction) will not be the same as those of 8 and 9. This is because the direction of the dipole moment of 6 is, as shown in Figure 7, not the same, but is rather roughly the reverse. Thus, the possibility exists that the dipole-dipole interaction might have aligned the enone and 6 predominantly in syn-(probably HH)-manner. In this particularly aligned pair, the turning over to the other anti-alignment, which was observed with olefins 8 and 9, might have been prohibited, thus yielding only the unproductive syn-biradical.

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* The dipole moment was calculated using the calculated value (1.58 D) for 8 (vide infra) as the basis. The value 2.36 D was used for the group moment of CF_3 group.

FIGURE 7

6

8 R = H

9 R = Me

We believe, therefore, that the apparent lack of reactivity of olefin 6 is due to a combination of steric and the dipole-dipole interaction effects. At this point any conclusion must, however, be tentative.

EXPERIMENTAL: PART ONE

GENERAL

Pmr spectra were taken on Varian T-60 or HA-100 instruments with TMS as internal standard. Chemical shifts are reported in ppm unit and coupling constants (H_Z) correspond to apparent splittings. Δ1/2 refers to half-height-width in H_z. Cmr spectra were measured on Varian XL-100 instrument with TMS as internal standard. Chemical shifts are expressed in ppm unit. Mass spectra were recorded on Varian M-66 spectrometer, Glc analyses were carried out on Varian Aerograph equipped with thermal conductivity detectors, unless otherwise mentioned. Four glc columns were used: 5, 10 and 20% Carbowax 20M on Chromosorb P, and 5% FFAP on Diaport S (abbreviated to column A, B, C and D, respectively). Tlc and preparative tlc were performed using Silica Gel 60 (Merck) and, for column chromatographies, Silica Gel 60 (Merck) was used, unless otherwise specified. Melting points were measured on Reichert hot stage and are uncorrected.

MATERIALS

2,3-Dihydrofuran (<u>8</u>) was prepared according to the method of R. Paul et all (17) and had bp 53.5-54.5°

(>99% purity by glc: column A, 54°). The pmr spectrum (100 Mc) showed signals at 6.31 ($-CH=C\underline{H}O-$), 4.93 ($-C\underline{H}=CHO-$), 4.27 ($-C\underline{H}_2O-$) and 2.58 ppm ($-C\underline{H}_2CH_2O-$). The coupling constant between the vinylic protons was J=2.4 Hz (18). The cmr showed signals at 145.95 ($-CH=\underline{C}HO-$), 99.29 ($-\underline{C}H=CHO-$), 69.52 ($-\underline{C}H_2O-$) and 29.29 ppm ($-\underline{C}H_2CH_2O-$). 2-Acetoxycyclopentenone (7) was freshly recrystallized and dried just before use. Irradiation solvents: isooctane, cyclohexane and n-hexane (all spectral grade) were passed through alumina (neutral, grade 1) and used immediately; ether (Mallinckrodt anhyd) was refluxed over sodium for several hours and freshly distilled before use; acetonitrile (BDH, Lab reagent) was refluxed over a mixture of phosphorous pentoxide and potassium carbonate for 6 hours and distilled before use; methanol (spectral grade) was used without further purification.

IRRADIATION

A Hanovia 450 W medium pressure lamp with a Pyrex filter was used for all irradiations, unless otherwise mentioned. All irradiations were conducted at room temperature.

3.3-Dimetylpent-4-en-1-al Dimethyl Acetal (14)

The following conditions are based on a reported method for preparing diethyl acetals (51). 3,3-Dimethylpent-

4-en-1-al (19) (2.2 g), trimethylorthoformate (12.7 g) and a catalytic amount of p-toleunesulfonic acid were dissolved in methanol (100 ml, dried over type 4A molecular sieves) and kept at room temperature for 2 days. The mixture was neutralized with sodium carbonate and extracted with ether. Isolation and distillation gave the acetal 14 (2.6 g; 84%) of bp 75°/52 mm: ir ($CHCl_3$) 3075, 2970, 2912, 1110, 1032 and 900 cm^{-1}; pmr ($CDCl_3$) δ 5.81 (dd, 1, J=18.0 and 10.0 Hz), 4.91 (dd, 1, J=18.0 and 1.0 Hz), 4.90 (dd, J=10.0 and 1.0 Hz), 4.35 (t, 1, J=5.0 Hz), 3.25 (s, 6), 1.61 (d, 2, J=5.0 Hz) and 1.02 (s, 6); mass spectrum (70 eV) m/e (rel intensity) 127 (5), 75 (100) and 69 (38).

Anal. Calcd for $C_9H_{18}O_2$: C, 68.31; H, 11.47. Found: C, 67.94; H, 11.56.

2-Methoxy-4, 4-dimethyltetrahydrofuran (16)

3,3-Dimethylpent-4-en-1-al dimethyl acetal (14) (1.00 g) in dry methanol (25 ml, dried over type 4A molecular sieves) was subjected to ozonolysis at -77°. The ozone supply was continued until a permanent blue color appeared (ca. 1 hour). Sodium borohydride (1 g) was added to the reaction in portions. The reaction was allowed to warm to room temperature and extracted with ether. Isolation and distillation yielded the methoxytetrahydrofuran 16 (620 mg, 75%). An analytical sample was collected by glc (column B, 100°) and bulb to bulb distilled, bp ca. 66°/105 mm: ir ($CHCl_3$) 2940, 1360, 1085 and 1026 cm^{-1}; pmr ($CDCl_3$) δ 5.03 (dd, 1, J=5.5 and 3.0 Hz, $-OC\underline{H}O-$), 3.63 (d, 1, J= 8.3 Hz, $-C\underline{H}_2O-$), 3.48 (d, 1, J=8.3 Hz, $-C\underline{H}_2O-$), 3.35 (s, 3, $-O\underline{Me}$), 1.93 (dd, 1, J=13.0 and 5.5 Hz, $-C\underline{H}_2CHOMe$), 1.64 (dd, 1, J=13.0 and 3.0 Hz, $-C\underline{H}_2CHOMe$), 1.14 (s, 3) and 1.08 (s, 3); mass spectrum (70 eV) (rel intensity) 100 (30), 99 (61), 85 (100), 70 (82), 55 (58), 43 (27) and 42 (21).

Anal. Calcd for $C_7H_{14}O_2$: C, 64.58; H, 10.84. Found: C, 64.35; H, 11.00.

2-Hydroxy-4,4-dimethyltetrahydrofuran (<u>17</u>)

2-Methoxy-4,4-dimethyltetrahydrofuran (<u>16</u>) (120 mg) and 10% aq. sulfuric acid (10 ml) was sealed in a glass tube and heated at 65-70° for 15 hours. The reaction was cooled, neutralized (Na_2CO_3) and extracted with ether. Drying ($MgSO_4$), evaporation and bulb to bulb distillation (ca. 60°/3 mm) of the residual oil gave the hydroxytetrahydrafuran <u>17</u> (73 mg, 68%): ir ($CHCl_3$) 3600, 3400, 1215 and 1015 cm^{-1}; pmr ($CDCl_3$) δ 5.56 (dd, 1, J=5.4 and 4.0 Hz, $-OC\underline{H}O-$), 3.62 (d, 1, J=8.0 Hz, $-C\underline{H}_2O-$), 3.47 (d, 1, J=8.0 Hz, $-C\underline{H}_2O-$), 1.99 (dd, 1, J=12.8 and 5.4 Hz, $-C\underline{H}_2CHOH$), 1.61 (dd, 1, J=12.8 and 4.0 Hz, $-C\underline{H}_2CHOH$), 1.16 (s, 3), 1.06 (s, 3) and ca. 4 (broad s, 1).

Reflux without use of a sealed tube led to very slow reaction. Increase of temperature (ca. 115°) also increased the complexity of the reaction.

3,3-Dimethyl-2,3-dihydrofuran (9)

2-Methoxy-4,4-dimethyltetrahydrofuran (16) (350 mg) was placed in a distillation flask (pre-washed with base and dried) which was fitted with a long column packed with finely powdered sodium bisulphate (pre-heated at 500° for 20 hours). The packed column was heated to ca. 240° during the distillation. With the aid of a nitrogen stream and a slight vacuum applied to the receiver compound 16 was volatilised (bath temperature: 40-50°) on to the column and thence into a cooled (dry ice-acetone) receiver which contained a few mgs of anhydrous sodium carbonate (≠). Distillation required ca. 15 hours. The distillate (302 mg) contained (column C, 100°) dimethyldihydrofuran (9), methanol and 16 in the ratio of 1.7:1.7:1.0, respectively (est. yield of 9: 54%).

To the mixture, ca. 5 mg of lithium alminium hydride (LAH) was added at -78° and the mixture gradually warmed to room temperature. This addition of LAH was repeated until no more hydrogen evolution was observed at room temperature. The mixture was distilled through a vigreux column (bath temperature ca. 60° ca. 130 mm) to give 9 of 97% purity (by glc). Analytical sample was obtained by a glc separation (columb B, 60°) and subsequent distillation: ir ($CHCl_3$) 2991, 2946, 1607, 1365, 1134, 1035 and 944 cm^{-1};

≠In the absence of sodium carbonate, the dihydrofuran (9) and methanol slowly reacted back to the starting material (16).

pmr ($CDCl_3$) δ 6.24 (d, 1, J=1.3 Hz, -CH=C$\underline{H}$O-), 4.86 (d, 1, J=1.3 Hz, -C$\underline{H}$=CHO-), 3.95 (s, 2) and 1.13 (s, 6); mass spectrum (70 eV) m/e (rel intensity) 98 (39), 83 (100), 67 (12), 55 (34) and 53 (17); cmr ($CDCl_3$) δ 144.05 (-CH=$\underline{C}$HO-), 111.59 (-$\underline{C}$H=CHO-), 82.22 (-$\underline{C}H_2O$-), 42.38 (=$\underline{C}Me_2$) and 27.93 (=$C\underline{Me}_2$).

Anal. Calcd for $C_6H_{10}O$: C, 73.48; H, 10.27. Found: C, 73.13; H, 10.46.

Dehydration of 2-hydroxy-4,4-dimethyltetrahydrofuran (17) using catalytic amounts of acids (sulfuric acid or p-toluenesulfonic acid) or of activated sodium bisulphate gave 9 (and water) in poor yields. Reproducibility was also poor.

4,4-Di(trifluoromethyl)-but-3-en-2-ol (18)

4,4-Di(trifluoromethyl)-but-3-en-2-one (22, 23) (76.24 g) and aluminium isopropoxide (190.00 g) were allowed to react in isopropanol (500 ml) [method of Plakhov and Gambaryan (22)]. The crude product was distilled (spinning band column) to give isopropanol (up to 82°), a few drops of material, bp 83-123°, and then the allylic alcohol 18 (44.3 g, 57.5%), bp 124-126°. The last fraction showed a single peak on glc (column C, 130°). [Lit. bp 125-126°, obtained as an azeotropic mixture containing 19.8% of diethyl ether (22)].

Acetoaldehyde Di-n-amyl Acetal

Acetoaldehyde di-n-amyl acetal was prepared from n-amyl alcohol (246 g), mercuric oxide (1.5 g) borotrifluoride etherate (1.5 ml) and vinyl acetate (129 g), following the general method of Croxall et al (52) for the preparation of di-n-butyl acetal of acetoaldehyde. The yield of the di-n-amyl acetal was 227 g (75%), bp 100-107°/ water pump pressure. [Lit. bp 114-118°/16 mm (53)].

n-Amyl Vinyl Ether (19)

n-Amyl vinyl ether was prepared from di-n-amyl acetal by the method of Voronkov (20). This reference does not adequate experimental details necessary for success. Technical grade sodium bisulphate was ground to a fine powder, then heated overnight in a porcelaine crucible in an oven at 500° (not heating or heating for longer times was found to give less satisfactory results). The material was allowed to cool in a desiccator over P_2O_5, then ground into a fine powder, and used at once.

Di-n-amyl acetal (101.0 g) and dried sodium bisulphate (0.09 g) were magnetically stirred in a distillation apparatus and heated to 190°. n-Amyl vinyl ether (19), n-amyl alcohol and a little di-n-amyl acetate slowly distilled at 110-130°, being collected in an ice-cooled flask containing a few mgs of anhydrous potassium carbonate. As the volume of reactants decreased, the bath temperature was gradually increased to 220° and after a total of 9 hours heating, a colorless distillate (90.59 g) had been collected. Glc (column C, 130°) indicated this to be ca. 1:1 n-amyl vinyl ether: n-amyl alcohol, plus a small quantity of di-n-amyl acetal. If correctly prepared catalyst is used, only slight yellowing of the reaction takes place, but otherwise a brown tar may form and much of the n-amyl vinyl ether is destroyed. Distillation of a portion of the mixture (36.20 g) (spinning band column) gave n-amyl vinyl ether (19) (13.90 g, 67%), bp 115-118.5°. The bulk of the sample distilled at 118-118.5°. [Lit. bp 111° (54) and 116-118° (55)].

Vinyl-2-[4,4-di(trifluoromethyl)-but-3-enyl]-ether (20)

Vinyl-2-[4,4-di(trifluoromethyl)-but-3-enyl]-ether was prepared by heating the allylic alcohol 18 and n-amyl vinyl ether with mercuric acetate, using a modified version of procedure A of Watanabe and Conlon (24). Commercial mercuric acetate (Fisher Certified Reagent) was used, further purification of the catalyst being found not necessary (25).

Allylic alcohol 18 (4.16 g), n-amyl vinyl ether (13.78 g) and mercuric acetate (1.50 g) were heated in a distillation apparatus (70-75°) at 50 mm for 11.5 hours. The receiver flask was connected to a cold finger trap, both being cooled by powdered dry ice. Material distilled over at or to ca. 48°.

Glc study (column C, 110°) of the material from both traps showed this was a mixture of the required product (<u>20</u>) and n-amyl vinyl ether, containing only a trace of the starting alcohol (<u>18</u>).

A further amount of mercuric acetate was added to the reaction flask and heating was continued until no more unreacted alcohol <u>18</u> remained (12.5 hours). As the volume of reactants in the flask decreased the temperature was raised to 80° (40 mm). The material from the two traps was combined and distilled (spinning band column) to give a mixture of n-amyl vinyl ether and vinyl ether <u>20</u> distilling up to 118° (5.05 g); estimated yield of <u>20</u> by glc was ca. 2.10 g (ca. 45%). Careful redistillation (spinning band column) gave >97% pure <u>20</u>, which was used for the preparation of <u>21</u>. An analytical sample was collected by glc (column C, 110°), bp 88-89°: ir (CCl_4) 1680, 1622 and 1200 cm^{-1}; pmr (CCl_4) δ 6.65 (d, 1, J=8.0 Hz, $(CF_3)_2C{=}C\underline{H}-$), ca. 6.2 (m, 1), 5.00 (m, 1), 4.20 (m, 2) and 1.41 (d, 3, J=7.0 Hz); mass spectrum (70 eV) m/e (rel intensity) 234 (15), 191 (3), 171 (23), 151 (12), 145 (50), 121 (12), 101 (10), 75 (12), 69 (18), 44 (100) and 43 (37).

Anal. Calcd for $C_8H_8F_6O$: C, 41.03; H, 3.41; F. 48.72. Found: C, 41.29; H, 3.28; F, 48.88.

Attempts to prepare the vinyl ether <u>20</u> at higher temperatures without applying reduced pressure gave unsatisfactory results. For example, allylic alcohol 18 (1.04 g), n-amyl vinyl ether (19) (1.44 g) and mercuric acetate (60 mg) were heated at 120° for 11 hours. The reaction mixture was then allowed to cool to room temperature and excess anhydrous potassium carbonate was added. Glc (column C, 110°) on the mixture showed three peaks (other than unreacted alcohol 18) in the ratio of 1.00:1.12:1.87 in the order of increasing retention time. The major component had identical pmr, ir and mass spectra to an authentic sample of acetoaldehyde di-n-amyl acetal. The first two peaks were separated by preparative glc and assigned as the diastereomeric mixed acetals, n-amyl-2-[4,4-di(trifluoromethyl)-but-3-enyl]-acetals of acetoaldehyde (40, first peak, and 41, second peak). Acetal 40 had: ir (film) 1675 and 1165 cm^{-1}; pmr (CCl_4) δ 6.58 (broad d, 1, J=9.0 Hz), ca. 4.8 (m, 1), 4.57 (q, 1, J=6.0 Hz), 1.6-0.8 (m, 9), 1.30 (d, 3, J=7.0 Hz) and 1.25 (d, 3, J=6.0 Hz); mass spectrum (70 eV) m/e (rel intensity) 307 (9), 235 (100), 191 (12), 171 (51), 151 (11), 145 (40), 121 (11) and 115 (44).

Acetal 41 had: ir (film) 1675 and 1165 cm^{-1}; pmr (CCl_4) δ 6.75 (broad d, 1, J=8.5 Hz), ca. 4.6 (m, 2), ca. 3.4 (m, 2), 1.6-0.8 (m, 9), 1.29 (d, 3, J=7.0 Hz) and 1.25 (d, 3, J=5.0 Hz); mass spectrum (70 eV) m/e (rel intensity) 307 (8), 235 (100), 191 (14), 171 (59), 151

(10), 145 (45), 121 (13) and 115 (47).

3,3-Di(trifluoromethyl)hex-4-en-1-al (21)

Vinyl ether 20 (9.70 g) was heated in a sealed tube under nitrogen at 200° for 2.5 hours. Glc (column C, 135°) of the reaction showed essentially quantiative conversion to the aldehyde 21. Distillation of the material under nitrogen gave 21 (6.62 g, 66%) of bp 146-148°: ir (CCl_4) 2860, 2760, 1730, 1700 and 1220 cm^{-1}; pmr (CCl_4) δ 9.62 (m, 1, -CHO), ca. 6.0 (m, 1), 5.58 (d, 1, J=16.0 Hz, -CH=CHMe), 2.85 (d, 2, J=3.0 Hz, $-CH_2CHO$), 1.87 (dd, 3, J=6.0 and 1.5 Hz, -CH=CHME); mass spectrum (70 eV) m/e (rel intensity) 235 (6), 234 (6), 219 (8), 192 (16), 191 (7), 171 (18), 167 (26), 164 (50), 145 (95), 121 (47), 95 (66), 77 (57) and 69 (100).

Anal. Calcd for $C_8H_8F_6O$: C, 41.03; H, 3.41; F, 48.72. Found: C, 41.19; H, 3.46; F, 48.85.

If oxygen was not excluded from the reaction system, several products were obtained, the major one being the allylic alcohol 18. The latter was presumably formed by acid catalysed fragmentation of the vinyl ether 20 (≠).

3,3-Di(trifluoromethyl)hex-4-en-1-al Dimethyl Acetal (22)

The following method is based on a reported

≠Control experiments showed that even under acid free conditions the alcohol 18 was formed. Possibly acid may have been generated by the air oxidation of the vinyl ether 20.

procedure for preparing diethyl acetals (51). 3,3-Di(trifluoromethyl)hex-4-en-1-al (21) (6.09 g), trimethylorthoformate (4.8 g) and a catalytic amount of p-toluenesulfornic acid (15 mg) in dry methanol (15 ml) were allowed to stand for 4 days (room temperature), by which time glc (column C, 135°) indicated ca. 95% reaction. The acetal was isolated with ether, and dried ($CaCl_2$). Distillation (vigreux column) gave the dimethyl acetal 22, bp 80-82° (ca. 30 mm), contaminated with a trace of methanol. Pure material (column C, 135°) had: ir (CCl_4) 1670 and 1230 cm^{-1}; pmr (CCl_4) δ ca. 6.0 (m, 1, -CH=C<u>H</u>Me), 5.47 (dd, 1, J=16.0 and 1.5 Hz, -C<u>H</u>=CHMe), 4.49 (t, 1, J=4.5 Hz, -C<u>H</u>$(OMe)_2$), 3.25 (s, 6, -O<u>Me</u>), 2.19 (d, 2, J=4.5 Hz, -$C\underline{H}_2CH(OMe)_2$), 1.86 (dd, 3, J=6.0 and 1.5 Hz, -CH=CH<u>Me</u>); mass spectrum (30 eV) m/e (rel intensity) 279 (2), 249 (100), 179 (16), 145 (14), 115 (14), 85 (15), 83 (25) and 75 (83).

Anal. Calcd for $C_{10}H_{14}F_6O_2$: C, 42.86; H, 5.00; F, 40.71. Found: C, 43.27; H, 5.23; F, 40.44.

<u>4-Hydroxy-3,3-di(trifluoromethyl)butyraldehyde Dimethyl Acetal (23).</u>

3,3-Di(triflurormethyl)hex-4-en-1-al dimethyl acetal (22) (0.771 g) in dry methanol (25 ml) was subjected to ozonolysis at -78° for 8 hours. This time was necessary to complete the reaction, although within 3.5 hours a permanent blue color appeared. Sodium borohydride (0.700 g) was added in portions to the cold solution, which was then allowed to warm to room temperature slowly. Isolation and distillation (70-75°/8 mm) gave the hydroxy dimethyl acetal 23 (0.695 g, 93%), >95% pure by glc (column B, 130°): ir (CCl_4) 3400 and 1240 cm^{-1}; pmr ($CDCl_3$) δ 4.68 (t, 1, J=5.0 Hz, $-C\underline{H}(OMe)_2$), 3.95 (broad s, 2, $-C\underline{H}_2OH$), 3.39 (s, 6), 2.82 (broad s, 1, $-O\underline{H}$) and 2.20 (d, 2, J=5.0 Hz, $-C\underline{H}_2CH(OMe)_2$); mass spectrum (70 eV) m/e (rel intensity) 239 (4), 221 (7), 207 (52), 189 (17), 139 (45), 75 (100) and 69 (69).

Anal. Calcd for $C_8H_{12}F_6O_2$: C, 35.56; H, 4.44. Found: C, 35.61; H, 4.14.

2-Methoxy- and 2-Hydroxy-4,4-di(trifluoromethyl)tetrahydrofuran (24 and 25)

4-Hydroxy-3,3-di(trifluoromethyl)-butyraldehyde dimethyl acetal (23) (0.400 g) in 5% aqueous sulfuric acid (25 ml) was heated in a sealed tube at 110-115° for 34 hours. The reaction was allowed to cool to room temperature, neutralized (Na_2CO_3) and extracted (ether). The extract was dried ($MgSO_2$) and the solvent removed (vigreux column). Bulb to bulb distillation (60-70°/10 mm) of the residual oil gave the hydroxytetrahydrofuran 25 (0.309 g, 93%), which showed a single peak on glc (column B, 120°): ir (CCl_4) 3440 and 1240 cm^{-1}; pmr ($CDCl_4$) δ 5.62 (m, 1, $-OC\underline{H}OH$), 4.23 (broad s, 2, $-C\underline{H}_2O-$), 3.27 (broad, 1, $-O\underline{H}$) and 2.40 (m, 2, $-C\underline{H}_2CHOH$); mass spectrum

(70 eV) m/e (rel intensity) 223 (8), 207 (100), 177 (8), 157 (23), 155 (17) and 145 (20).

Anal. Calcd for $C_6H_6F_6O_2$: C, 32.14; H, 2.68; F, 50.89. Found: C, 31.86; H, 2.49; F, 50.63.

In order to complete the reaction, heating at least 34 hours was required. If heating was curtailed to a few hours, methoxytetrahydrofuran 24 was isolated as the predominant product. The product 24 was collected by glc: ir (CCl_4) 1300 and 1240 cm^{-1}; pmr (CCl_4) δ 5.09 (m, 1, -OC$\underline{H}$OMe), 4.15 (d, 1, J=10.0 Hz, -C$\underline{H}_2$O-), 4.05 (dd, 1, J=10.0 and 1.5 Hz, -C$\underline{H}_2$O-), 3.30 (s, 3) and ca. 2.35 (m, 2); mass spectrum (70 eV) m/e (rel intensity) 237 (8), 207 (100), 189 (21), 177 (15) and 139 (13).

3,3-Di(trifluoromethyl)-2,3-dihydrofuran (6)

Hydroxytetrahydrofuran 25 (0.148 g) was placed in a distillation apparatus and heated under nitrogen at 120-125° for 8 hours in the presence of a catalytic amount of concentrated sulfuric acid, while the distillate was collected in a receiver cooled in dry ice. At a later stage it was necessary to raise the temperature gradually to 200° in order to complete the reaction. The distillate appeared as two layers. The bottom organic layer was separated (0.107 gr, 72%) from the aqueous layer. Its pmr spectrum showed the presence of the dihydrofuran 6 as an only detectable product. An analytical sample (glc; column

C, 55°, and distillation) had: ir (CCl_4) 1623 and 1240 cm^{-1}; pmr δ 6.61 (d, 1, J=3.0 Hz, $-CH{=}C\underline{H}O$), 4.96 (d, 1, J=3.0 Hz, $-C\underline{H}{=}CHO-$), 4.52 (s, 2, $-C\underline{H}_2O-$); mass spectrum (50 eV) m/e (rel intensity) 206 (45), 139 (22), 137 (100), 117 (12), 89 (28) and 69 (22); cmr ($CDCl_3$) δ 153.57 ($-CH{=}\underline{C}HO-$), 93.25 ($-\underline{C}H{=}CHO-$) and 70.24 ($-\underline{C}H_2O-$).

Anal. Calcd for $C_6H_4F_6O$: C, 34.95; H, 1.94. Found: C, 34.95; H, 2.02.

With larger amounts of conc. sulfuric acid or at higher initial temperatures, the yield of 6 decreased, with the formation of tars. Activated sodium bisulphate could also catalyse the dehydration under comparable conditions.

Attempts to convert methoxytetrahydrofuran 24 to 6 by elimination of methanol with acids (conc. sulfuric acid, p-tolulenesulfonic acid and 85% o-phosphoric acid) or sodium bisulphate, failed.

Irradiation of 2-Acetoxycyclopentenone (7) and 3,3-Di(trifluoromethyl)-2,3-dihydrofuran (6)

2-Acetoxycyclopentenone (7) and the dihydrofuran 6 were irradiated in n-hexane, cyclohexane, ether and acetonitrile as solvents, or in the absence of additional solvent. A typical experiment consisted of the enone (4 mg) and the olefin (140 mg) in the presence of solvent (1 ml). In all cases, no adducts were detected by either tlc or glc (Hifi aerograph equipped with hydrogen flame detector, column B and D, 200°) other than a dimer of the enone. This was identified as adduct 31 by mmp and ir. This compound was also formed when the enone (4 mg) in acetonitrile (1 ml) was irradiated in the absence of the dihydrofuran.

When a mixture (1 ml) of methanol and water (9:1) was used as solvent (enone, 3 mg, and olefin, 75 mg), two new peaks appeared on glc (column D, 200°). But the same peaks were observed when the enone was irradiated in the mixed solvent in the absence of the dihydrofuran. The nature of these compounds was not investigated further.

Irradiation of 2-Acetoxycyclopentenone and 2,3-Dihydrofuran (8)

2-Acetoxycyclopentenone (1.00 g) and 2,3-dihydrofuran (5 ml) were irradiated in a mixed solvent of ether (15 ml) and cyclohexane (50 ml) for 16 hours, until the enone disappeared completely (ir). The solvent was evaporated and glc of the residual oil showed two peaks (column B, 200°) with ratio 35:65 (the minor component with the shorter retention time). The corresponding compounds were isolated as white crystals by preparative tlc (petrol ether, bp 60-80°, : ether, 3:1); the minor compound 26 with larger Rf value, mp 64.0-64.5°, and the major compound 27, mp 79.5-80.0°. Both compounds were recrystallized from petrol ether (60-80°). Compound 26 had: ir ($CHCl_3$) 1732 cm^{-1}; pmr ($CDCl_3$) δ 4.63 (dd, 1, J=6.7 and 7.2 Hz), 3.98 (dt, 1, J=9.3, 9.3 and 5.9 Hz), 3.76 (dt, 1, J=9.3, 9.3 and 7.4 Hz), 3.26 (m, 1), 2.83 (m, 1) and 2.05 (s, 3). δ 4.63 proton coupled with 3.26 and 2.83 protons with J= 7.2 and 6.7 Hz, respectively (double irradiation); mass spectrum (70 eV) m/e 168, 151, 150, 141; 122, 99, 70, 69, 55, 43, 42 and 41.

Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found; C, 63.22; H, 6.82.

Compound 27 had: ir ($CHCl_3$) 1735 and 1745 (sh) cm^{-1}; pmr ($CHCl_3$) δ 4.26 (dd, 1, J=5.4 and 1.6 Hz), 4.15 (ddd, 1, J=9.0, 7.6 and 1.4 Hz), 3.78 (ddd, 1, J=10.8, 9.0 and 5.4 Hz), 2.94 (broad dd, 1, J=9.0 and 5.4 Hz, Δ1/2=3.6 Hz) and 2.07 (s, 3). δ 4.26 proton coupled with 2.94 proton with J=5.4 Hz (double irradiation); mass spectrum (70 eV) m/e (rel intensity) 168 (21), 151 (67), 150 (25), 141 (15), 122 (77), 99 (35), 70 (100), 69 (27), 55 (27) 43 (70), 42 (47) and 41 (27).

Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found: C, 63.00; H, 6.75.

The effect of dihydrofuran 6 on the photocycloaddition of 2-acetoxycyclopentenone (7) and 2,3-dihydrofuran (8) was investigated in acetonitrile. Three samples, A-C, each of which consisted of 7 (3.51 mg) and 8 (46.50 mg) in acetonitrile (2.3 ml), were irradiated in the presence of

6 (128 mg in sample A and 64 mg in sample B) or in the absence of 6 (sample C). The irradiations were performed in a merry-go-round apparatus (λ=366 nm) for 34 hours. Photoadducts 26 and 27 were formed in all cases and the % conversion was calculated by glc (Hifi aerograph with hydrogen flame detector, column D, 200°) using benzophenone as the calibration material. The % conversions were 1.1, 1.3 and 1.5% for samples A, B and C, respectively.

Irradiation of 2-Acetoxycyclopentenone and 3,3-Dimethyl-2,3-dihydrofuran (9)

2-Acetoxycyclopentenone (256 mg) and 3,3-dimethyl-2,3-dihydrofuran (1.305 g) were irradiated for 6 days, by which time the bulk of the enone had been consumed (glc: column B, 220°). A small quantity of colorless crystals were observed on the wall of the irradiation tube. The crystals, compound 31 (4 mg), were collected. The filtrate showed two product peaks on glc (column B, 220°; under these conditions a peak corresponding to 31 was not observed). Tlc (petrol ether, 30-60°, and ether, 1:1) showed two spots other than compound 31 and unreacted enone. The two fractions were isolated by preparative glc (column B, 220°); compound 32 (shorter retention time) as colorless crystals (122 mg), and crude compound 33 as a colorless liquid (92 mg). The latter was contaminated with a trace of 32 (by tlc), and subjected to preparative tlc (petrol ether, 60-80°, and ether, 1:1) to give compound 33.

Compound 31 was recrystallized (CH_2Cl_2/ether, 1:1), mp 224.0-225.5° (with sublimation): ir ($CHCl_3$) 1740 and 1220 cm^{-1}; mass spectrum (50 eV) m/e (rel intensity) 280 (9), 238 (12), 210 (5), 196 (23), 195 (24), 179 (23), 167 (12), 150 (100), 140 (13), 122 (71), 108 (51) and 99 (16).

Anal. Calcd for $C_{14}H_{16}O_6$: C, 67.32; H, 8.22. Found: C, 66.88; H, 8.33.

Compound 32, on recrystallization (petrol ether, 60-80°), had mp 87.5-88.0°: ir ($CHCl_3$) 1740 (broad), 1372 and 1245 (broad) cm^{-1}; pmr ($CDCl_3$) δ 4.22 (dd, 1, J=5.0 and 1.5 Hz), 3.78 (d, 1, J=8.8 Hz), 3.62 (d, 1, J=8.8 Hz), ca. 2.7 (m, 1), 2.36 (broad d, 1, J=5 Hz), 2.06 (s, 3), 1.33 (s, 3) and 0.98 (s, 3). δ 4.22 proton coupled with 2.7 and 2.36 protons with J=1.5 and 5.0 Hz, respectively (double irradiation); mass spectrum (70 eV) m/e (rel intensity) 196 (2), 195 (5), 179 (72), 178 (32), 163 (44), 150 (27), 135 (17), 98 (49), 83 (100), 55 (31) and 43 (62).

Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.44; H, 7.80.

An analytical sample of compound 33 was obtained (glc: column A, 195° and distillation ca. 95°/2 mm, successively). The colorless liquid had: ir ($CHCl_3$) 1735 (broad), 1380, 1245 and 1210 cm^{-1}; pmr ($CDCl_3$) δ 4.44

(d, 1, J=5.0 Hz), 3.72 (d, 1, J=8.5 Hz), 3.62 (d, 1, J=8.5 Hz), ca. 2.7 (m, 1), 2.09 (s, 3), 2.08 (broad t, 1, J=5 Hz), 1.10 (s, 3) and 1.03 (s, 3). δ 4.44 proton coupled with 2.08 proton (double irradiation).

Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.47; H, 7.52.

Solvent Effects on Product Ratio

The solvent effects on the photocycloadditions of 2-acetoxycyclopentenone with dihydrofurans 8 and 9 were investigated in three solvents, isooctane, ether and acetonitrile. For each solvent and olefin pair, three samples were made with different concentrations of enone and olefin ([olefin] < 0.9 M^{-1} l^{-1}), while the molar ratio of enone to olefin was kept constant (1:20). The irradiations were conducted in a merry-go-round apparatus with λ_{max} 366 nm light (<30% conversion). Controlled experiments showed product ratio was constant at least up to 30% conversion.

When the irradiation was over, the solvent was evaporated at room temperature with a nitrogen stream and a known amount of calibration compound was added; benzophenone and 2-acylnaphthalene were used as the calibration material for the reaction with 8 and 9, respectively. Product ratio as well as percentage conversion were measured on Hifi aerograph (model 600-C) equipped with hydrogen flame detector. Columns B (200°) and D (200°) were used for the reactions with 8 and 9, respectively. For each sample, three glc runs were made and the averaged ratio was calibrated and percentage conversion was determined. Product ratio in each solvent was obtained by extrapolating to zero substrate concentration, and the values, thus obtained, are listed in Table 3.

Base Catalysed Rearrangements of The Photoadducts 26, 27, 32 and 33

A typical example of the rearrangement is as follows: ca. 50 mg of a photoadduct was absorbed on basic alumina (5 g) packed in a column and left for ca. 2 hours (liquid phase: ether). Then the product was eluted with ether and methanol. Upon evaporation of the solvents, crude rearranged product was obtained.

i) Keto-alcohol 28

Crude 28 (30 mg) was obtained as a liquid from photoadduct 26 (50 mg). Upon exposure to moist air, this liquid was transformed into a crystalline hydrate 30, mp ca. 110°, which resisted solution in ether, benzene, or chloroform, but did dissolve in methanol and acetone. The keto-alcohol 28, which was soluble in any of the solvents, was regenerated from the hydrate by simply evaporating methanol from a methanol solution of the latter. It was purified by glc (column A, 195°) and subsequent bulb to bulb distillation, and obtained as a viscous liquid: ir ($CHCl_3$) 3560, 3430 (broad) and 1785 cm^{-1}: pmr ($CDCl_3$) δ 4.36 (dd, 1, J=9.5 and 4.9 Hz), 4.17 (ddd, 1, J=9.0, 7.4 and 5.8 Hz), 3.90 (dt, 1, J=9.0, 9.0 and 7.3 Hz), ca. 2.8 (broad s, 1, OH) and ca. 2.5 (m, 1). δ 4.36 proton coupled with ca. 2.5 proton with J=9.5 Hz (double irradiation); mass spectrum (50 eV) m/e (rel intensity) 168 (6), 140 (26), 122 (35), 96 (88), 95 (23), 84 (80), 83 (100), 70 (25), 69 (92), 55 (55), 43 (59), 42 (36) and 41 (49).

The hydrate 30 was recrystallized from tetrahydrofuran and petrol ether: ir (KBr) 3350 (broad) cm^{-1}; mass spectrum (70 eV) m/e (rel intensity) 168 (24), 140 (61), 122 (51), 96 (100), 95 (39), 84 (85), 83 (95), 70 (42), 69 (67), 55 (39) and 41 (38).

Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 58.32; H, 7.76.

ii) Keto-alcohol 29

Crude keto-alcohol 29 (35 mg) was obtained as a liquid from photoadduct 27 (50 mg). The keto-alcohol 29 was purified, successively, by preparative tlc (ether), glc (column A, 195°) and bulb to bulb distillation, and obtained as a colorless liquid. All attempts to make the corresponding hydrate were unsuccessful. The compound had: ir ($CHCl_3$) 3540, 3420 (broad) and 1782 cm^{-1}; pmr

($CDCl_3$) δ 4.23 (dd, 1, J=8.0 and 0.15 Hz), 3.85 (dddd, 1, J=8.7, 7.8, 3.5 and 0.2 Hz), 3.53 (dt, 1, J=8.7, 8.7 and 6.0 Hz), 2.70 (dddd, 1, J=9.3, 8.0, 6.8 and 0.2 Hz), ca. 2.7 (broad s, 1, OH) and 2.21 (broad d, 1, J=4.2 Hz). δ 4.23 proton coupled with 2.21 proton with J=1.1 Hz (double irradiation); mass spectrum (70 eV) m/e (rel intensity) 168 (5), 140 (4), 96 (14), 84 (11), 83 (14), 74 (100), 69 (12), 59 (74), 45 (59) and 43 (45).

Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.01; H, 7.26.

iii) Keto-alcohol 34

Crude keto-alcohol 34 (43 mg) was obtained from photoadduct 32 (56 mg). Upon preparative tlc (ether and petrol ether, 2:1), the keto-alcohol 34 gave pale yellow crystals (37 mg), which was recrystallized from ether and petrol ether, yielding colorless crystals, mp 76.5-77.0°: ir ($CHCl_3$) 3560 and 1777 cm^{-1}; pmr ($CDCl_3$) δ 4.46 (d, 1, J=8.0 Hz, Δ1/2=2.5 Hz), 3.42 (d, 1, J=8.5 Hz), 3.28 (d, 1, J=8.5 Hz), 2.69 (s, 1, OH), 2.29 (d, 1, J=8.0 Hz, Δ1/2=2.0Hz), 2.21 (m, 1) and 1.15 (s, 6); mass spectrum (50 eV) m/e (rel intensity) 196 (19), 153 (10), 138 (12), 123 (11), 112 (16), 98 (44), 97 (60), 96 (100), 95 (49), 83 (86) and 70 (16).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22 Found: C, 67.49; H, 8.15.

iv) Keto-alcohol 35

Pale yellow crystals of keto-alcohol 35 were obtained from photoadduct 33. The crude products were recrystallized twice from a mixture of ether and cyclohexane, yielding colorless crystals (44 mg), mp 91.5-92.0°: ir ($CHCl_3$) 3560 and 1780 cm^{-1}; pmr ($CDCl_3$) δ 4.27 (d, 1, J=7.3 Hz, $\Delta 1/2$=1.2 Hz), 3.48 (d, 1, J=9.0 Hz), 3.32 (d, 1, J=9.0 Hz), ca. 3.0 (broad s, 1, OH), 2.29 (d, 1, J=7.3 Hz, $\Delta 1/2$=2.0 Hz), 2.06 (broad s, 1), 1.13 (s, 3) and 1.03 (s, 3); mass spectrum (50 eV) m/e (rel intensity) 196 (29), 153 (10), 141 (34), 99 (30), 98 (95), 96 (73), 95 (31), 83 (100), 81 (44) and 70 (35).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 66.88; H, 8.33.

Eu(fod)$_3$ Effects

The effect of the europium shift reagent was investigated on adducts 32 and 33, and keto-alcohols 27, 34 and 35. All measurements were made in $CDCl_3$ at 30°, using Varian HA-100 instrument. Each sample consisted of substrate (ca. 20 mg) in $CDCl_3$ (ca. 0.25 ml), and at least three measurements were taken at three different concentrations of the reagent (typically, 4, 10 and 18 mg). In all cases, linear relationship between Δppm of protons and concentration of Eu(fod)$_3$ was observed.

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PART TWO

ATTEMPTED SYNTHESES OF BIRADICAL PRECURSORS IN ENONE PHOTOCYCLOADDITION

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INTRODUCTION

THE GEOMETRY AND ELECTRONIC NATURE OF ENONE TRIPLETS

It appears well-established that the reactive species in the photocycloaddition of cyclic enones and simple substituted enones are triplets having energies in the 70-kcal/mole region (1, 2, 3) (≠). The two lowest spectroscopic states in the enone triplet manifold are the nπ* and ππ*. Recent calculations (6, 7, 8) have shown the variation in energy of these states with molecular distortion. It has been shown that the vertically generated planar nπ* and ππ* triplet states (Frank-Condon states) undergo different relaxation processes.. The nπ* state relaxes primarily by bond-stretching, remaining planar, while the ππ* state relaxes largely by rotation around the C_2-C_3 bond and out-of-plane deformation of H-C_2 bond

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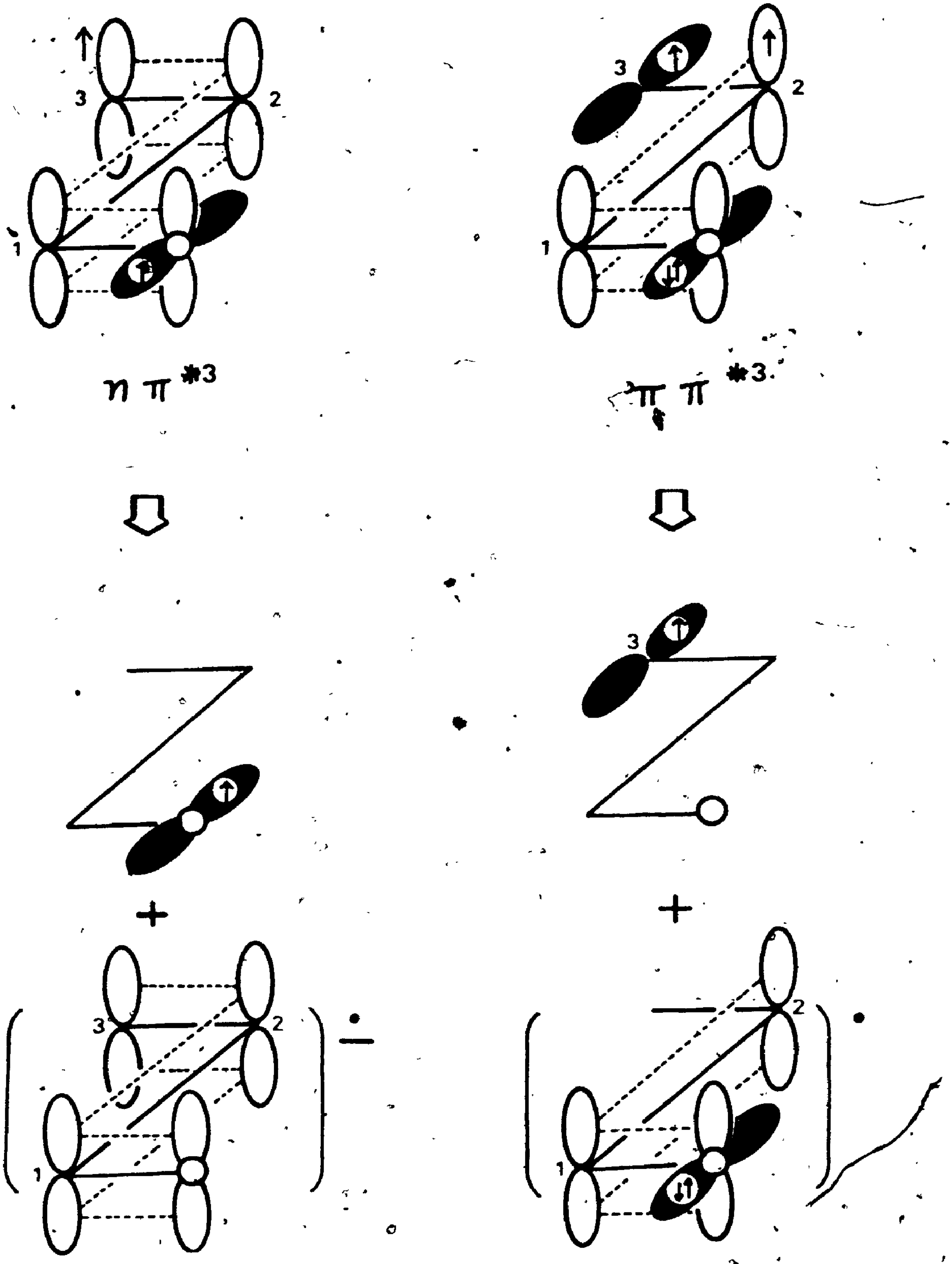
≠However, certain cyclic enones conjugated with a further double bond (4) or with a phenyl group (5) are reported to undergo the photocycloadditions via a singlet excited state.

in addition to bond stretching. Since this geometrical change provides a large amount of stabilization energy, the $\pi\pi^*$ state, although energetically higher than the $n\pi^*$ state in a planar geometry, becomes the lowest triplet upon full relaxation. Then, by a process resembling the decay of olefin triplets, a rapid crossing to the ground state hypersurface may occur. The triplet may then provide a rapid decay route to the ground state. Consequently, simple alicyclic enones and large-membered cyclic enones ($\geq$ 7) which are flexible enough to undergo the rotation around C_2-C_3 bond have the $\pi\pi^*$ triplet state below the $n\pi^*$ triplet state. If the ring size is small enough to restrict complete relaxation by rotation yet still permit the crossing of the $n\pi^*$ and $\pi\pi^*$ surfaces the excited species may have a long enough life time to undergo processes such as cycloaddition. Such appears to be the case for cyclopentenones and cyclohexenones. Although the extent of the distortion in these cyclic enones is not known, it is very likely that the $n\pi^*$ and $\pi\pi^*$ states are energetically very close to each other. This is supported by the recent emission studies on geometrically rigid cyclopentenones (9).

An understanding of the difference in the reactivity of these triplet excited states is, as we shall discuss shortly, important in terms of the orientation and stereochemistry in photocycloaddition. A rough estimation of their reactivity on the basis of recent calculations (7, 8) seems possible

N. C. Baird showed, in his calculations (7), that spin distribution in the relaxed nπ* triplet state was rather similar to that of an anion radical of an α, β-unsaturated ketone (10). Therefore, the nπ* triplet state may be considered as consisting of two independent reactive species: an oxygen radical (in-plane) and an anion radical of an α, β-unsaturated ketone (out-of-plane) (Figure 1). Consequently, this state may show two completely different reactivities corresponding to these hypothetical species. The oxygen radical type behaviour of the triplet requires an in-plane approach of a reacting partner to the oxygen. An example is the reported oxetane formation between 4,4-dimethylcyclohexenone and tetramethylethylene (11). The reactions of the anion radical of an α, β-unsaturated ketone with olefinic compounds are not well-understood at the present time. Since the spin density is known to be highest at C_3 of the anion radical (10), it seems likely that C_3 of the excited enone is the reactive center toward olefins, provided that this type of anion radical does indeed undergo typical radical reactions, e.g., in particular, addition to olefinic bonds. Furthermore, according to his calculations, C_3 of the triplet enone bears a negative net charge, a fact which is in agreement with Devaquet's calculations (8). Considering

FIGURE 1



these facts, it seems likely that, if the nπ* state participates in enone cycloadditions, the reactive site should be C_3. This center may well behave like a nucleophilic radical. The reactions must under these conditions take place in an out-of-plane manner.

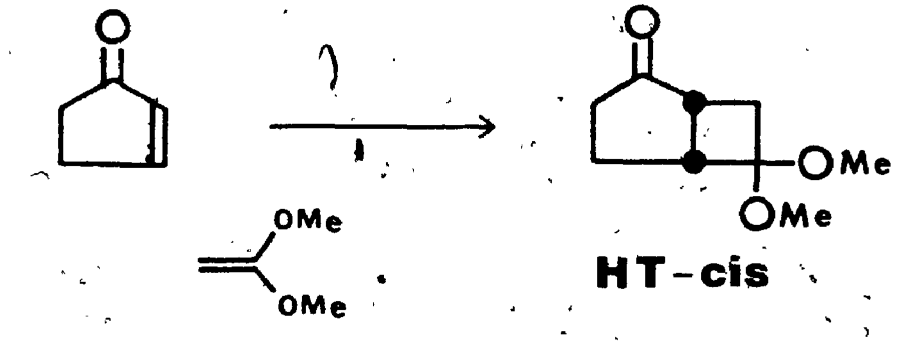
Similarly, the fully relaxed ππ* state can be considered as consisting of two reactive species: a carbon radical at C_3 and an oxa-allyl radical with the highest spin density at C_2. According to Baird's calculations (7), these two reactive centers have very similar energies (≠), but they differ in electron densities: C_2 is clearly electron-deficient, while C_3 is electronically neutral, a fact which is basically in agreement with Devaquet's results (8). Therefore, if an enone ππ* state participates in cycloaddition, both C_2 and C_3 could be imagined as being the relevant reactive species with C_2 being more electrophilic. The olefin-attack on C_2 is in an out-of-plane mode, while the attack to C_3 may vary from near in-plane to near out-of-plane depending upon the degree of rotation around C_2-C_3 bond.

THE STEREOCHEMISTRY OF PRODUCTS

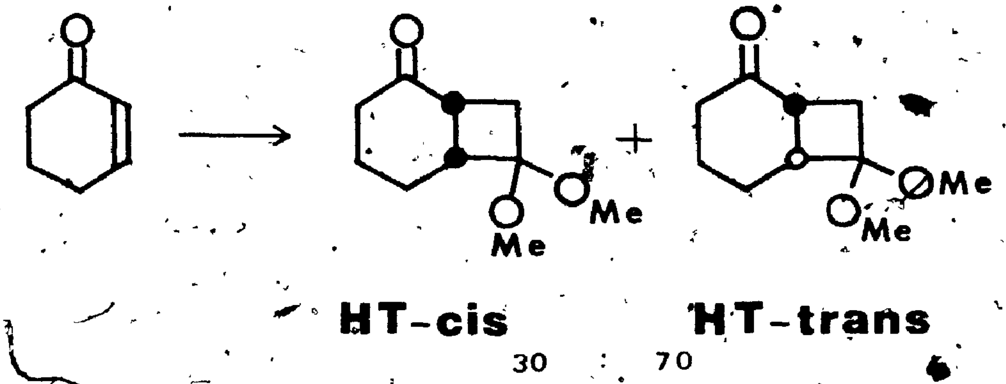
It seems that both cyclopentenones and cyclohexenones

≠According to the calculations (7), the fully twisted ππ* triplet state of acrolein has two nearly degenerated HOMO's; the NBMO of the "C_3-radical" is slightly above the HOMO of the "oxa-allyl radical".

react rather similarly in terms of regiospecificity as shown in reactions 1 and 2 (12).

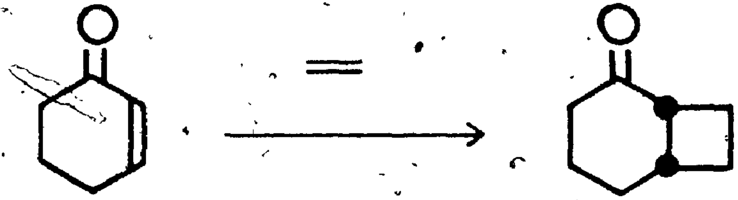


(1)

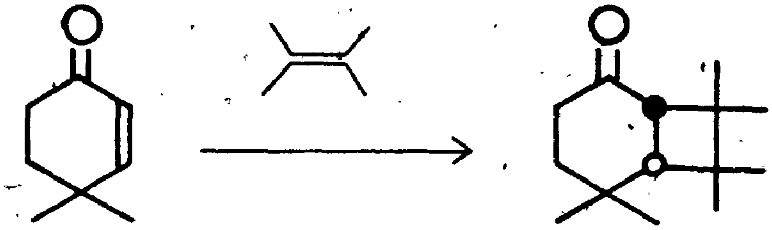


(2)

However, there is frequently a distinct difference in the stereochemistry of the products; that is, the stereochemistry of their ring junctions: cyclopentenones are known to yield only cis-fused products, while cyclohexenones are known to yield cis- as well as trans-fused products (12, 13, 14). The extent of formation of the trans-product varies, depending on the nature of the reacting pairs, from nil (reaction 3) (15) to 100% (reaction 4) (11).



(3)



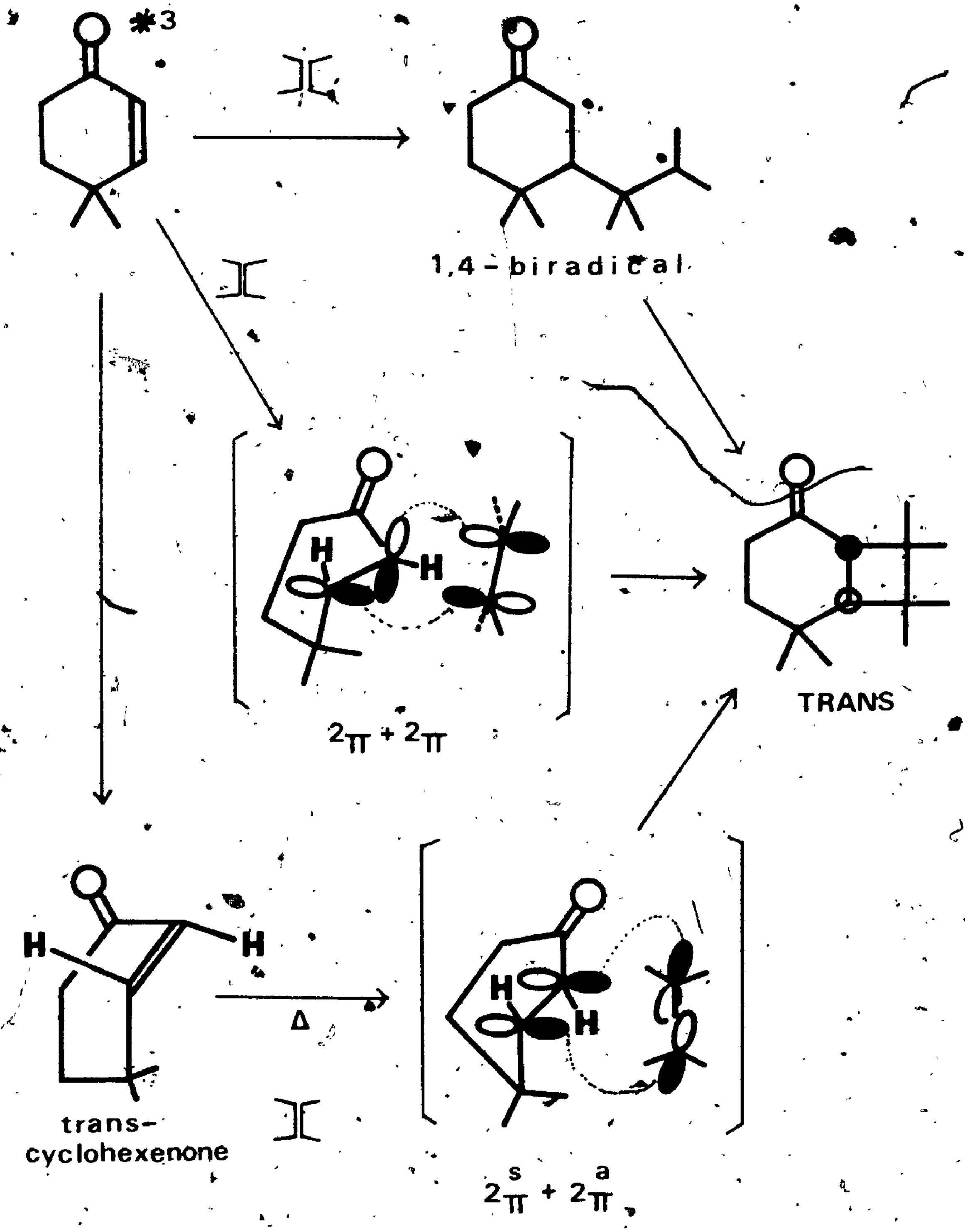
(4)

It is well known that these trans-products readily epimerize to the corresponding cis-products under mildly basic conditions (e.g., alumina) or under usual glc conditions. This is simply a consequence of the additional strain introduced by the trans ring juncture (12, 16).

Several mechanistic possibilities to rationalize the formation of these strained species have been discussed in the literature. These are: stepwise reactions via triplet 1,4-biradicals (14, 17, 18); concerted photochemical [2π+2π] reactions between distorted enone triplets and olefins (8, 19); and concerted thermal [2π+2π] reactions between trans-cyclohexenones and olefins (14, 16). These possibilities are shown in Illustration 1, taking reaction 4 as an example.

Although the concerted reactions are interesting

ILLUSTRATION 1



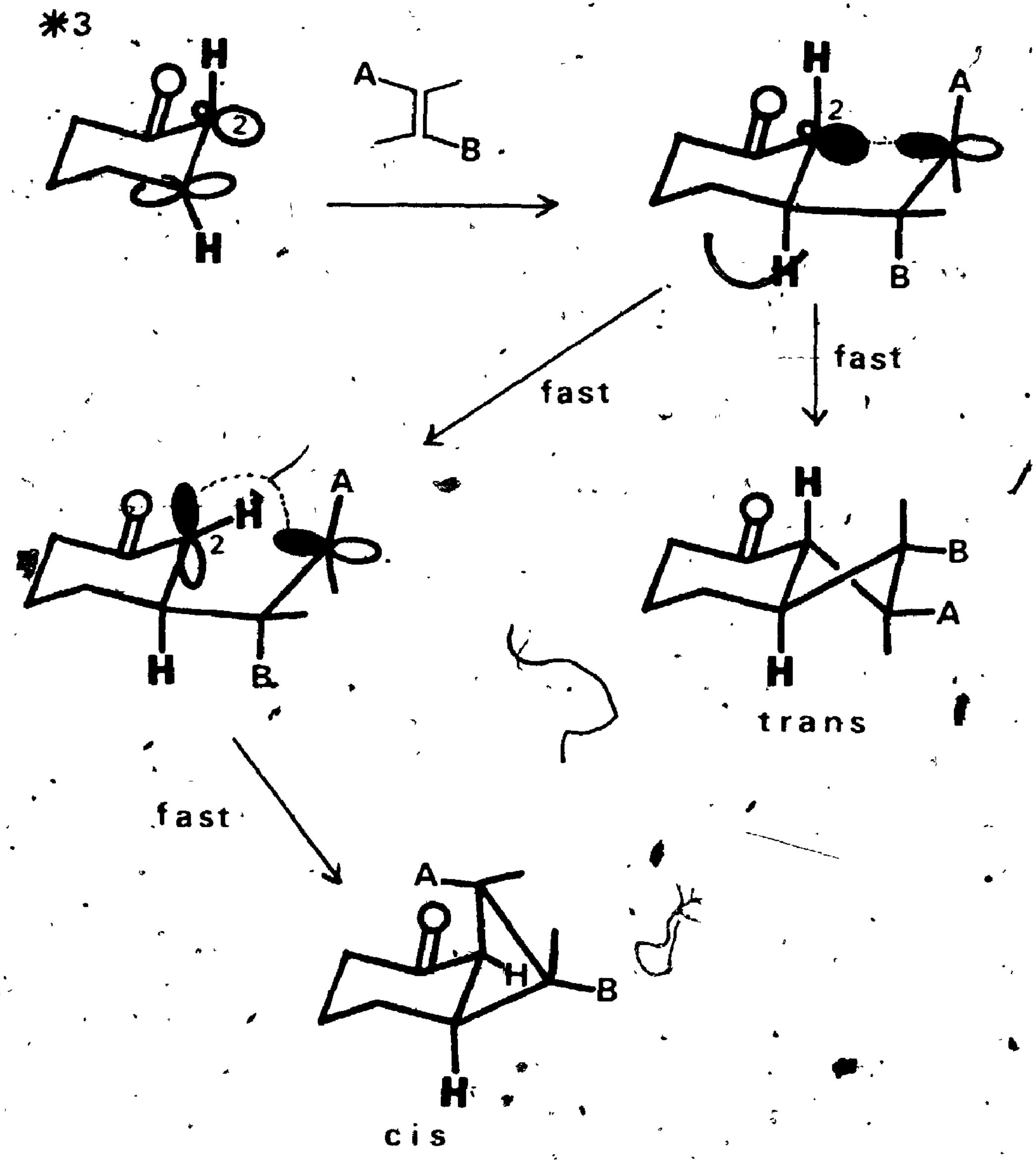
possibilities (≠), it seems reasonable to assume, on the basis of the presently known facts (12, 14, 21, 22, 23) that triplet 1,4-biradicals are intermediates in enone cycloadditions. Therefore, any satisfactory explanation for the formation of the trans-products should be based on the view that these 1,4-biradicals or some closely related species are the immediate precursors.

Assuming the intermediacy of triplet 1,4-biradicals, there are two different approaches to the problem (14). One approach (14, 17) assumes a very short life time for the triplet biradicals so that they could lead to trans-product formation before relaxation at C_2. Rapid closure after relaxation at C_2 would give cis-products (see Illustration 2). Alternatively, the other approach proposed by Bauslaugh assumes a relatively long life time for the biradicals so that conformational equilibrium can be established. Then, certain conformers would preferentially lead to trans-products, while others would give cis-products (see Illustration 3). The result would depend on the populations of the corresponding conformers and the magnitude of the steric interactions encountered during these ring closures (18).

The former analysis requires preferential retention

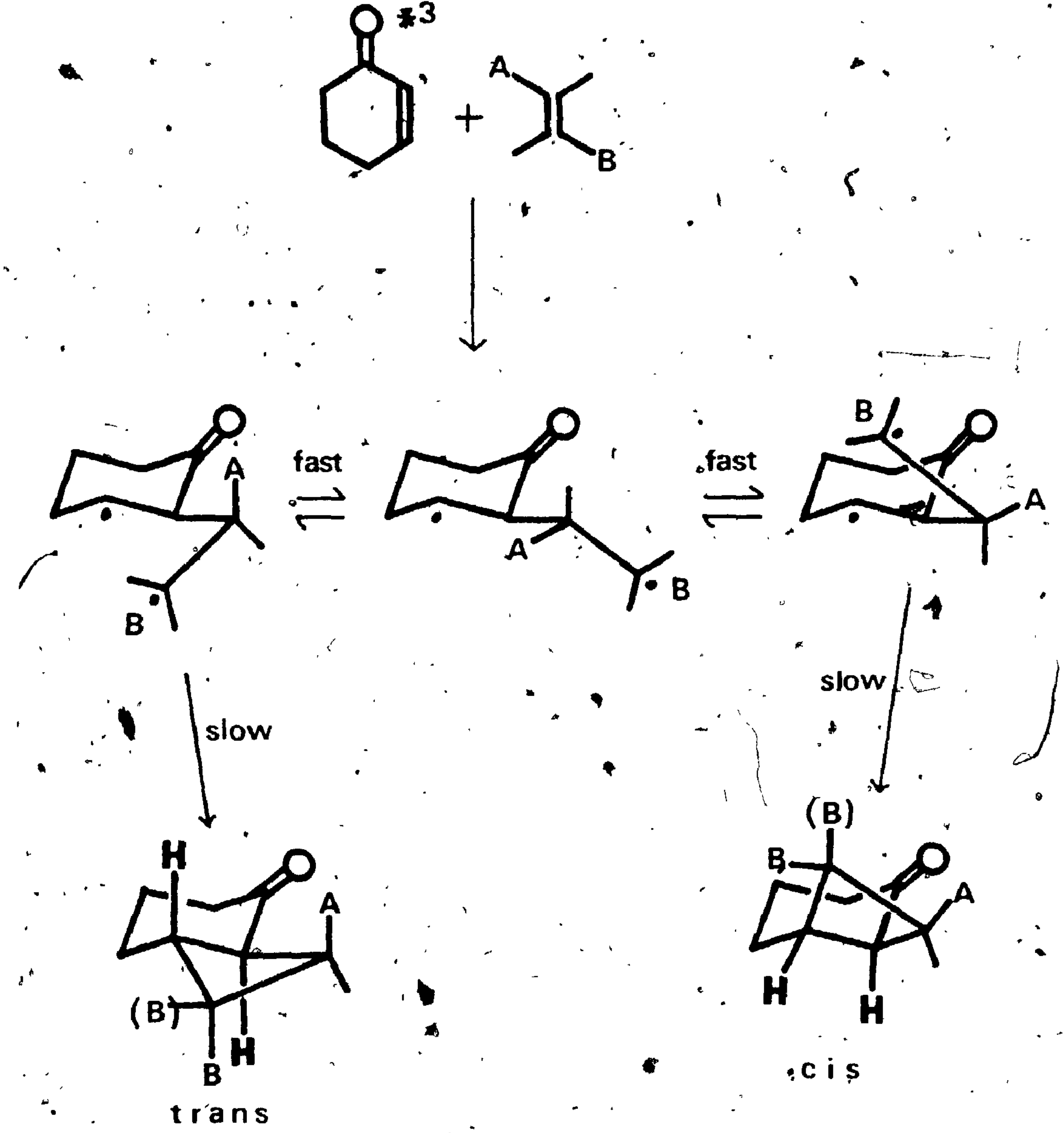
≠The thermal [2π+2π] reaction is least likely in view of the known behavior of strained trans-cycloalkenes (20). Since the latter react in an antarafacial manner, the adducts should be cis-fused.

ILLUSTRATION 2



of olefin stereochemistry in the products (14) since the ring closure is assumed to be very rapid at least as rapid as a small geometric relaxation (at C_2). However, studies on the detailed stereochemistry of the products, such as in the cycloadditions between cyclohexenone and cis- and trans-2-butene (12), and between cyclopentenone

ILLUSTRATION 3



and cis-and trans-1,2-dichloroethylene (22, 23), do not agree with this expectation. Furthermore, although rapid ring closures which would lead to more trans-products would be expected for small olefins with little steric hindrance rather than bulky olefins (≠), the limited observed results (reactions 3 and 4, also see reactions 2 and 9) are not in agreement with expectation. Furthermore, according to this approach, the C_2-radical orbital must be in an equatorial position in the deformed ππ* triplet enone (see Illustration 2). This is highly unlikely because in this orientation the pyramidal C_2-orbital can not effectively conjugate with the adjacent C_1-(ketone)-orbital. It seems possible, therefore, that this approach is not the most appropriate to rationalize the problem of trans-product formation.

On the other hand, Bauslaugh's analysis is in agreement with the mixed stereochemical results concerning olefin stereochemistry in products (18). However, examination of models reveals that his conformational analyses and consequent arguments concerning why trans-products should be formed from certain conformers, are not, as pointed out by de Mayo (14), as persuasive as would be desired. Furthermore, it is not clear why biradicals of a certain configuration, such as 1 (Figure 2) produced in the reaction between 4,4-dimethylcyclohexenone and tetramethylethylene (reaction 4), should be

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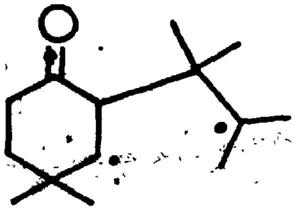
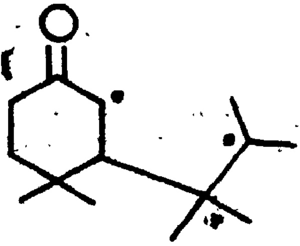
≠The steric effect on ring-closure of triplet 1,4-biradicals is presently unknown. The only available data relevant to the steric effect is, however, the reported steric effects on the rate constant of free radical coupling reactions. The rate constants for methyl, n-propyl, cyclohexyl and t-butyl radicals are 8.9, 3.4, 2.7 and 2.1 x 10^9, respectively (24).

FIGURE 2



1

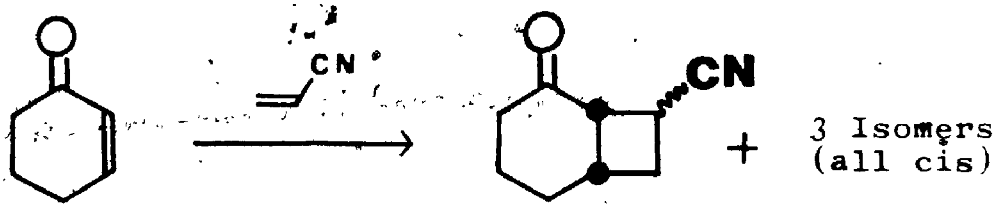


2

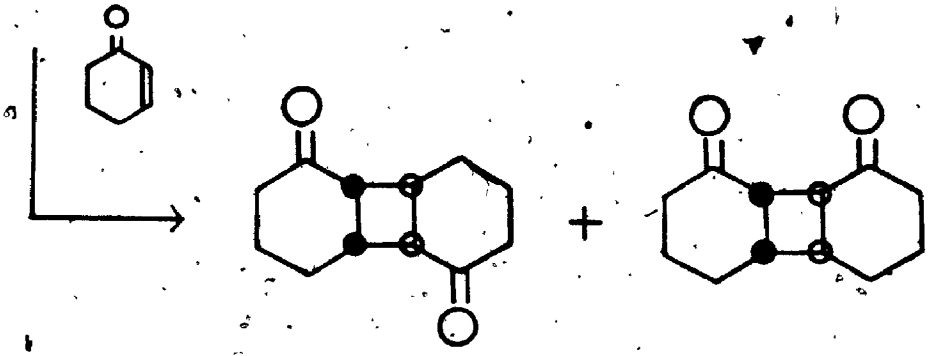
formed preferentially over alternatives, such as 2 (18). This suggests that, although his basic direction of approach to the problem might be reasonable, additional and more detailed considerations are apparently needed. For this purpose, the available literature was reviewed.

Eaton first stated that olefins conjugated with electron-withdrawing groups did not appear to yield trans-fused products (13). This observation was based on the fact that cyclohexenone, when reacting with electron-poor olefins (acrylonitrile (12) or cyclohexenone itself (3, 25)), did not give any trans-product (reaction 5 and 6). However, this apparent generality as since pointed out (14), does not hold in certain steroidal enone systems; equation 7 (26) and 8 (27).

Another possible generalization which might be made is that trans-products are only formed with HT-

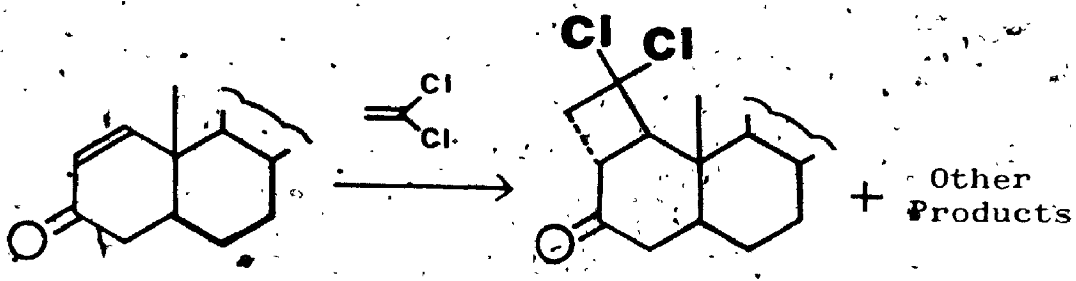


(5)

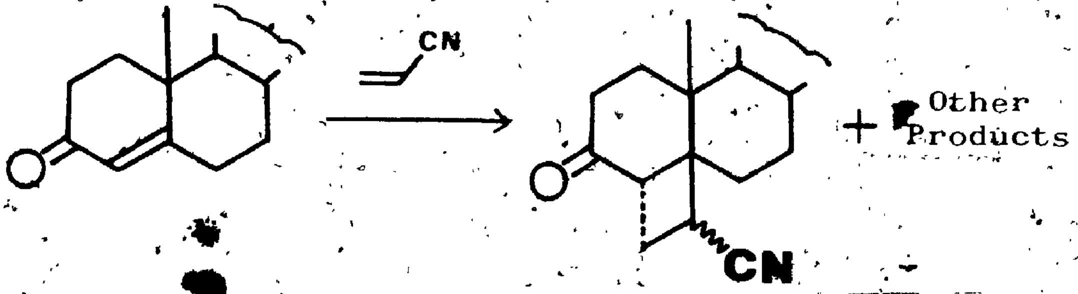


(6)

n-hexane	85	:	15
methanol	40	:	60



(7)



(8)

orientation regardless of the nature of the olefins used. (This statement will become the basis of the present analysis and be substantiated later). If correct, this generality implies that triplet 1,4-biradicals (HT-biradicals), leading to HT-oriented products, must have some special characteristic which opens the possibility of giving trans-products, while triplet 1,4-biradicals (HH-biradicals), leading to HH-oriented products lack this feature (see Figure 3 for the specific biradicals). Since the orientation of the adduct is determined by the first bond formed between enone and olefin, it is important to learn about this first bond formation step.

FIGURE 3

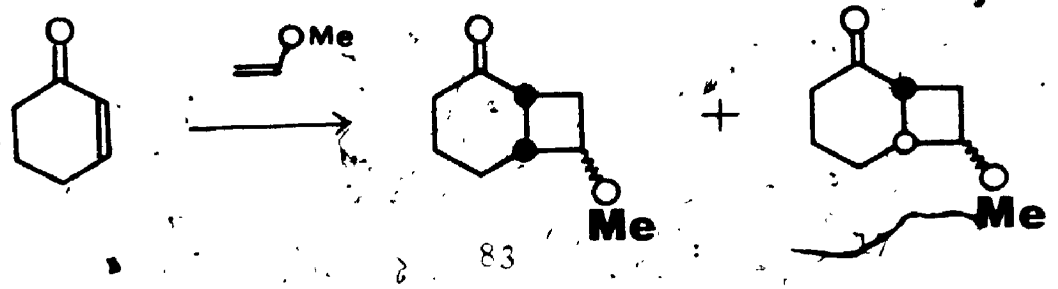
HT - biradical **HH** - biradical

THE FIRST BOND-FORMATION STEP AND THE FORMATION OF TRANS-FUSED PRODUCTS

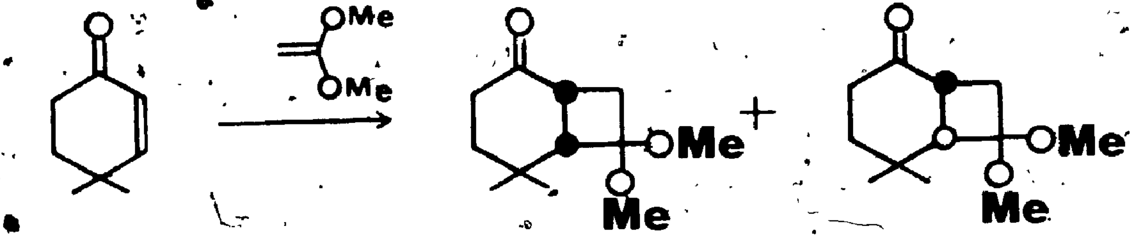
The triplet biradicals may be formed either directly from triplet enones, ~~or~~ indirectly via triplet exciplexes. This has been discussed by Corey (12), de Mayo (14), McCullough (17) and Cantrell (16). In either case, it seems reasonable to assume that the electronic nature of triplet enones ($n\pi^*$ and $\pi\pi^*$) is important in deciding the first bond formation. The triplet enones are known to react with olefinic bonds at both C_2 and C_3 (12, 23, 28). However, the reactivity of these sites are expected to be quite different, as discussed previously: that is, there is electrophilic radical character at C_2 ($\pi\pi^*$), and neutral ($\pi\pi^*$) as well as nucleophilic ($n\pi^*$) radical character at C_3.

Since the reactivity of these triplet states toward olefins seems to vary (as I shall discuss shortly), depending on electronic nature of olefins, it is convenient to classify unsymmetrical olefins commonly used in enone cycloadditions into three types: olefins bearing electron-releasing polar substituents (<u>electron-rich polarized olefins</u> such as methoxyethylene and 1,1-dimethoxyethylene); olefins bearing alkyl groups (<u>non-polarized olefins</u> such as isobutylene); olefins conjugated with electron-withdrawing polar substituents (<u>electron-poor polarized olefins</u> such as acrylonitrile and cyclohexenone). When an electron-rich polarized olefin approaches the enone triplet under the control of dipole-dipole interactions (3, 14, 29) in a HT-manner, the initial bond formation should most likely take place between C_2 and the unsubstituted end of the olefin. This is mainly due to two factors: the electronic effect and dipole-dipole interactions. The latter arranges the approaching molecules in HT-oriented manner so that C_2 and the unsubstituted end of the olefin are in close vicinity. The former suggests, as in Corey's oriented complexes (12), that the partially positive C_2 ($\pi\pi^*$ state) interacts strongly with the partially negative end of the olefin (7, 8). Furthermore, the olefin has the highest free valence at that position, making that position the most reactive toward radical species. This bond formation at C_2 of enone leads to a HT-oriented biradical (Figure 3). In fact, when this type of olefin is used, only HT-products are obtained (reactions 2, 9-13) (12, 16, 30, 31). The probability of producing trans-fused products from HT-biradicals is dependent on the enone and olefin used. With cyclohexenone, the bulkier olefin (dimethoxyethylene) tends to give the higher yield of trans-product than the sterically smaller olefin (methoxyethelene). This tendency is held even using non-polarized olefins (including symmetrical olefins): see reactions 3, 4 and 15. The methyl substituents on C_5 do not appear to affect the yield of trans-product (compare reaction 11 with 12). The effect of substituents on C_4 is not known since the yield of the trans-product in reaction 10 was not reported (30).

When less polarized olefins (non-polarized olefins)


OMe
OMe
OMe
83 :

(9)


OMe
OMe
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Me
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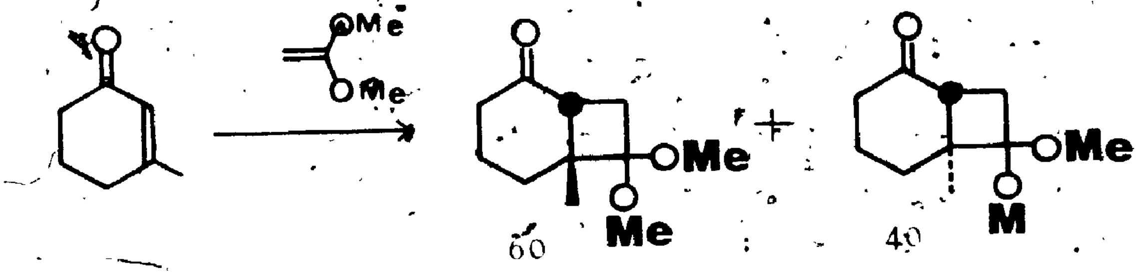
Me

(10)


OMe
OMe
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Me
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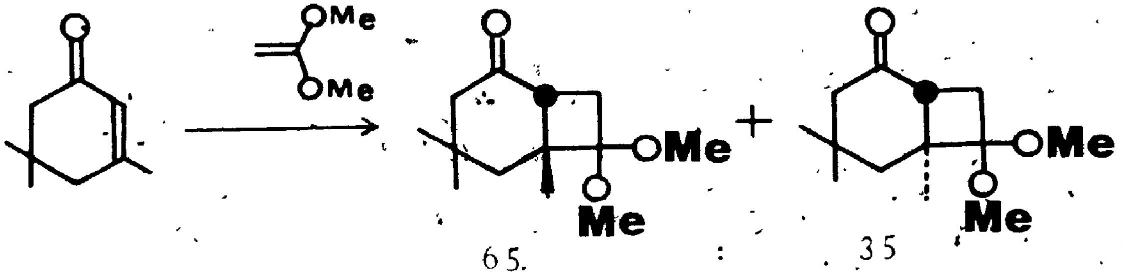
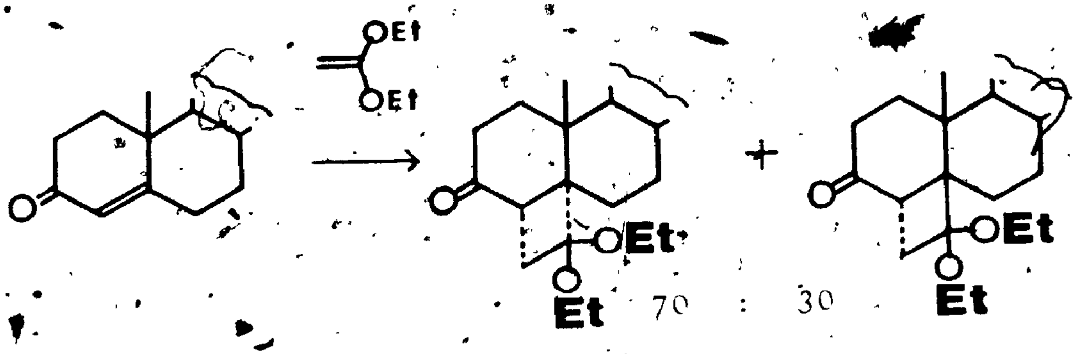
M
60 : 40

(11)


OMe
OMe
OMe
Me
OMe
Me
65. : 35

(12)


OEt
OEt
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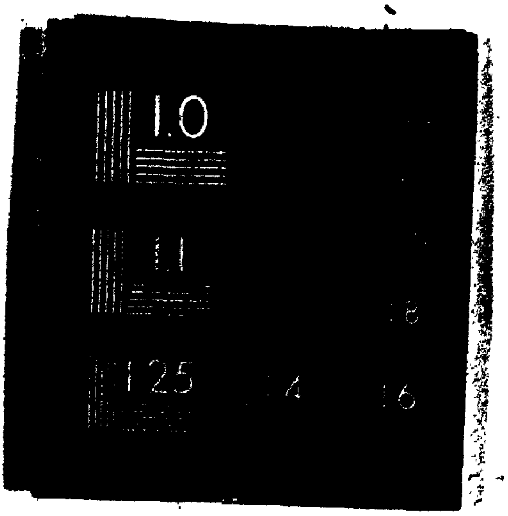
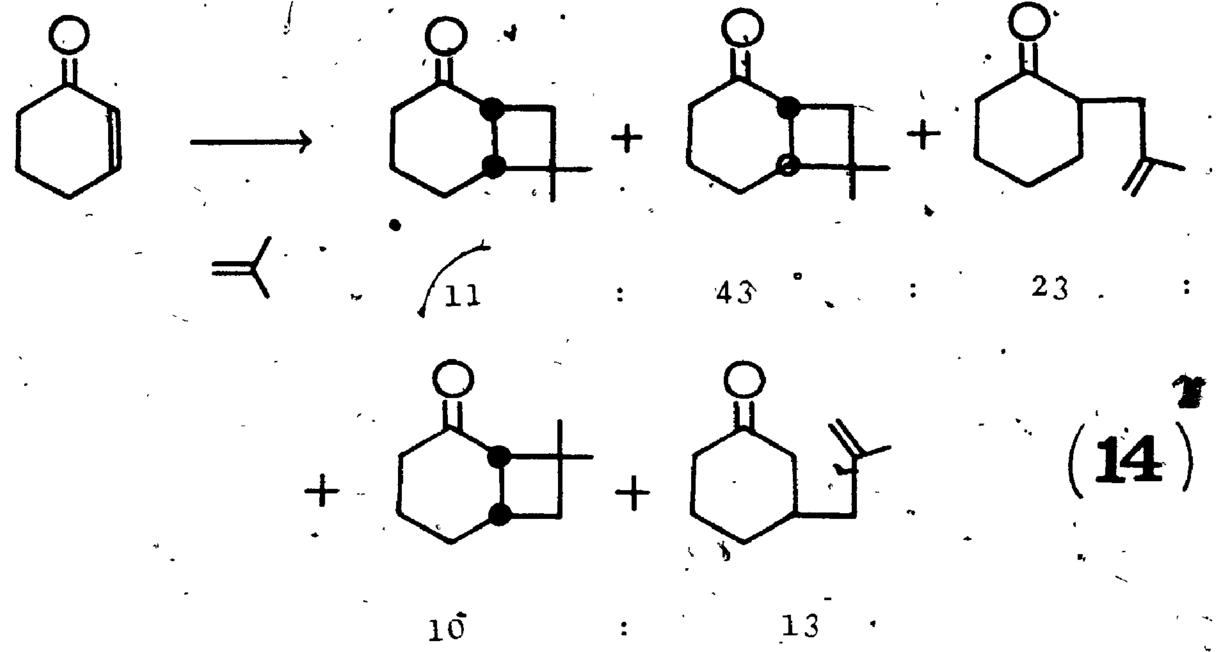
OEt
Et
70 : 30

(13)

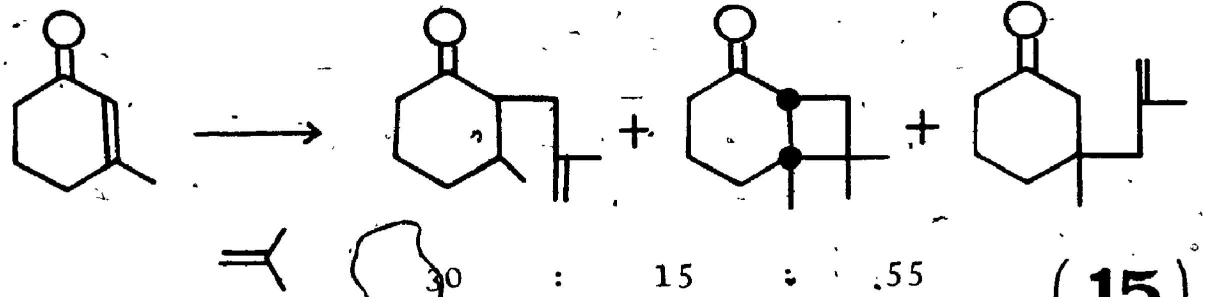
2 OF/DE 3



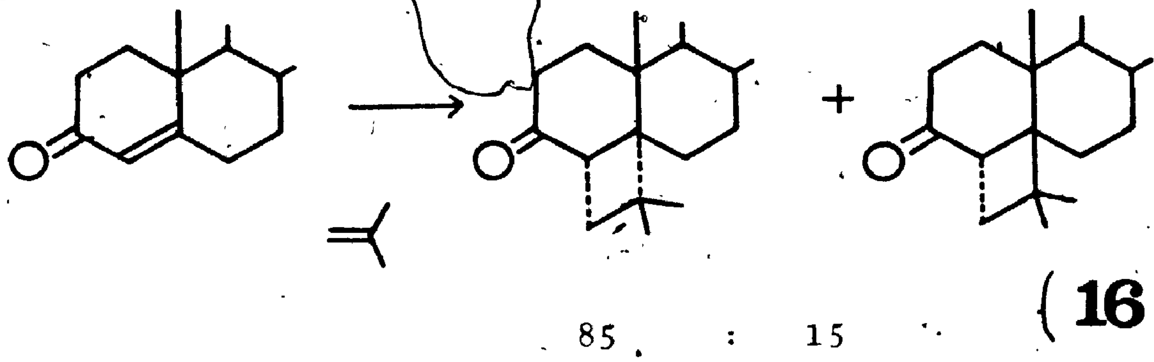
are used, the orientational preference becomes less obvious, primarily because of the reduced dipole-dipole interaction between triplet enones and the non-polar olefins. Which type of biradicals are formed predominantly is, therefore, mainly dependent on the electronic nature of both the enone triplet and the olefin. If C_2 of the enone reacts with the unsubstituted end of the double bond, a HT-biradical is produced, while if C_3 reacts at the same position of the olefin, a HH-biradical is produced (Figure 3). Experimentally, both types of products are observed in reactions between simple cyclohexenones and isobutylene (including the olefinic products shown in reaction 14 and 15) (12, 16). The ratios (HT/HH) are 77:23 for cyclohexenone and 45:55 for 3-methylcyclohexenone. However, the reaction between the steroidal 4-en-3-one system and isobutylene gave only HT-products (reaction 16) (31). The apparent relative reactivity of the steroidal C_4 position, as compared with C_2 of 3-methylcyclohexenone, might be attributed to steric factors. The planar $n\pi^*$ triplet state probably has rings A and B in half-chair and chair conformations, respectively (Figure 4). In this conformation, the α-side of C_4 is least hindered (see arrow in Figure 4). The $\pi\pi^*$ triplet state, on the other hand, is likely to be twisted about the C_4-C_5 bond, in order to minimize the repulsive overlap between the C_4 and C_5 orbitals and maximize the overlap between



(14)

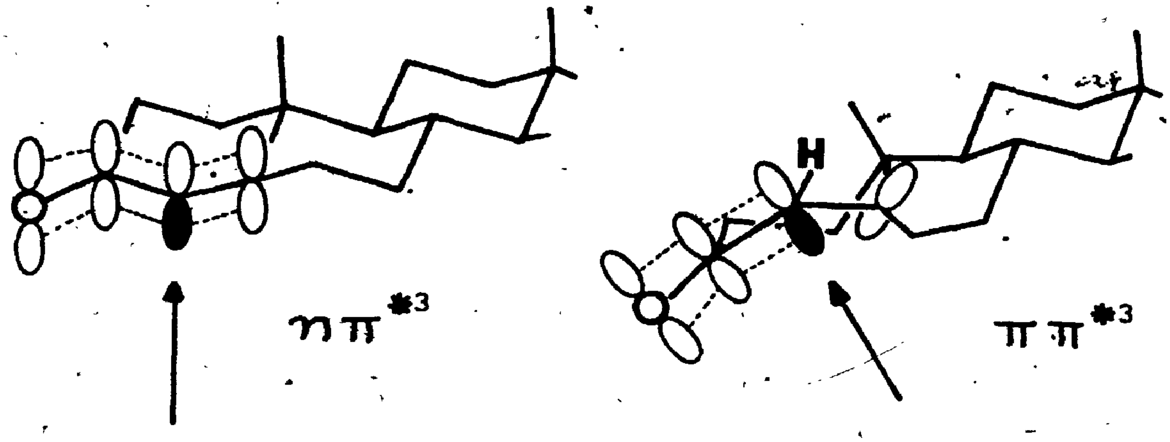


(15)



(16)

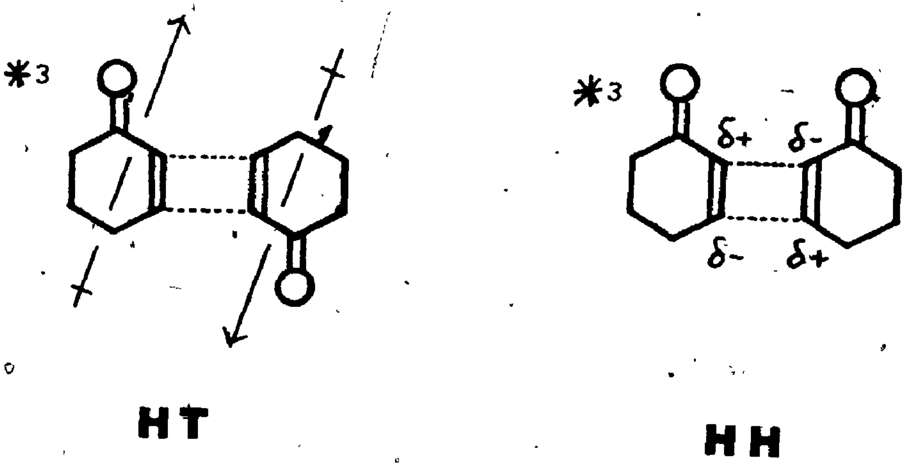
FIGURE 4.



the C_4 and C_3 (ketone) orbitals (7, 8). To achieve this geometry, the C_5 orbital must occupy a quasi-equatorial position with respect to ring A. Therefore, the most likely conformation of the $\pi\pi^*$ triplet state has rings A and B in half-chair and quasi-boat forms, respectively (Figure 4). In this conformation, the α-side of C_4 is again least hindered. This steric approach control can explain the apparent high relative reactivity at C_4 (leading to more HT-biradicals than in cyclohexenones), as well as the observed stereochemistry of the products in reaction 16 (31). It is clearly shown in reaction 14 (12) that although both HH- and HT-products are formed from cyclohexenone and isobutylene, a trans-product is formed only with HT-orientation.

When electron-poor polarized olefins are used in enone cycloadditions, the situation is not as clear as that in the other cases. This is because the dipole-dipole interaction effect is acting against the electronic effect: the former arranges the molecules in HT-manner, while the latter favors HH-orientation as shown in Figure 5 in the case of cyclohexenone dimerization (reaction 6) (3). The dipole-dipole interaction between solutes is known to be dependent on the polarity of the solvent used, becoming less important in more polar solvents (32). Thus, in an extremely polar solvent, the electronic effect may play a more significant role in determining the orientation of products than the dipole-dipole interaction effect, and consequently the HH-product may predominate. On the other hand, in non-polar solvents, the dipole-dipole effect appears to be more important, leading to HT-product formation (for an example, see reaction 6).

FIGURE 5



Regardless of the orientation of products, the addition of the triplet enone to an electron-deficient olefin (e.g., cyclohexenone itself) may have taken place at C_3 of the enone. This is because this position has either a neutral ($\pi\pi^*$ state) or nucleophilic ($n\pi^*$ state) radical character. The enone C_2 position, on the other hand, is electrophilic.

Experimentally it would appear that the HT-biradicals, which are formed by the addition of C_3 of the triplet enone, do not give trans-fused products: the trans-products have not been isolated in the HT-dimerization of cyclohexenone (3, 25) and isophorone (33). On the other hand, when the HT-biradicals are, for steric reasons, derived from the reaction of C_2 ($\pi\pi^*$ state) of the enone (e.g., in the steroidal 4-en-3-one system), these biradicals seem to behave normally and give trans-fused products (reaction 8) (27).

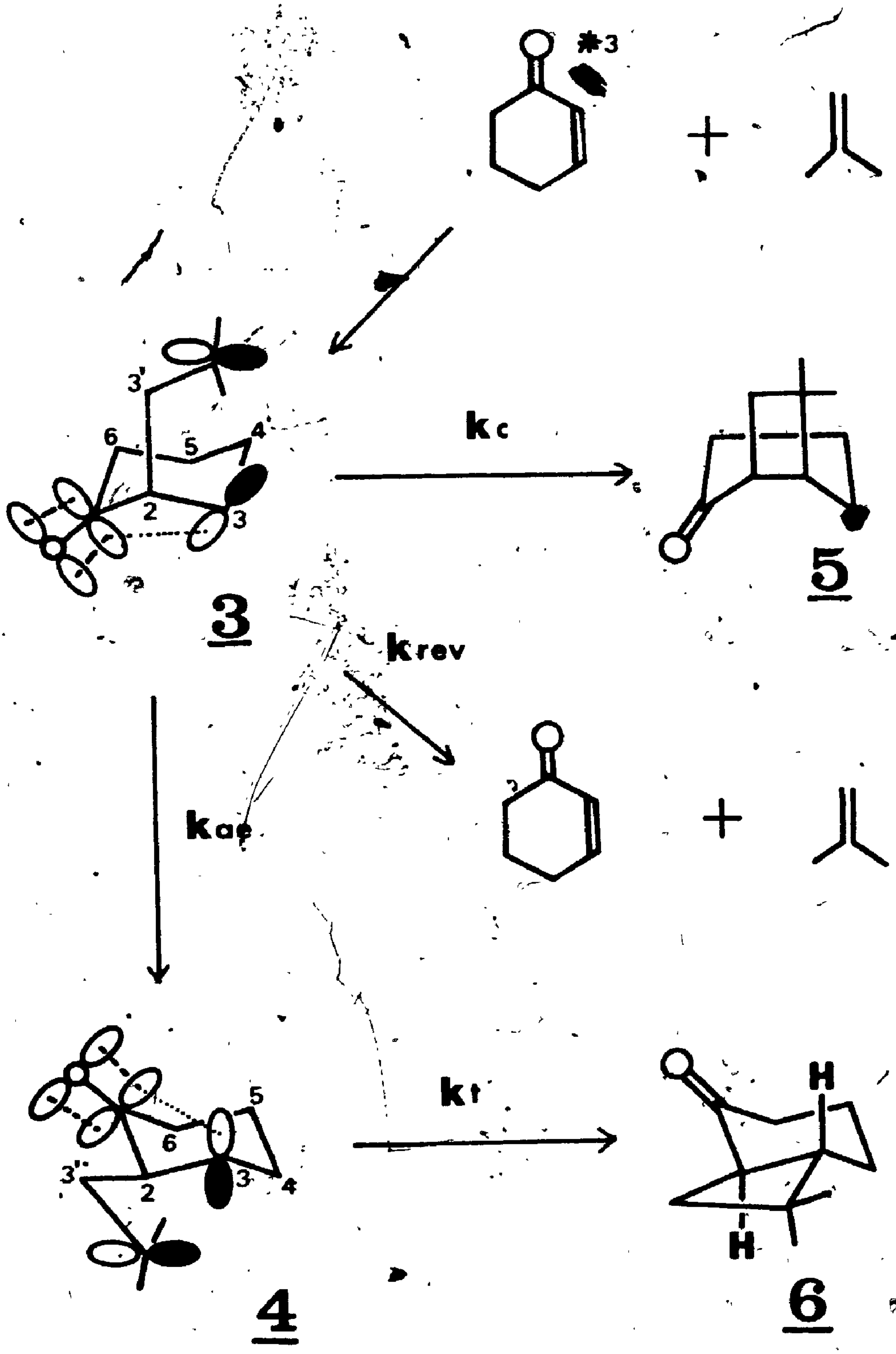
Thus, the HT-biradicals, which are produced by addition of C_2 of triplet enones ($\pi\pi^*$ state) to olefins, seem to be capable of giving trans-fused products. However, the extent of trans-formation from these HT-biradicals varies considerably in the case of simple cyclohexenones, though much less so in the steroidal 4-en-3-one system. The former effect may be due to the bulkiness of the olefins used. The question then remains: why should trans-products be formed only from HT-biradicals?

What factors control the probability of trans-product formation from HT-biradicals? To answer these questions, let us examine probable reaction pathways open for the two types of biradicals; for example, those formed between cyclohexenone and isobutylene.

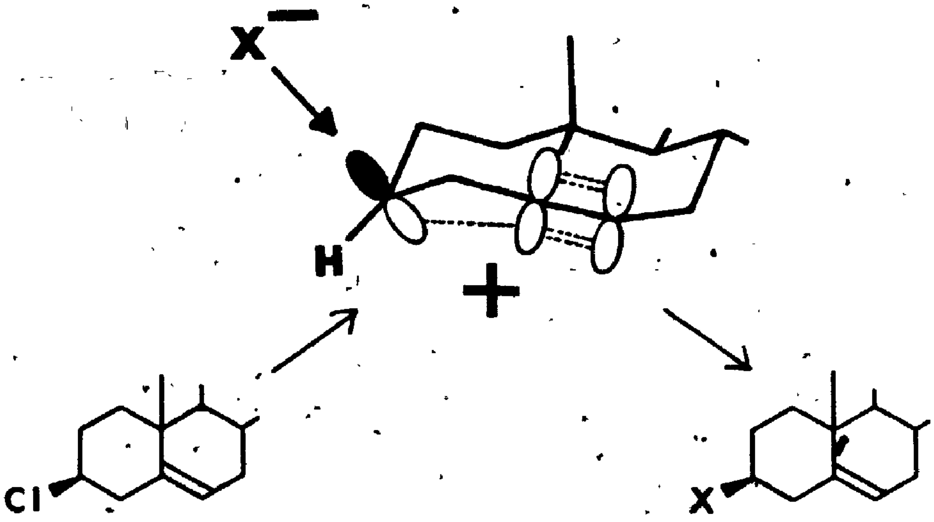
WHY SHOULD TRANS-FUSED PRODUCTS BE FORMED?

The bond formation of C_2 ($\pi\pi^*$ triplet enone) giving the HT-biradical is probably stereo-electronically controlled and leads to an axially substituted triplet cyclohexanone biradical (3) as the initial product. This subsequently follows one of the three possible pathways: cis-cyclization (k_c) to cis-fused product (5); conformational relaxation (k_{ae}) to the isomeric biradical with an equatorial substituent (4); or cleavage (k_{rev}) to cyclohexenone and isobuylene. These possibilities are illustrated in Scheme 1. Cleavage, the reversal of the addition process if the biradical is still a triplet, or the generation of the ground state components if a singlet, is possible in 3, because the radical orbitals and the C_2-C_3' bond (see scheme) are in the same plane (34). On the other hand, cleavage is retarded in the equatorial conformer (4) because the C_2-C_3' bond is orthogonal to the orbital at C_3. Once 4 is formed, the most probable reaction path open for this biradical is thus ring-

SCHEME 1



closure (≠). The cyclization may, in contrast to that of 3, lead to a trans-fused product (6), if one assumes the presence of 1,3-carbonyl-radical interaction (shown in Scheme 1) (≠≠). If such is important, the reaction should take place from the side opposite to this 1,3-interaction. The equivalent is well-known in cation chemistry. For example, the solvolysis of the steroidal 3β-chloro-5-ene system gives a product with retention of stereochemistry at C_3 (reaction 17) (36). This specificity



(17)

(≠) The reversion of 4 to 3 may also be possible. However, this process is not considered here because it should have a relatively high activation energy compared with that of ring closure (kt).

(≠≠) This type of homoallylic carbonyl-radical interaction of 1,4-biradicals is presently unknown in the literature. However, the well-known facile rearrangements of triplet β,r-unsaturated ketones to the corresponding cyclopropyl ketones (35) might be interpreted on the basis of has been explained on the basis of homoallylic back-side participation of the $\Delta^{5,6}$ π electrons (37). Attack of the entering anion then occurs with S_N2 inversion at the homoallylic center. A similar participation may be responsible for the preferential formation of the trans-fused product (6) from the equatorially substituted biradical (4).

The 1,3-carbonyl-radical interaction is only possible in HT-oriented biradicals and this explains the general observation that trans-products are only formed in HT-products.

Assuming the correctness of the above arguments, it becomes possible to analyse the general observation discussed previously in more detail. The probability that a HT-biradical will give a trans-product depends mainly, therefore, on the ratio of $k_{ae}/(k_c + k_{rev})$. The ring closure, k_c, from 3 to 5 will evidently be more rapid the less the steric hindrance of this process. Hence with the less substituted olefins, HT-radical would, on this basis, be expected to give less trans-fused products. A comparison of reaction 2 and 9 substantiates

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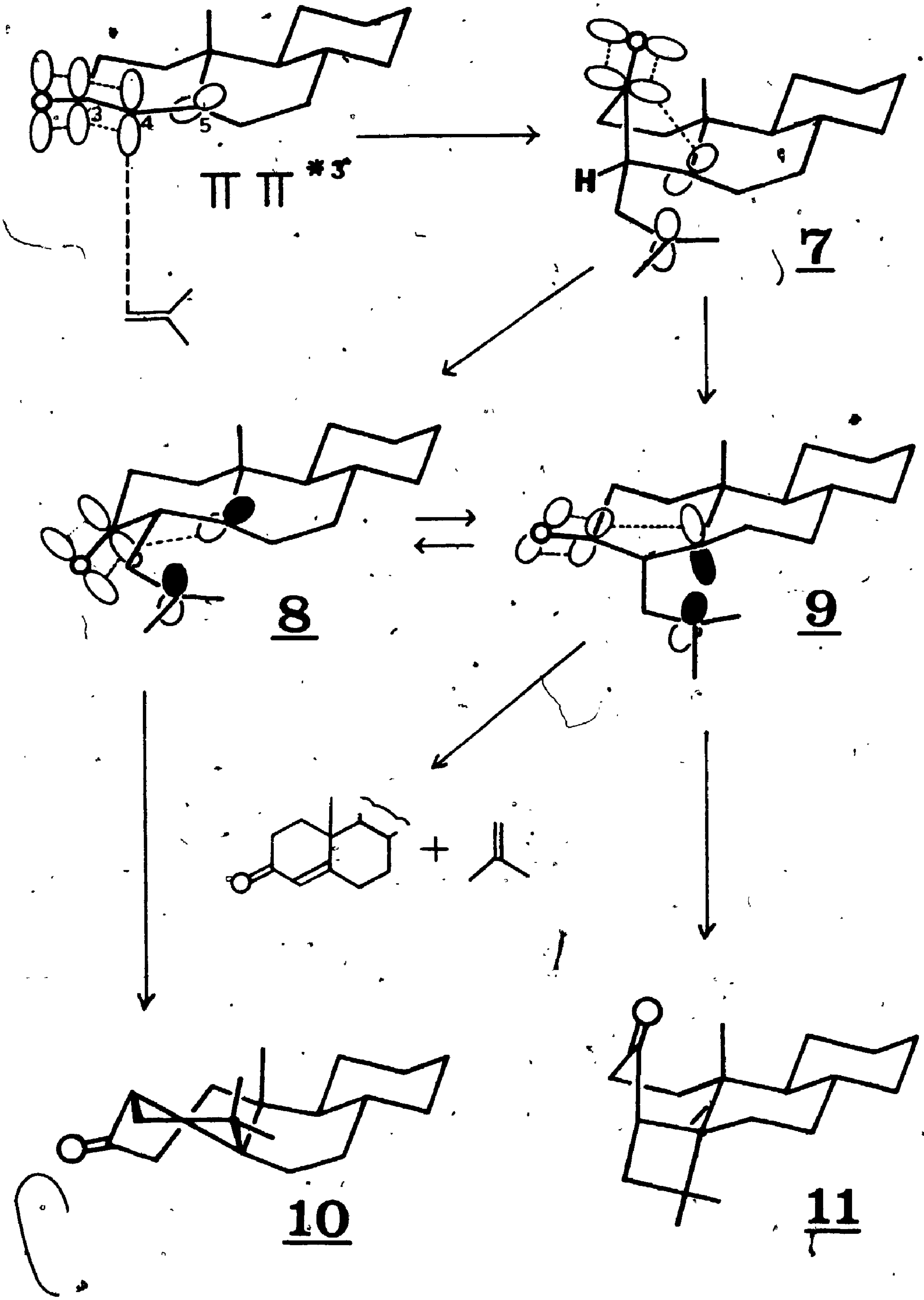
homoallylic interaction of 1,2-biradical species with an olefin. The homoallylic interaction, pictured in Scheme 1 and in other schemes in this thesis, does not necessarily mean full interaction between the relevant orbitals. These interactions could involve only partial overlap between the 1,3-orbitals to gain the maximum stabilization energy possible: that is, delocalization energy minus strain energy.

this. As regards the effect of substituents on the enone ring, it appears, on the basis of model examinations, that substituents on C_5 do not affect ~~the~~ steric interactions appreciably. Substituents on C_4, on the other hand, do appear to increase the interactions. Therefore, one would predict that the yield of trans-products will be insensitive to the presence of substituents on C_5, but sensitive to that at C_4. In fact, it was previously shown that C_5-substitution did not affect the yield of trans-products (compare reaction 11 with 12). Examples of a C_4-substituent effect have not been found in the literature, but the reaction between 4,4-dimethylcyclohexenone and tetramethylethylene (reaction 4) can be explained on the basis of this effect (see below).

The conformational aspects of HT-biradicals in the steroidal 4-en-3-one system may similarly be analysed. The steroidal enone in its ππ* triplet state has probably the B ring in a boat type conformation (see above). When an olefin (for instance isobutylene) approaches this enone at C_4 from the α-side, taking the least hindered side approach, the initial product may well be formed under stereoelectronic control; that is, the biradical 7 may be formed. Both rings A and B are then in a boat type conformation and the substituent at C_4 in quasi-axial position. This biradical is expected to change its conformation very rapidly because of the large 1,4-boat

SCHEME 2

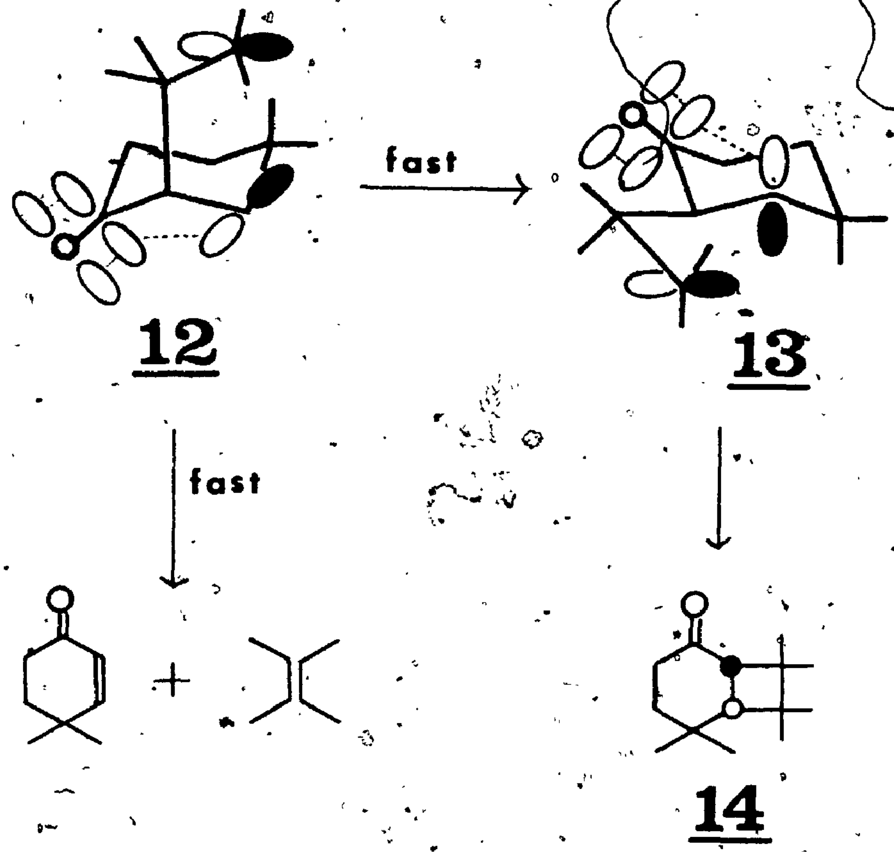


interaction between the α-H on C_1 and the C_4 substituent, and because of the ring strain inherent in this system. Conformers <u>8</u> and <u>9</u> are, then, probably produced from <u>7</u>. Conformer <u>8</u> has rings A and B in a quasi-chair and a quasi-boat form, respectively, with the C_4 substituent in a quasi-equatorial position. Conformer <u>9</u> has the reverse arrangement; that is, these rings in a quasi-boat and a quasi-chair, respectively. the C_4 substituent is now in a quasi-axial position (the quasi-axial nature of the C_4 substituent in <u>9</u> does not cause any severe non-bonding interaction). Conformer <u>8</u> can lead to the trans-product <u>10</u> due to the favourable 1,3-carbonyl-radical interaction, whereas conformer <u>9</u> can give the cis-product <u>11</u>. The conformer <u>9</u> can also revert back to the steroidal enone and isobutylene. This reversibility is at least partially responsible for the generally low quantum yield for steroidal cycloadditions, for instance, Φ = ca. 7×10^{-2} for testosterone propionate and cyclopentene (38). Therefore, although apparent yields of trans-products from HT-biradicals are commonly 15-30% (15% for isobutylene and 30% for diethoxyethylene, see reactions 14 and 17), the mechanistic significance of these yields will not be clear before the nature of the process(es) by which >90% of the energy is dissipated are understood.

When symmetrical olefins (e.g., ethylene, cyclopentene and tetramethylethylene) are used in enone cycloadditions, the analysis of trans-fused product formation is rather difficult, because there is no way to distinguish between two types (HH and HT) of biradicals by examining the structure of the products. Nonetheless trans-products should be formed from biradicals similar to HT-biradicals; that is, by reaction at C_2. If no trans-products are produced (see reaction 3), the reason is, according to my interpretation, either that there is no reaction at C_2 or that the HT-type of biradicals fail to give trans-products. In this respect, it seems worthwhile to consider why the reaction between 4,4-dimethylcyclohexenone and tetramethylethylene gave only trans-fused product (reaction 4) (11).

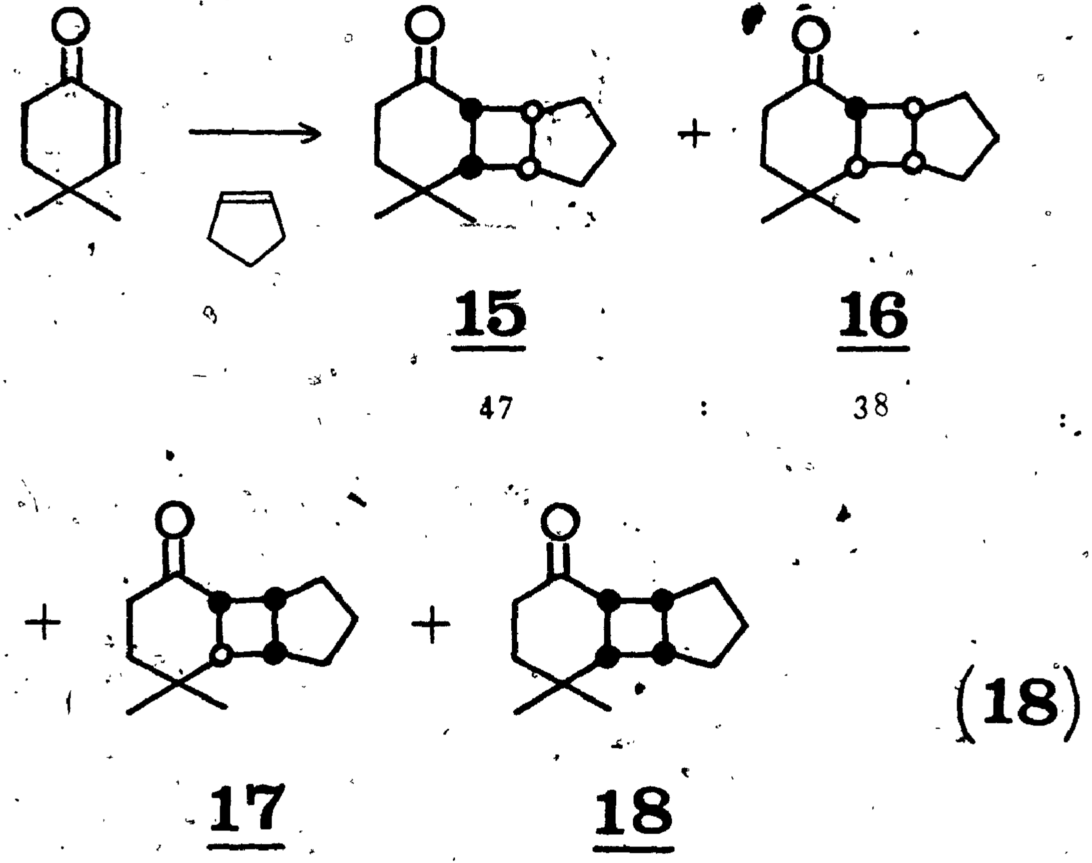
The enone may, in principle, react either at C_2 or C_3. The experimental result implies that only C_2 reacted with the olefin to form a HT-type of biradical <u>12</u>, as shown in Scheme 3. This could be for two reasons. First, the olefin is electron-rich (the C_2 of the $\pi\pi^*$ triplet enone is slightly electrophilic) and, second, the steric approach control favors the first bond formation at C_2 rather than C_3 (C_3 is of neopentyl type and the both ends of the olefin are sterically hindered). The biradical (<u>12</u>) either cleaves to the enone and the olefin, or relaxes conformationally to the equatorial biradical (<u>13</u>). These processes are expected to be very fast because the axial substituent on C_2 is as bulky as a

SCHEME 3



t-butyl group and, furthermore, this substituent is in a 1,3-diaxial relation with the axial C_4 methyl group. Therefore, there seems to be little chance for the biradical (12) to ring-close to cis-fused product. The portion of the biradical (12) which produces the isomeric biradical (13) should give only trans-fused product (14), if the contribution of the 1,3-carbonyl-radical interaction is accepted. This rationalization could lead to the generalization that C_4-substituted cyclohexenones should tend to give more trans-products from HT-biradicals than the corresponding non-substituted cyclohexenones (see above).

Similar considerations may be used to explain the product distribution in the cycloaddition of 4,4-dimethylcyclohexenone to cyclopentene (reaction 18) (17).



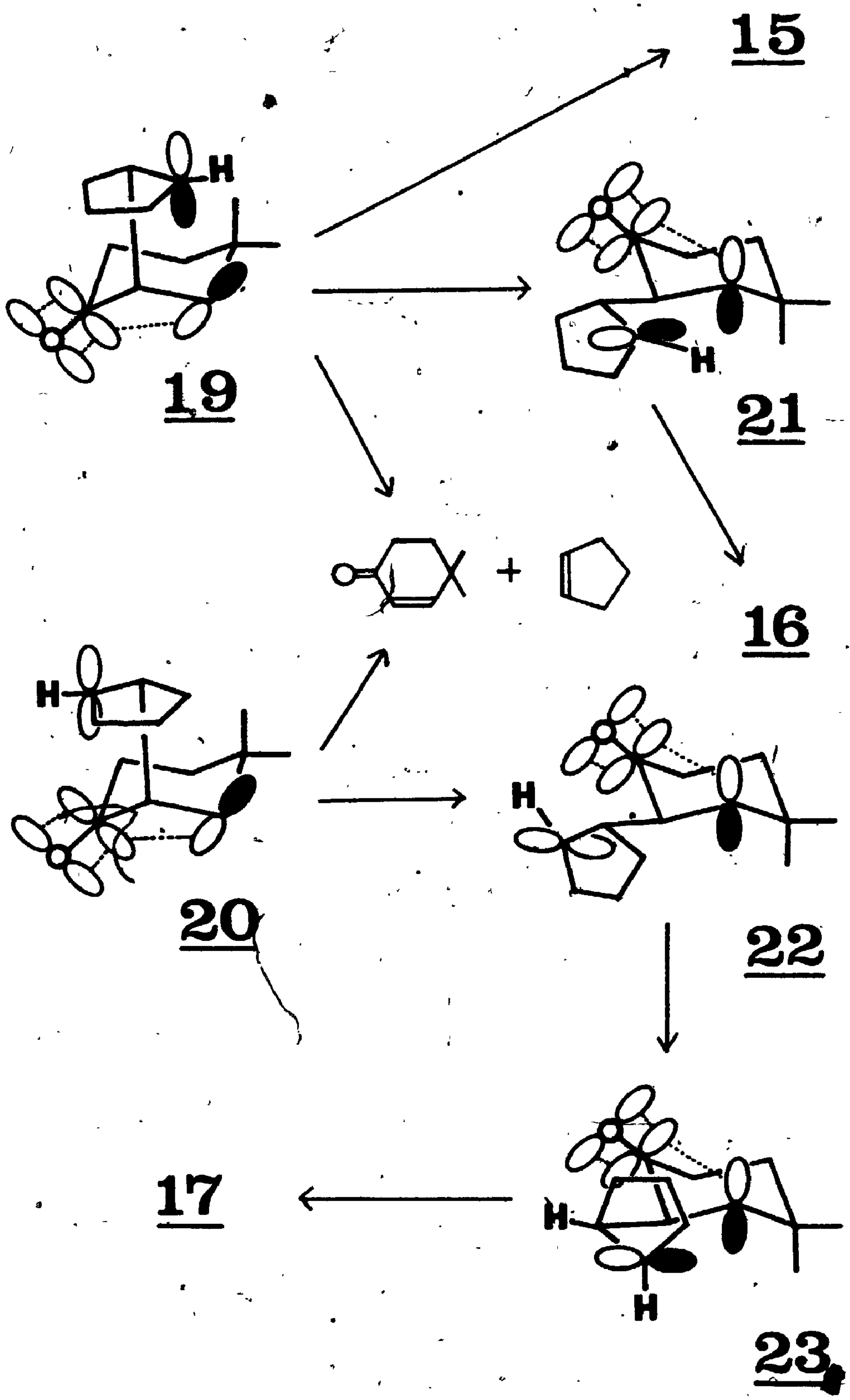
15 : **16** : **17** : **18**

47 : 38 : 15 : 0

(18)

Under the steric approach control, C_2 of the enone preferentially reacts with the double bond of cyclopentene, giving two types of biradicals (<u>19</u> and <u>20</u>) as shown in Scheme 4. Biradical <u>19</u> can cleave to two starting

SCHEME 4



materials, cyclize to the cis-product (15), or/and conformationally relax to biradical 21. The latter could cyclize to the trans-product 16. On the other hand, biradical 20 can not cyclize readily to the corresponding cis-product (18), because rotation of the cyclopentane ring is apparently severely restricted by interaction with the C_4 methyl group. Therefore, biradical 20 either cleaves to the enone and the olefin or relaxes to biradical 22. Here the rotation of the cyclopentane is not restricted and leads to its conformer (23) which would produce trans-product (17).

Thus, these considerations seem to rationalize the basic problems of trans-fused product formation in the enone cycloadditions. However, it is not clear on the basis of the present analysis why trans-fused products have never been identified in the dimerization of simple cyclohexenones, although HT-dimers are frequently obtained as the major products (see above). There are a few possible ways to rationalize this observation.

One possibility is, as already pointed out, that in the dimerization as well as in the cycloaddition of simple cyclohexenones to electron-poor polarized olefins, the triplet enones may react predominantly at C_3. The biradicals, thus produced, which eventually lead to HT-products, might give only cis-fused products. This possibility, however, does not seem to hold in the case of dimerization, because the same biradicals could, in principle, be also formed by reaction at C_2 of triplet enones. However, examination of the conformation of the HT-dimeric biradicals suggests that these biradicals prefer to give cis-fused products. This is illustrated in Scheme 5 for the dimerization of cyclohexenone.

Reaction at C_3 of the triplet enone gives initially a diaxial biradical 24. This biradical, because of a severe 1,4-boat interaction, rapidly relaxes to its conformers 25 (axial-equatorial) and 26 (diequatorial), 26 being more stable than 25. Since the cleavage to regenerate the starting material is forbidden in both radicals (≠), they might establish a conformational equilibrium. Biradical 25 gives a cis-fused dimer, while 26 gives, in principle, a trans-fused dimer. However, the latter trans-formation seems to be unlikely, because the radical centers in 26 are far apart from each other due to the diequatorial conformation 26. Therefore, cis-cyclization from 25 may predominate.

Another possibility is as follows. The HT-products are probably formed mainly because of the effect of the dipole-dipole interaction. This interaction may bring the two reacting molecules into such a close proximity

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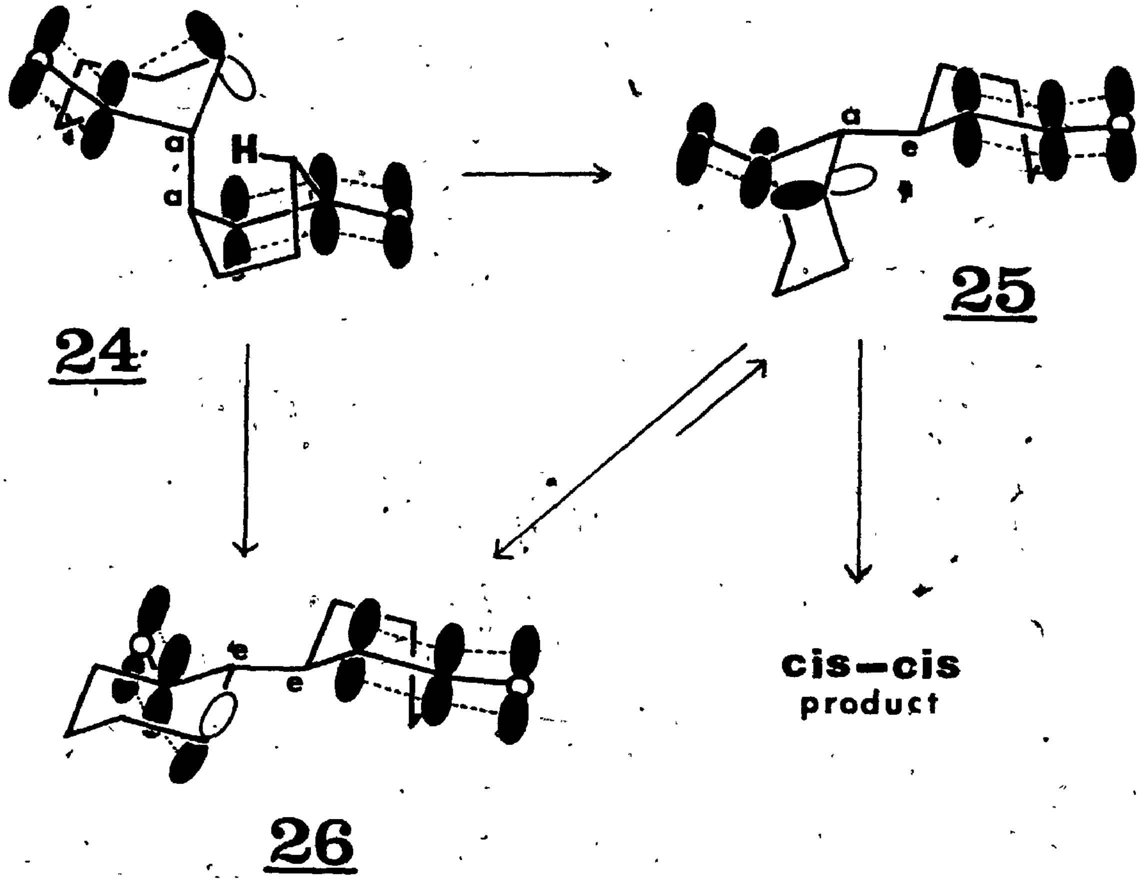
≠The probability of the biradicals giving products is roughly 75% in the dimerization of cyclohexenone (3). This suggests that cleavage to the starting material is inefficient.

SCHEME 5



(possibly with excimer formation) that a considerable change in the electronic nature of the triplet enone may take place. This is because the dipole-dipole effect is acting against the electronic effect (see above). Consequently, the course of cyclization from these strongly dipole-oriented species might be different (giving only cis-products) from that produced under electronic effect control.

It is evident that the rationalization of the trans-fused product formation process is of some complexity. Nonetheless, there remain other factors which have not yet been considered. These are: (1) question of spin inversion; (2) the effects of solvents on product ratios; and (3) the problem of reversibility in 1,4-biradicals. The last two are of considerable consequence because the basis of the foregoing mechanistic discussion has been the analysis of product ratios.

The magnitude of the solvent effects varies considerably depending on the nature of reacting pairs (2, 3, 13, 25, 29, 30, 39). This fact makes a complete analysis of the solvent effects and, consequently, product ratios difficult. In this thesis, it has been attempted, as much as possible, to compare product ratios obtained in similar region of solvent polarity.

The reversibility of 1,4-biradicals is reflected in the size of the quantum yields for addition extrapolated to infinite concentration (21). It appears to be a general tendency that the quantum yields of the enone cycloadditions are much higher when simple cyclohexenones are used (14) than when the steroidal 4-en-3-one system is used (see above). Therefore, an analysis of mechanism on the basis of product formation is much more reliable in the former case.

There have been numerous discussions in the literature with regards the spin-inversion step in cycloaddition (40, 41, 42, 43). As yet there is no agreement, even among theoreticians, and no experimental evidence to indicate the rate of this process and exactly at which point on the energy surface the crossing takes place. Therefore, it has been necessary to ignore this important aspect.

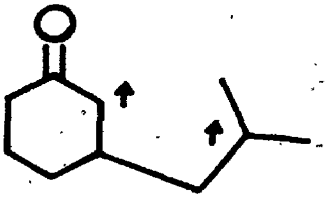
THE EXPERIMENTAL PROPOSAL

The present analysis of the reasons for the formation of trans-fused products appears to rationalize the general mechanism of enone cycloadditions. However, the analysis is largely based on two assumptions: that triplet 1,4-biradicals are intermediates in the cycloadditions, and that only HT-oriented biradicals have the opportunity to give trans-product. HH-oriented biradicals are presumed to give only cis-products. Experimentally, these assumptions should be justified. To do this, syntheses of suitable triplet 1,4-biradicals by routes other than via the enone cycloadditions are required. This will permit a comparison between the reactions of these "authentic" biradicals and the corresponding enone cycloaddition biradicals to be made.

Which particular 1,4-biradicals should be the synthetic objectives? As already pointed out, steroidal

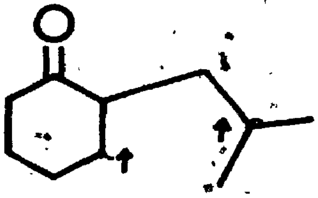
4-en-3-one systems are less efficient in giving products. Thus, the cycloadditions of simple cyclohexenones are probably more suited for the present purpose. Of the known cycloadditions in this category, only one reaction is reported to give both HT- and HH-products with both cis- and trans-stereochemistries at their ring junctions. This is the cycloaddition between cyclohexenone and isobutylene (12). Therefore, this reaction is a logical choice for the present study. Consequently, the synthetic objectives are the two triplet 1,4-biradicals (27 and 28) shown in Figure 6.

FIGURE 6



27

(HH)



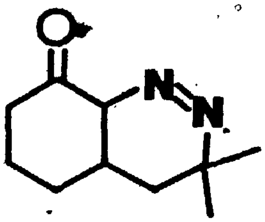
28

(HT)

Although several methods are known for the generation of 1,4-biradicals (41, 42), photolysis of six-membered ring azo compounds seems to be the best choice in the present case. This route appears to have been most generally followed, and hence possesses the greatest body of information (44). Although the multiplicities and mechanisms of the photochemical nitrogen-eliminations are not certain in some direct photolyses (45, 46), it is reasonable to assume that triplet biradicals are formed with sensitized photolysis (40, 41, 44, 47, 48, 49). Therefore, the precursors to the triplet biradicals (27 and 28) are the corresponding two azo compounds (29 and 30) shown in Figure 7.

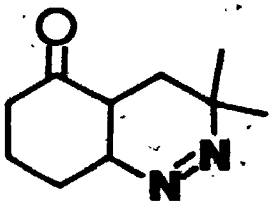
Apart from specific interest with regard the enone cycloaddition, the photolyses of the azo compounds (29 and 30) are in themselves rather interesting in view of the contradicting opinions appearing in the literature

FIGURE 7



29

(HH)



30

(HT)

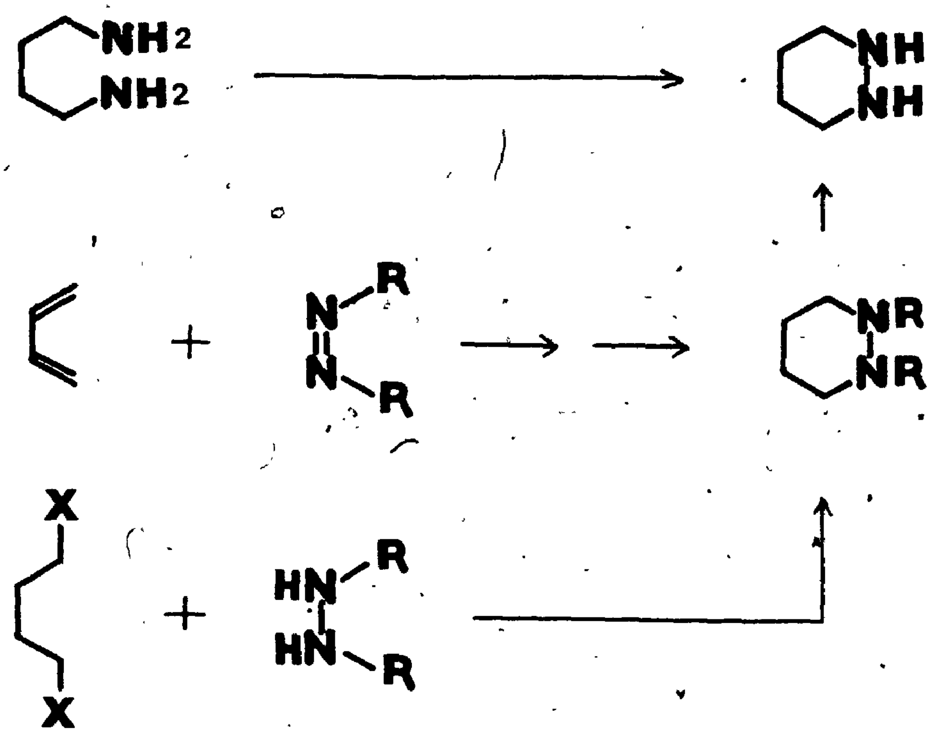
concerning the photochemically reactive state of azo compounds. Steel has suggested, on the basis of his photokinetic studies of bicyclic azo compounds, a common reactive state in both direct and sensitized photolysis (46). However, spin-correlation effects, which have been generally recognized in the photochemistry of azo compounds (41, 47, 49, 50), suggest that this is not so. With the azo compounds (29 and 30) available the problem may be solved.

The efforts toward the synthetic objectives (29 and 30) are discussed in the following sections.

RESULTS AND DISCUSSION

BASIC SYNTHETIC PLANNING

Known procedures for the preparation of six-membered cyclic azo compounds are generally (though not always (51)) oxidation of the corresponding hydrazines. It is convenient to divide the general routes to cyclic hydrazines into two classes: coupling reactions between two amino groups; and formal [4+2] cycloaddition reactions using an N-N unit as the 2 unit. These reactions are illustrated in general terms in equations 19 and 20. The coupling reactions can be achieved either directly (49, 52) or via sulfamides (-NH-SO_2-NH-) (53). Two reactions are commonly used for the cycloaddition reaction process: a Diels-Alder reaction between diene and a dienophile (R-N=N-R) (54, 55, 56); and a sequential double substitution (57). Of these two reactions, the



(19)

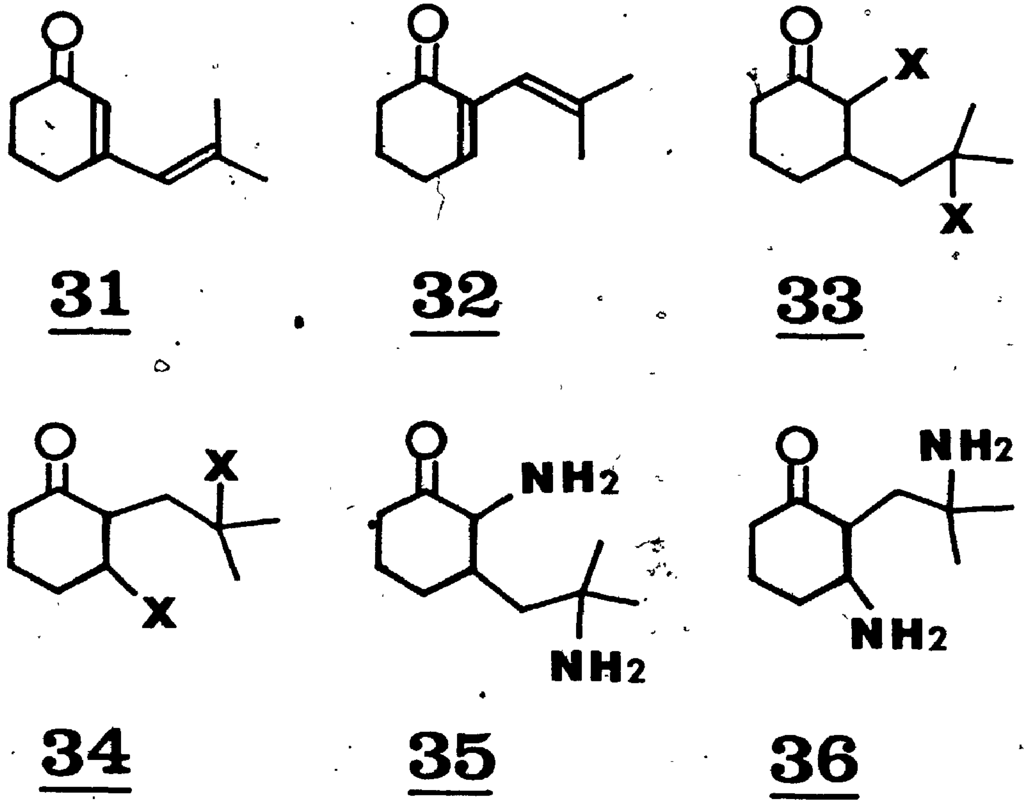
(20)

Diels-Alder reaction has been the more frequently used (44).

The use of the coupling reactions affords the direct preparation of the cyclic hydrazines from the corresponding diamines. In contrast, the other method requires extra manipulation for the removal of the substituent to generate the free hydrazines. However, other important aspects of the application of these methods to the syntheses of <u>29</u> and <u>30</u> must be considered.

The potential intermediates (<u>31</u> - <u>36</u>) for the syntheses of <u>29</u> and <u>30</u> necessitated in these methods are shown in Figure 8: 31 and 32 for the Diels-Alder reactions; 33 and 34 for the double substitution reactions; and 35 and 36 for the coupling reactions. The ketone groups of 35 and 36 would be subject to condensation with the amino groups, and the aminoketones might

FIGURE 8



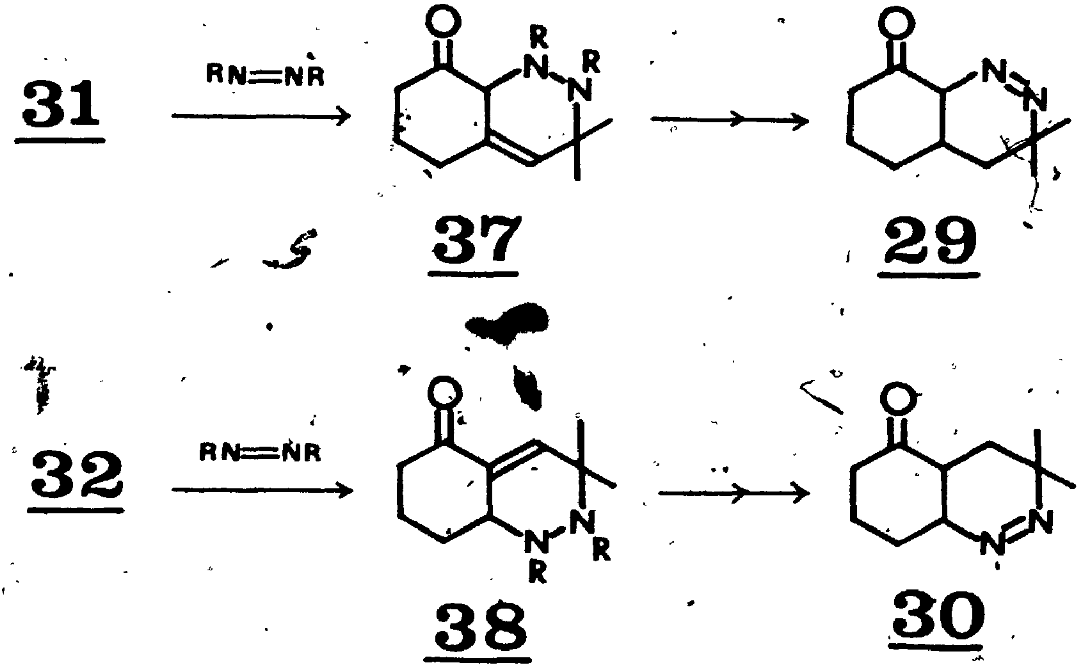
31 32 33

34 35 36

be difficult to isolate. The application of the double substitution reactions also has an obvious problem in that one of the leaving groups (X) of 33 and 34 is on a tertiary carbon. The application of the Diels-Alder reactions may also produce some difficulties, since the dienes (<u>31</u> and <u>32</u>) are probably not co-planar in their s-cis-forms, the planar s-cis-forms being known to be preferred for the smooth cycloadditions (58, 59). However, the latter problem seemed the most easy to overcome by choosing a powerful dienophile (58, 59).

For this reason, the Diels-Alder reaction was chosen for the key reaction in the syntheses of <u>29</u> and <u>30</u>. Thus, the prime synthetic targets were the dienones (<u>31</u> and <u>32</u>). These, by reaction with a suitable dienophile (R-N=N-R), should lead to the adducts (<u>37</u> and <u>38</u>) which were suitable

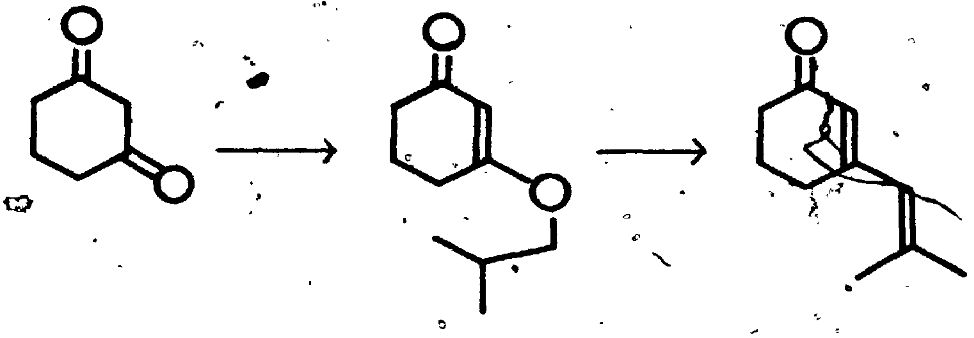
SCHEME 6



precursors for 29 and 30 (Scheme 6).

SYNTHESES OF 2- AND 3-ISOBUTENYLCYCLOHEX-2-EN-1-ONE (31 AND 32)

3-Isobutenylcyclohex-2-en-1-one (31) is a known substance (60) and was prepared from 1,3-cyclohexandione (39) as outlined in equation 21. Following the procedure



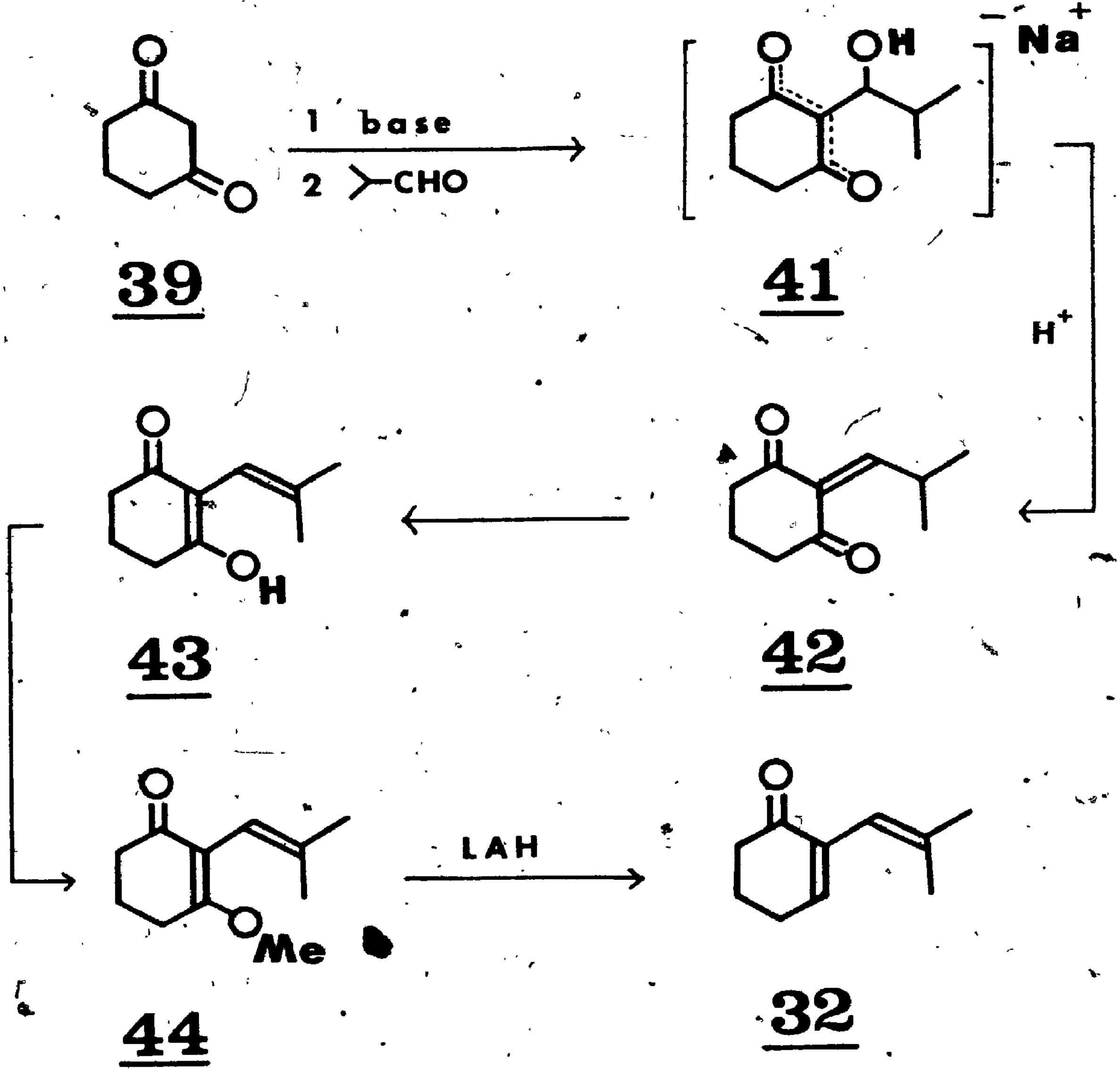
(21)

39 **40** **31**

of Eschenmoser (61) for preparing 2-methyl-3-isobutoxycyclohex-2-en-1-one, etherification of 39 was carried out using isobutanol in the presence of a catalytic amount of p-toluenesulfonic acid. The product (40) was converted to 31, following the general procedure of Crisan and Normant (60), using isobutenyl magnesium bromide.

2-Isobutenylcyclohex-2-en-1-one (32) was an unknown compound and was synthesized from 39 as indicated

SCHEME 7



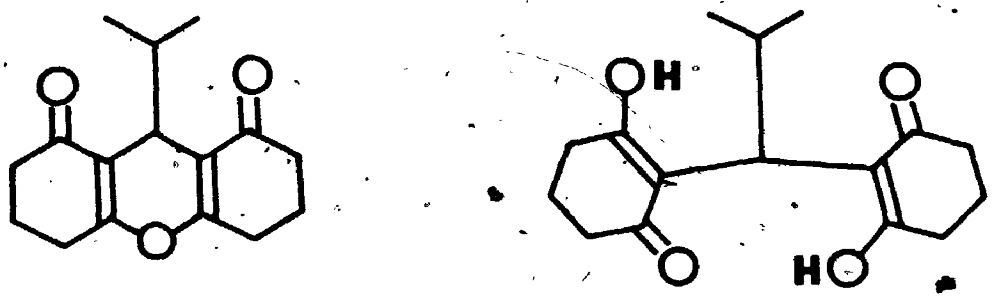
in Scheme 7. The key step of this synthesis was the condensation reaction between 39 and isobutyraldehyde. It is generally known that condensation of 39 (or its analogues) with an aldehyde often leads to 2:1 adducts instead of 1:1 adduct (62). Recently, Polansky and Margaretha investigated the condensation reactions between dimedone and arylaldehydes, and found suitable conditions under which the 1:1 adducts were formed preferentially (63), and their method was applied.

The sodium salt of 39 was treated with excess isobutyraldehyde in dry methanol under refluxing conditions for one hour. After evaporation of the solvent and the excess aldehyde, a slightly colored precipitate was obtained. Presumably this precipitate consisted largely of 41. Upon treatment with dry hydrochloric acid in ether, the pricipitate gave a mixture of products, enedione 42 predominating. This compound (42) showed its methyl signals as a doublet ([illegible]=6.0 H_z) at 1.09 ppm and its vinylic proton also as a doublet (J=10.0 H_z) at 7.15 ppm in the pmr spectrum of the reaction mixture.

When this reaction mixture was kept under nitrogen or under reduced pressure (room temperature) 42 gradually disappeared and 43 started to appear. After 16 hours, 42 was completely converted to 43; the other by-products remained unchanged. Compoung 43 showed its allylic methyl groups at 1.50 and 1.80 ppm and its vinylic proton at 5.53 ppm. Double irradiation experiments showed that the latter proton had a long range coupling with the former protons (J=1.0 H_z).

All attempts to isolate 42 and 43 from the reaction mixture by means of distillation and preparative tlc were unsuccessful. Instead, upon preparative tlc, two major by-products, 45 and 46, were isolated as colorless crystals,

FIGURE 9



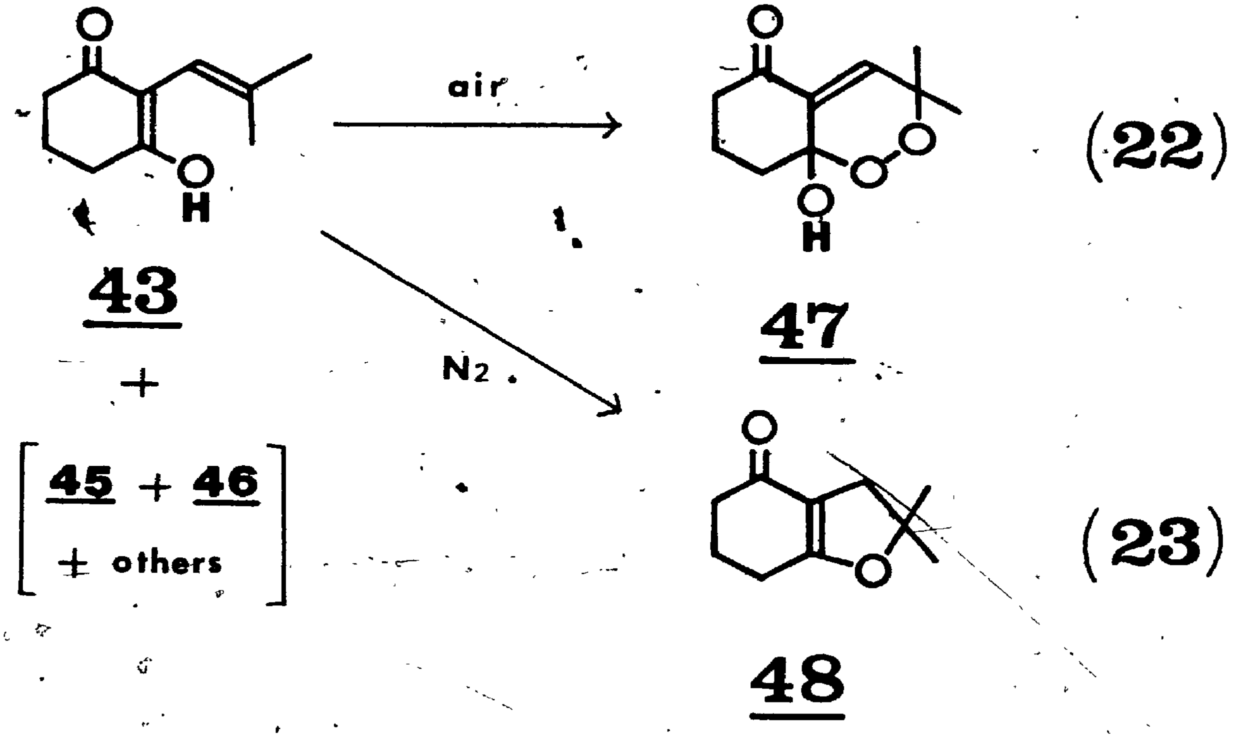
45

46

mp 98.0-98.5° and 189.0-190.0°, respectively. On the basis of their spectroscopic properties and the known analogies (62), the products were assigned as the 2:1 adducts (Figure 9).

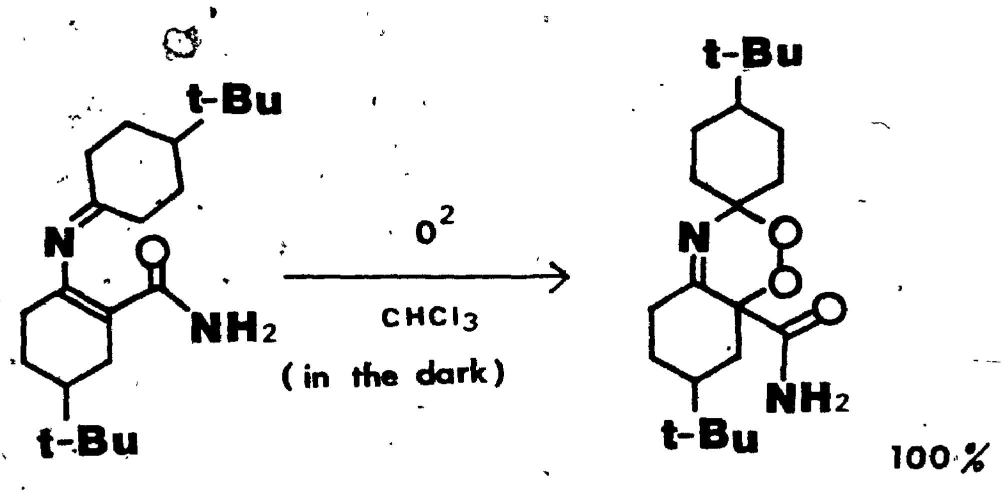
When the reaction mixture, containing 43 as the major constituent, was exposed to air, colorless crystals were gradually formed (overnight for a 50 mg mixture). The crystals, mp 153.5-150.0°, showed a positive NaI test suggesting the presence of a peroxide group, and had a hydroxyl group (3600 cm^{-1}) and an unsaturated ketone group

(1695 and 1645 cm^{-1}; 227 nm (ε 7000)). The structure 47 was assigned to this substance (reaction 22). The fact



that the formation of 47 took place even in the dark implies that singlet oxygen was not responsible for the addition reaction (64). The facile addition of ground state oxygen to 43 is not common, but there is an analogy reported in the literature (65) (reaction 24).

In the absence of air, the formation of 47 was completely supressed. Instead, 43 very slowly gave a new compound (half life time of 43: ca. two weeks at ca. 25°). This compound was an isomer of 43, because it had a molecular ion peak at m/e 166. This substance showed a sharp

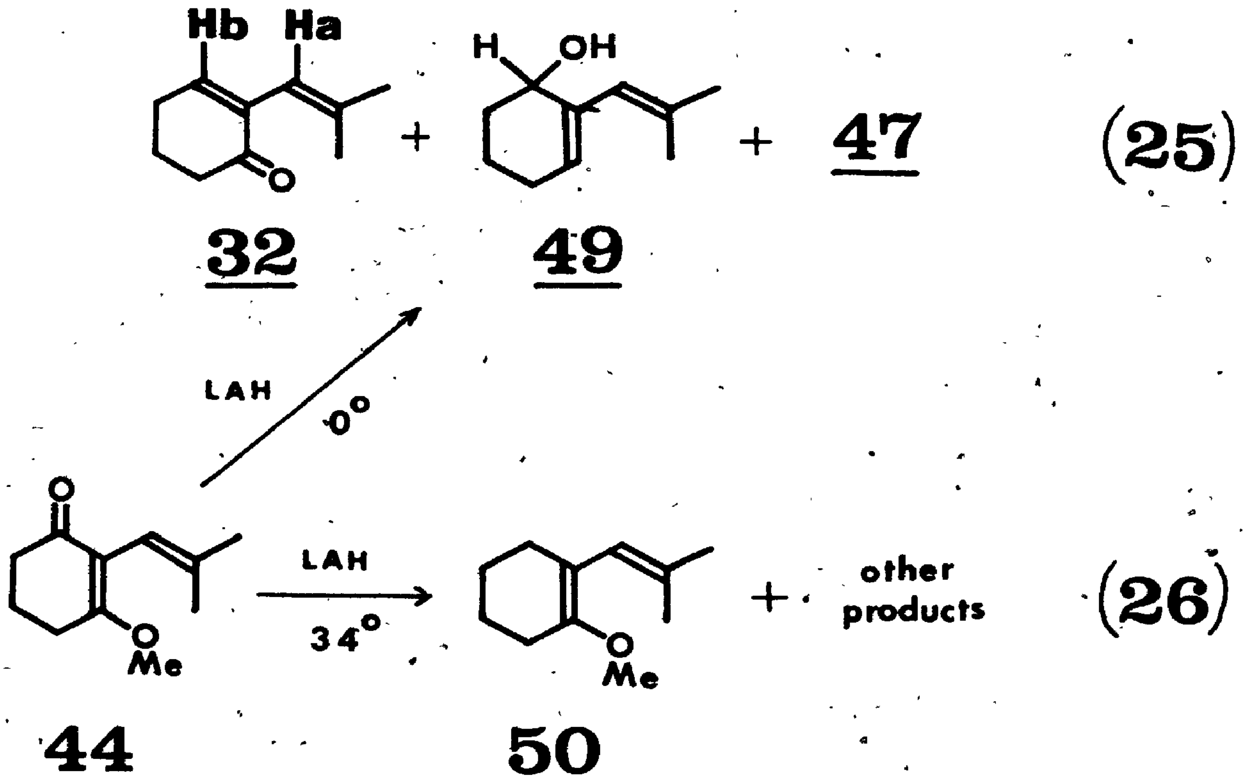


(24)

singlet (1.41 ppm) for the geminal methyl groups, implying probable existance of a plane of symmetry. The presence of a 1,3-diketone enol ether was suggested in its ir and uv spectra (1655 and 1635 cm^{-1}, and 271 nm (ε 15000)) (61). The structure <u>48</u> was assigned for this compound (reaction 23): its formation was probably induced by traces of acid catalyst.

In order to optimize etherification of <u>43</u>, the reaction mixture, containing mainly <u>42</u>, must be kept free of oxygen, and be treated with diazomethane (66) as soon as the isomerization of <u>42</u> to <u>43</u> is completed. The complete transformation to <u>43</u> is necessary to avoid a possible [1,3] dipolar cycloaddition of ~~the~~ diazomethane to the double bond of <u>42</u> (58). The yield of isolated <u>44</u> was ca. 30% based on the amount of <u>39</u> consumed. This substance showed the expected properties: the methoxy group (3.78 ppm); the isobutenyl group (two allylic methyls at 1.47 and 1.84 ppm, and a vinylic proton at 5.65 ppm).

Upon lithium aluminium hydride reduction (0°, ether), 44 gave three products; 32, 49 and the oxygen adduct (47) (equation 25). Compound 32 showed the expected spectral data for 2-isobutenylcyclohex-2-en-1-one. The cross conjugated dienone moiety was observed in its pmr (two allylic methyl groups and two vinylic protons, Ha and Hb; the Ha coupled with Hb and the methyl protons) (equation 25). The substance had a strong



absorption at 1665 cm^{-1}. Its uv absorption was 212 (ε 17800) and 269 nm (ε 3700).

The structure of 49 was assigned largely because of the following data: a molecular ion peak at 152 and the presence of a hydroxyl group (ir), a conjugated diene (uv), two allylic methyl groups and two vinylic protons (pmr).

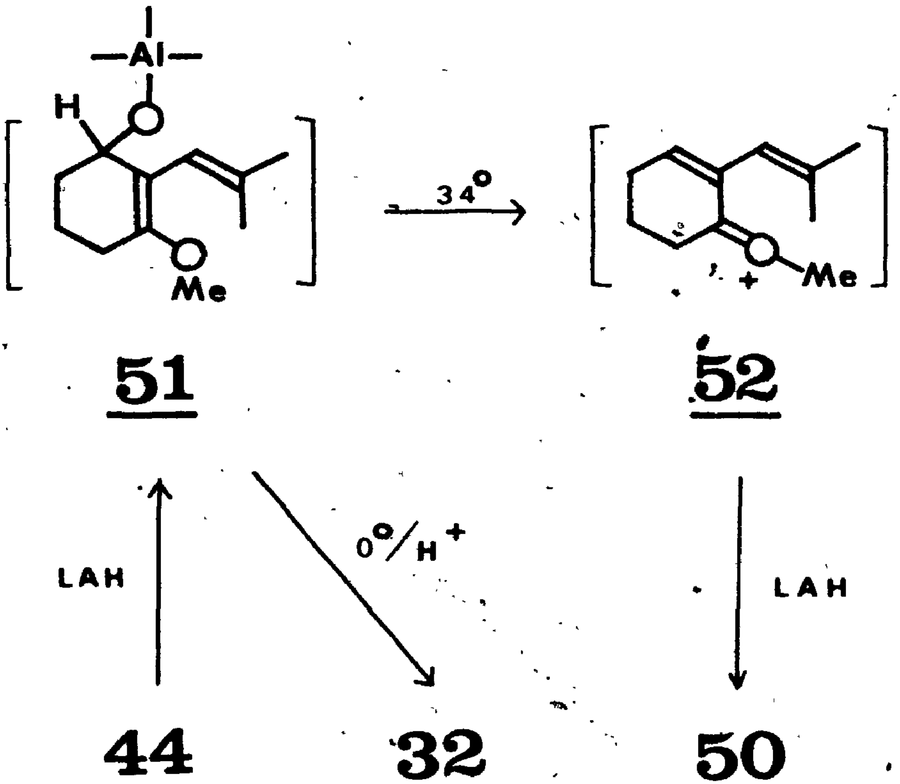
The oxygen adduct 47 was formed presumably by addition of oxygen to 43; it, in turn, probably produced from unreacted starting material (44) during the acidic isolation step (10% HCl).

The product ratio (32/49) was affected by the amount of lithium aluminium hydride (LAH) used. On the other hand, the combined yield (32 + 49) was not affected to any great extent (70-80%). The ratio(32/49) increased from 1.8 to 7.8 when the molar equivalent ratio of LAH/43 was decreased from 14.3 to 2.6.

When the reduction of 44 was conducted at a higher temperature (boiling ether conditions), a mixture of products was obtained, which did not include 32. The major product, isolated, showed a moleculr ion peak at m/e 166 and had a partial structure, $Me_2C{=}CH{-}C{=}C(OMe)$, (pmr). The structure 50 (reaction 26) was assigned to this substance; its probable formation being as outlined in

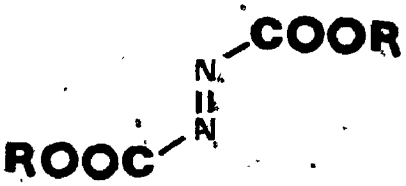
Scheme 8. The intermediate 51, one of the possible precursors for the desired product (32), may have been transformed to 52. The latter, upon 1,4-reduction by LAH, would produce 50.

SCHEME 8

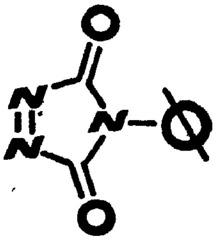


DIELS-ALDER REACTIONS AND DIRECT APPROACHES TO THE AZOKETONES (29 and 30)

In order to prepare a 3,4,5,6-tetrahydropyridazine derivative using a Diels-Alder reaction, the nitrogen substituents must be easily removable. The choice of dienophile has, therefore, a two-fold importance; its dienophilicity and facility of removing its substituent groups at a later stage of the synthesis. The most commonly used dienophiles are diethylazodicarboxylate (53, R=Et) and 4-phenyl-1,2,4-triazoline-3,5-dione (54). The former has a rather poor dienophilicity, consequently reactions with sterically crowded dienes yield ene



53

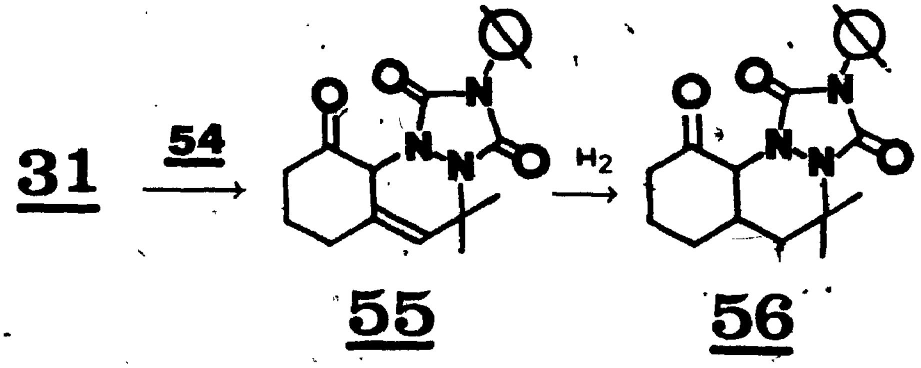


54

reactions rather than Diels-Alder reactions (67). However, if a Diels-Alder reaction does take place, this dienophile has substituents which can be easily removed by base. The latter dienophile (54) (59, 68, 69) is one of the best dienophiles known, and will add to sterically crowded dienes that refuse to accept most common dienophiles, e.g., maleic anhydride (51). The disadvantage of using this dienophile is the conversion of the product to a hydrazine after the Diels-Alder reaction.

The compound 54 was chosen for the present syntheses, because it was required to react with sterically crowded dienes like 31, 32 and 44, even though it could pose problems in the later stages of the synthesis.

The Diels-Alder reaction of dienone 31 and its subsequent transformations are outlined in equation 27. Upon addition of 54, 31 gave adduct 55 as colorless crystals, mp 150.0-15[illegible].5°, in 82% yield. This substance showed the expected properties: a molecular ion peak at m/e 325, a single vinyl proton (5.38 ppm), two methyl groups (1.42 and 1.71 ppm), the aromatic protons and the methine proton (α to the ketone group) (5.02 ppm). The presence of the urazole moiety is apparent in the ir spectrum (69). Upon hydrogenation (5% Pd/c), 55 yielded 56, mp 185.0-187.0°, in 91% yield. This compound had its molecular ion peak at m/e 327 and showed no vinylic proton in its pmr spectrum. This compound was probably not a mixture of the two possible diastereomers (cis and trans at the ring junction), since it showed only a pair of singlets for the geminal methyl groups and only one



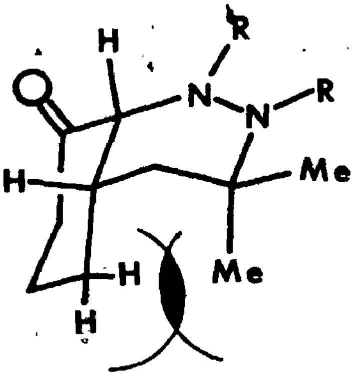
(27)

kind of the methine proton α to ketone. Furthemore, that this compound had the thermodynamically more stable ring junction was shown by its resistance to epimerization under basic conditions (KOH in MeOH in water).

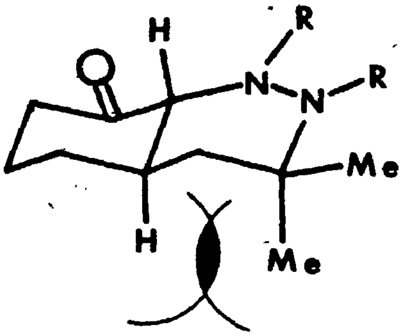
Dreiding models of the two isomers showed that the cis-isomer has either 1,3-diaxial non-bonding interaction between CH_2/Me in conformation 57, or between H/Me and H/CH_2 in 58 (Figure 10). On the other hand, the trans-isomer (59) has only one equivalent interaction between H/Me. It is thus likely that the trans-isomer is the thermodynamically more stable isomer. Hence, 56 probably has a trans junction.

The synthesis of compound 61 was carried out following two different routes as outlined in Scheme 9. The Diels-Alder reaction between 44 and 54 gave the adduct (60), mp 141.0-142.5°. This adduct had the

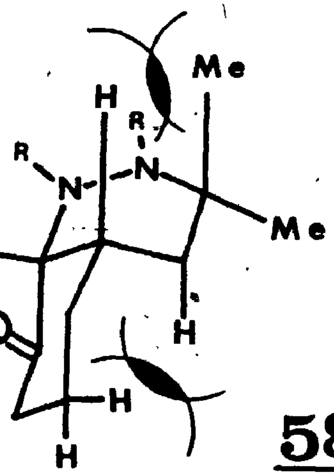
FIGURE 10



57



59

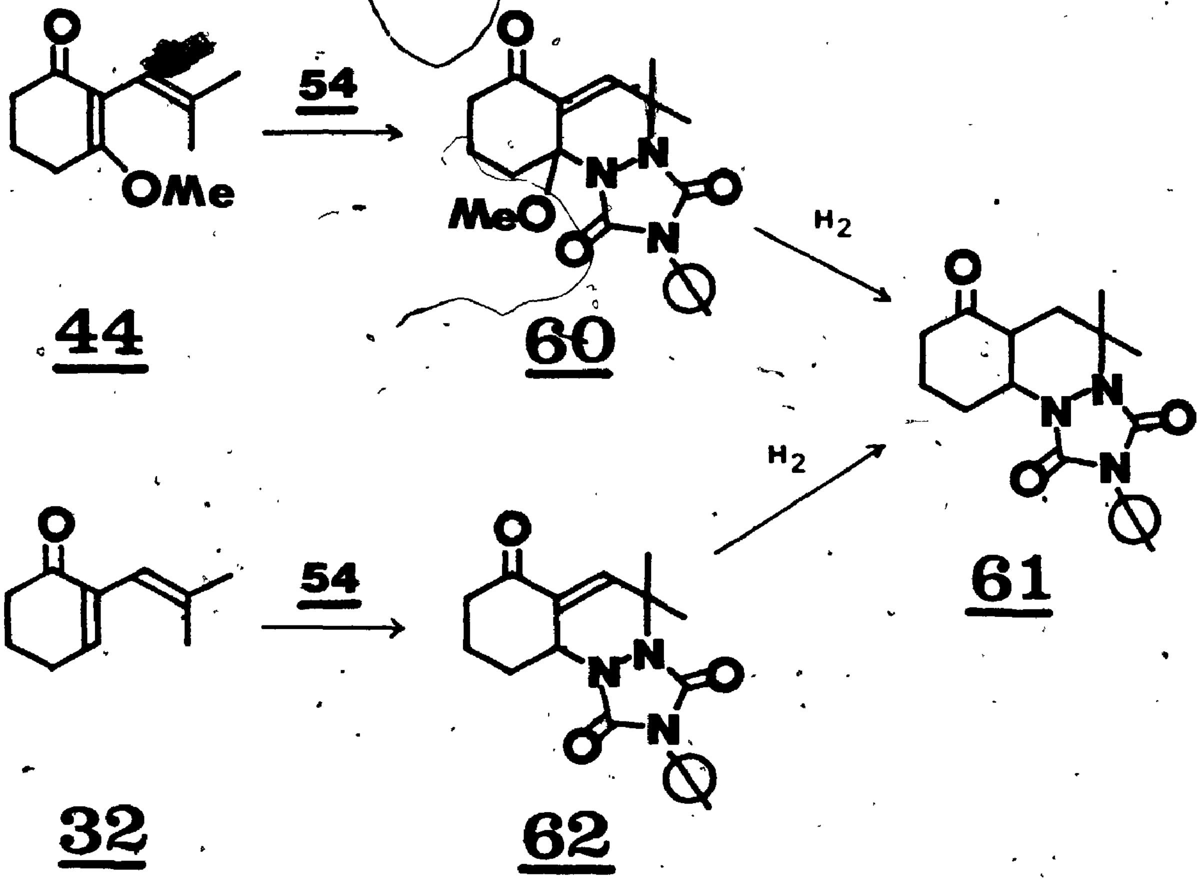


58

expected trisubstituted olefin conjugated with ketone (1650 cm^{-1}, strong, and 6.45 ppm, singlet) and the geminal methyl groups (1.47 and 1.88 ppm). The presence of the methoxy group (pmr) and the urazole moiety (ir) was apparent.

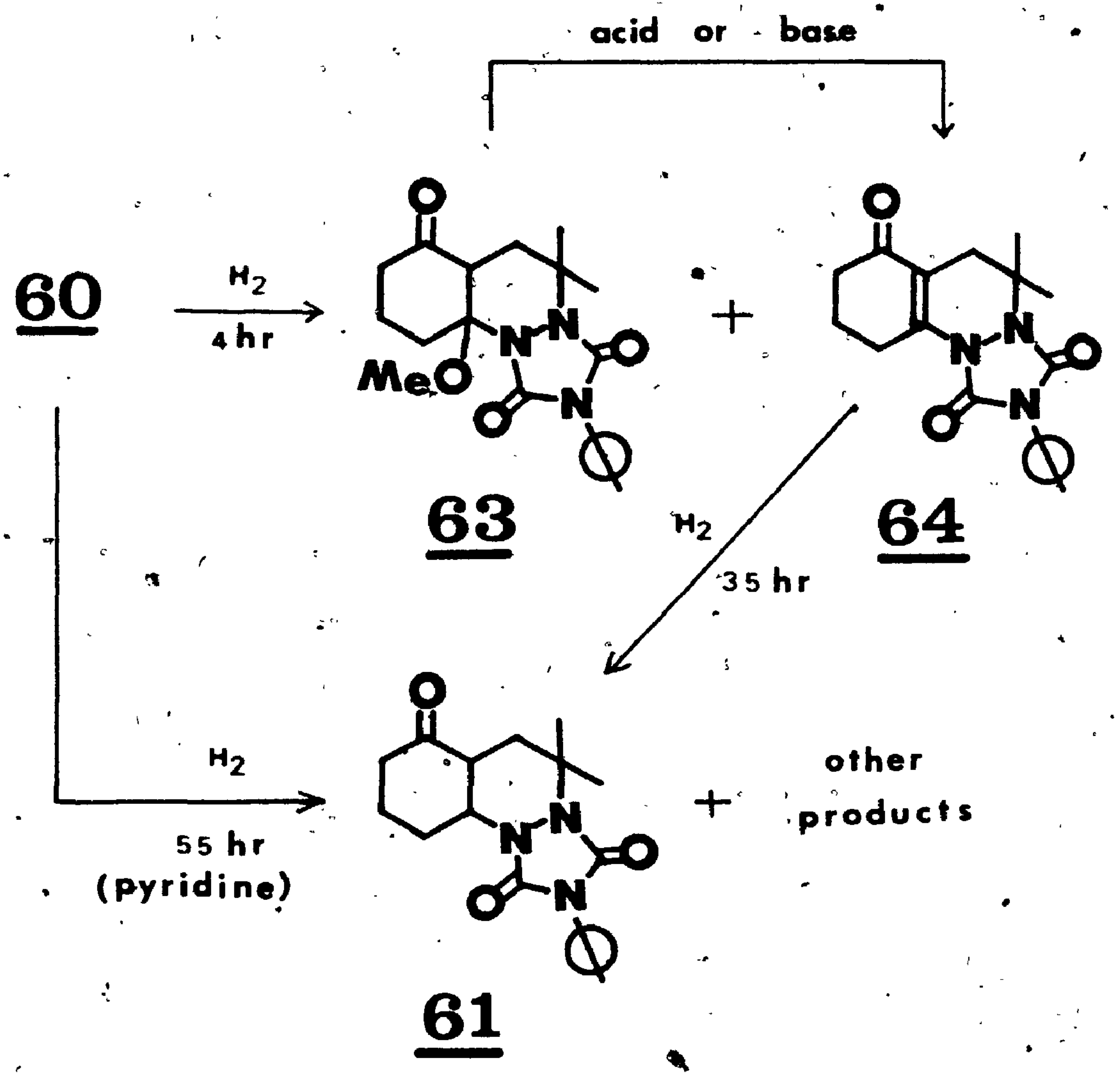
Upon hydrogenation (four hours) in ethanol using 5% Pd/c as the catalyst, 60 gave two products, 63 and 64, mp 223.0-224.5° and 162.0-163.0°, respectively (Scheme 10). The former had a molecular ion peak at m/e 357, a methoxy group (3.18 ppm) and a geminal methyl groups (1.33

SCHEME 9



and 1.83 ppm). No olefinic protons were observed. The compound was assigned the structure 63. This compound was most likely only one of the two possible stereoisomers and not a mixture, because it showed a sharp melting point and no methyl signals other than those mentioned above. Its stereochemistry was not investigated. The second compound 64 showed a sharp singlet (1.59 ppm) ~~for~~ the

SCHEME 10



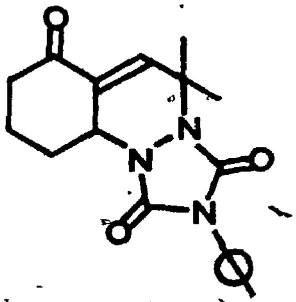
geminal methyl groups, implying the presence of a plane of symmetry. Two pairs of allylic protons were observed (2.51 and 3.25 ppm) and these pairs had a long range coupling (J=2.0 H_z) between them. The uv absorption of 64, 215 (ε 5800) and 301 nm (ε 13000), was considerably red-shifted in comparison with that of the saturated analogue (63), 217 nm (ϵ 13800). This compound was readily obtained from 63 by elimination of methanol under acidic or basic conditions. Thus, the structure shown in Scheme 10 was established for this substance.

Hydrogenation of 64 for 35 hours using 5% Pd/c, led to the formation of 61 in rather poor yield (ca. 39%). The major portion of the reaction product was a mixture of unidentified substances. A similar mixture of products was obtained upon direct hydrogenation (55 hours) of 60 in the presence of a few drops of pyridine, and 61 was isolated in ca. 41% yield from this mixture (Scheme 10).

Compound 61 had a mp 185.0-187.5° and showed the expected molecular ion peak (m/e 327). The two methyl groups appeared as singlets (1.38 and 1.80 ppm) and the methine proton α to the ketone appeared as a doublet of triplets (3.00 ppm, J=13.5, 5.0 and 5.0 H_z). This substance was, judging by the pmr spectrum (see above), a single stereoisomer.

Thus, compound 61 could be prepared by the hydrogenation of either 60 or 64, but the yield was rather low and the reproduceability of these hydrogenations was poor. Another route to 61 via the Diels-Alder reaction between 32 and 54 was investigated (Scheme 9), with better success.

Upon addition of 54, 32 gave adduct 62, mp 157.0-159.5°, in 87% yield. This substance showed the expected trisubstituted olefin conjugated with the ketone group ($1645\ cm^{-1}$, strong, and 6.34 ppm, 1H) and the geminal methyl groups (1.60 and 1.68 ppm). The allylic methine

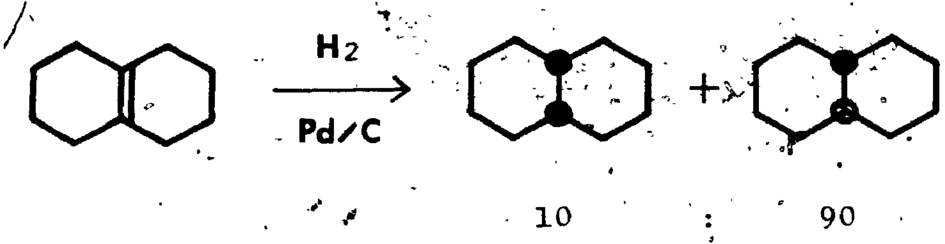


62

proton appeared at 4.45 ppm and this proton had a long range coupling ($J=2.5\ H_z$) with the vinylic proton.

Using 5% $Pd/BaCO_3$ as a catalyst, hydrogenation in ethanol containing a few drops of pyridine gave 61, mp 184.0-186.0°, in 93% yield. This product was identified by comparison with an authentic sample obtained by hydrogenation of 64. In the absence of pyridine the yield of 61 decreased to ca. 70%. The yield also decreased (50-60%) when the hydrogenation was conducted using 5% Pd/c instead of 5% $Pd/BaCO_3$.

Compound 61, thus prepared by hydrogenation of either 62 or 64, was believed to be one of the two possible cis- and trans-stereoisomers as already discussed. The stereochemistry of 61 should be cis, provided that the hydrogenation of 64 proceeded with cis-addition of hydrogen. However, trans-addition of hydrogen has been recorded in certain cases; an example is shown in equation 28 (70). The cis-isomer was expected to be

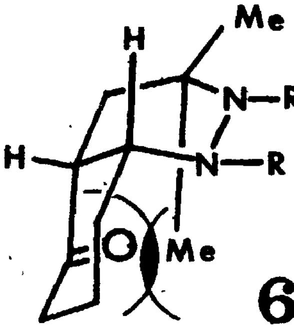


(28)

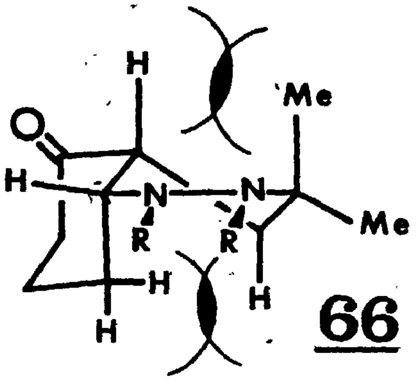
the thermodynamically less stable in that this isomer had larger non-bonding interactions. (1,3-quasidiaxial interactions between Me/CO in 65 and between H/Me and H/CH_2 in 66 as shown in Figure 11) than the other isomer (between H/Me in 67). An attempt to epimerize the ring junction of 61 using triethyl amine was unsuccessful, and, under stronger basic conditions, 61 gave 68 (the formation of 68 will be discussed in a later section). The stereochemistry of the junction is thus not known.

The conversion of 56 and 61 to the corresponding keto-hydrazines, 69 and 70, respectively, was attempted

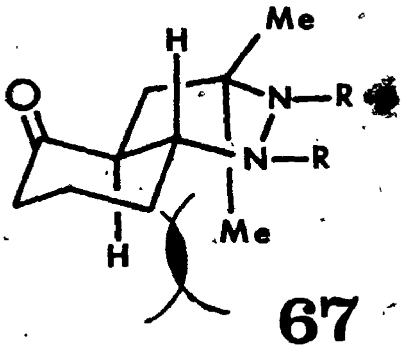
FIGURE 11



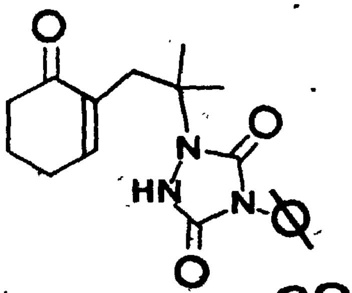
65



66

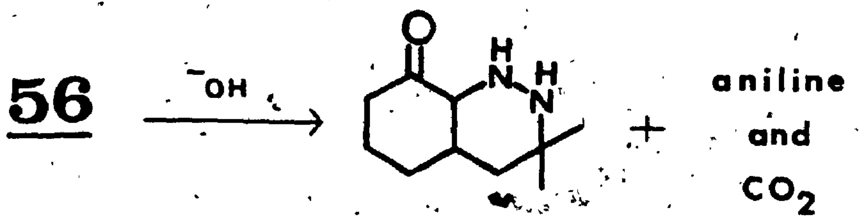


67



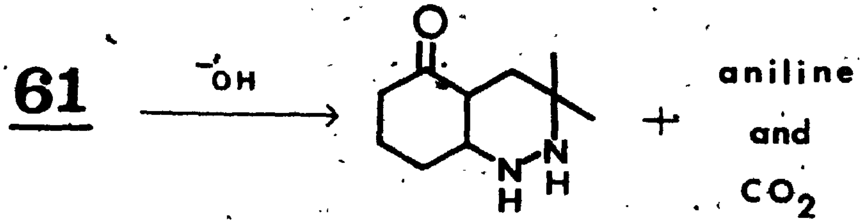
68

by basic hydrolysis (reactions 29 and 30). The reactions were easily followed by examining the formation of aniline. When 56 was treated with potassium hydroxide at room temperature in water and methanol, no reaction occured and only starting material was recovered. At 105° (18 hours) in a sealed tube under nitrogen, a single product (as well as aniline) was detected in the pmr spectrum of the reaction mixture. This product had an NH group (ca. 3.7 ppm, exchanged with D_2O) but did not have the saturated



69

(29)

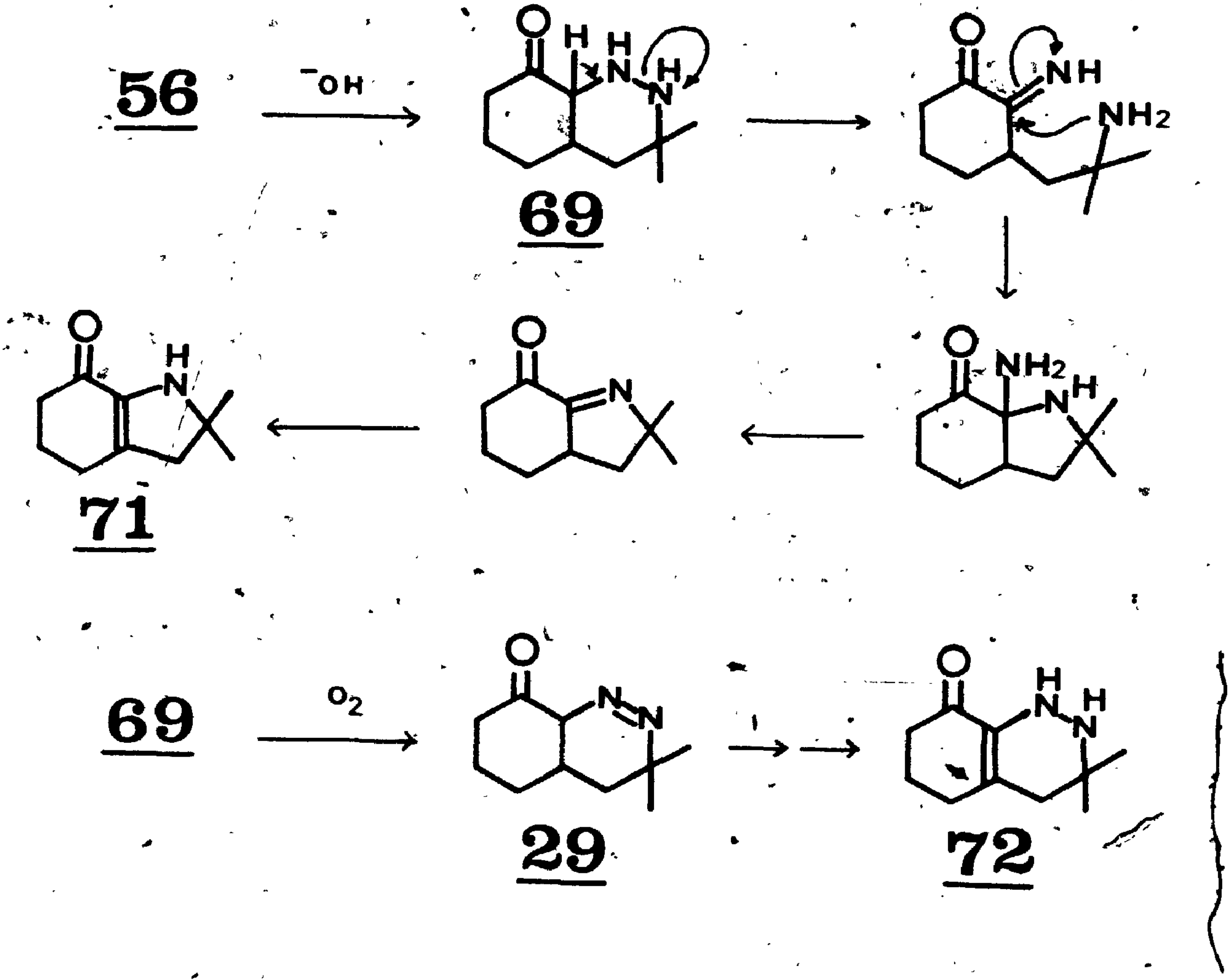


70

(30)

carbonyl group expected for 69. Instead, an absorption corresponding to α-aminoenone (71) was observed (1655 and 1603 cm^{-1}). The pmr showed a sharp singlet for the geminal methyl groups, implying that a plane of symmetry existed in the product. Two possible structures, 71 and 72, were considered for this product, based on the above data (Scheme 11). The cleavage of the N-N bond of 69 (a probable intermediate) and subsequent closure to form a five membered ring would lead to 71. Alternatively, the product might be 72, the formation of which would require the oxidation of 69, possibly by oxygen, during the hydrolysis or the isolation. When the reaction and

SCHEME 11.



isolation were conducted with the strict exclusion of oxygen, the reaction yielded the same product. This fact suggested that the structure of the product was 71 rather than 72. Attempts to isolate the compound by means of preparative tlc and distillation were unsuccessful.

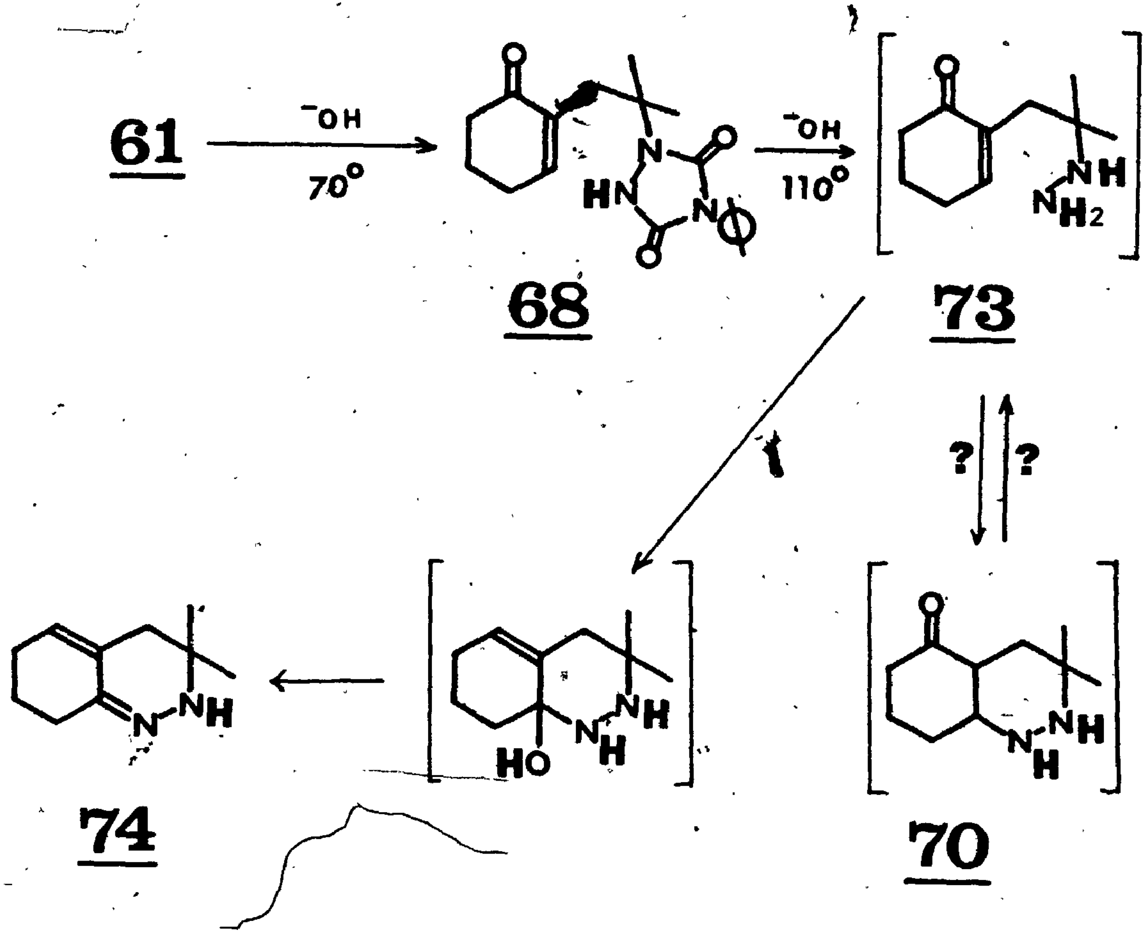
The hydrolysis of 61 at 70° (2 days) using potassium hydroxide in methanol and water, gave 68 as the only product

(Scheme 12). This substance (not isolated in pure form) had a β-vinylic proton of α,β-unsaturated ketone at 6.80 ppm (triplet, J=4.0 H_z), implying that the cleavage of the β-(C-N) bond, in 61 had occured. The geminal methyl groups gave a sharp singlet (1.47 ppm), supporting the previous assignment.

When the hydrolysis temperature was raised to 110-115° (84 hours), a new product was formed together with aniline. This compound was very sensitive to air and was isolated only in the absence of oxygen. It was obtained as colorless cyrstals, mp 54.0-56.0°, upon removing the by-product, aniline, by distillation. Its physical properties were measured either under nitrogen or in degassed solvents. This compound did not show any carbonyl group at all, thereby excluding the structure 70. It showed a molecular ion peak at m/e 164 corresponding to structure 74, and had an NH group (3340 and 3260 cm^{-1}) and a trisubstituted olefin (a vinylic proton at 5.65 ppm, multiplet). The conjugated nature of this olefin was apparent from its uv spectrum (λ_{max} 225 and 287 nm). Based on these data, the tentative structure 74 was assigned to this substance (Scheme 12).

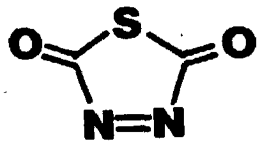
These results clearly showed that under these strongly basic conditions, the formation of either 69 or 70 could not be achieved; the basic conditions were

SCHEME 12

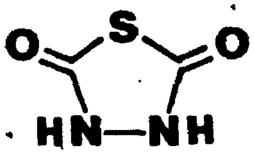


necessary for the hydrolysis of the urazole, but too severe for the survival of the probably formed initial products (69, and 70 or 73). A dienophile was required from which the hydrazines could be generated under milder conditions.

Very recently, Corey and Snider reported the synthesis of 1,3,4-thiadiazoline-2,5-dione (75) and its use as a dienophilic reagent (72). The advantage of this dienophile was that the resulting thiaurazoles were very readily hydrolysed to hydrazines. For example, relatively

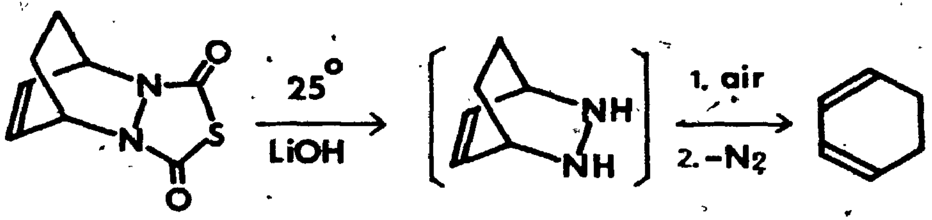


75



76

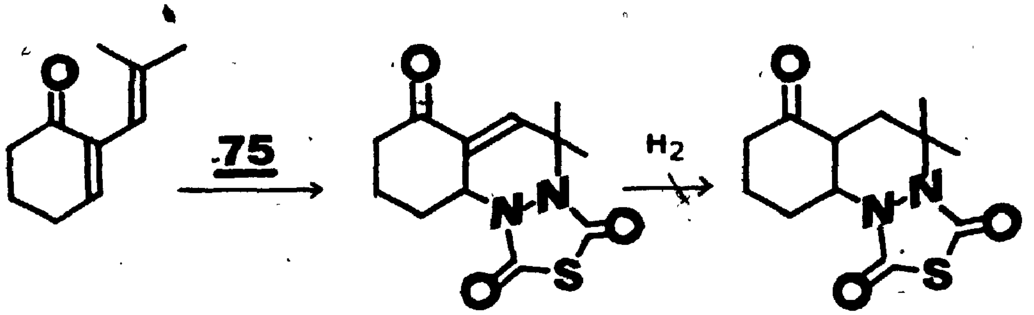
mild conditions (0.1 N lithium hydroxide in water-diglyme at 25°) were sufficient for the hydrolysis shown in reaction 31. The disadvantage of this dienophile was that



(31)

it was only stable at low temperatures (<-20°). Following the procedure of Corey and Snider, 75 was prepared, in situ, from 1,3,4-thiadiazolidine-2,5-dione (76) (72) and the Diels-Alder reaction between 31 and 75 was attempted.

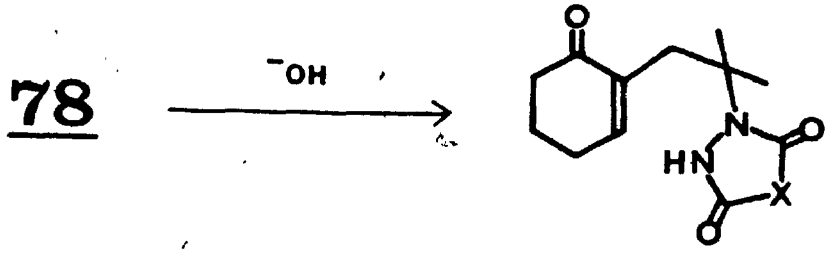
Unfortunately, the diene was found to be unreactive at the low temperature. In contrast, the other dienone (32) reacted smoothly even at -78°, to yield an adduct (77), mp 155.5-160.0° (reaction 32). This adduct showed a similar pmr spectrum as that corresponding to the triazoline dione adduct (62) with the exception of the aromatic protons. Upon hydrogenation, 77 gave 78, mp 124.0-125.0° (reaction 32). This compound had the expected molecular ion peak (m/e 268) and showed a similar pmr spectrum to that of 61. This substance was believed to be a single stereoisomer, because only one pair of methyl signals (1.41 and 1.81 ppm) was observed. Its stereochemistry was not investigated.



(32)

32 **77** **78**

Upon basic hydrolysis (LiOH, water-THF) at room temperature (2 hours), 78 disappeared completely and a new compound (79) appeared. This product was not the expected basic material (70). It showed a sharp singlet for the geminal methyl groups (1.53 ppm), and a triplet for the β-vinylic proton of an α,β-unsaturated carbonyl group (6.88 ppm, J=4.0 $\mathrm{H_z}$). The structure 79, with either



79 X = S or O

(33)

a thiaurazole (X=S) or oxaurazole (X=O) moiety, was assigned to this substance (reaction 33): the oxaurazole might have been produced from the corresponding thiaurazole by sulfur-oxygen exchange under the basic conditions. Compound 79, upon treatment with acid, gradually disappeared, and was replaced by a compound which had an identical pmr spectrum to that of the starting material (78). This substance (not isolated in pure state) was most probably either 78 itself or its oxygen analogue.

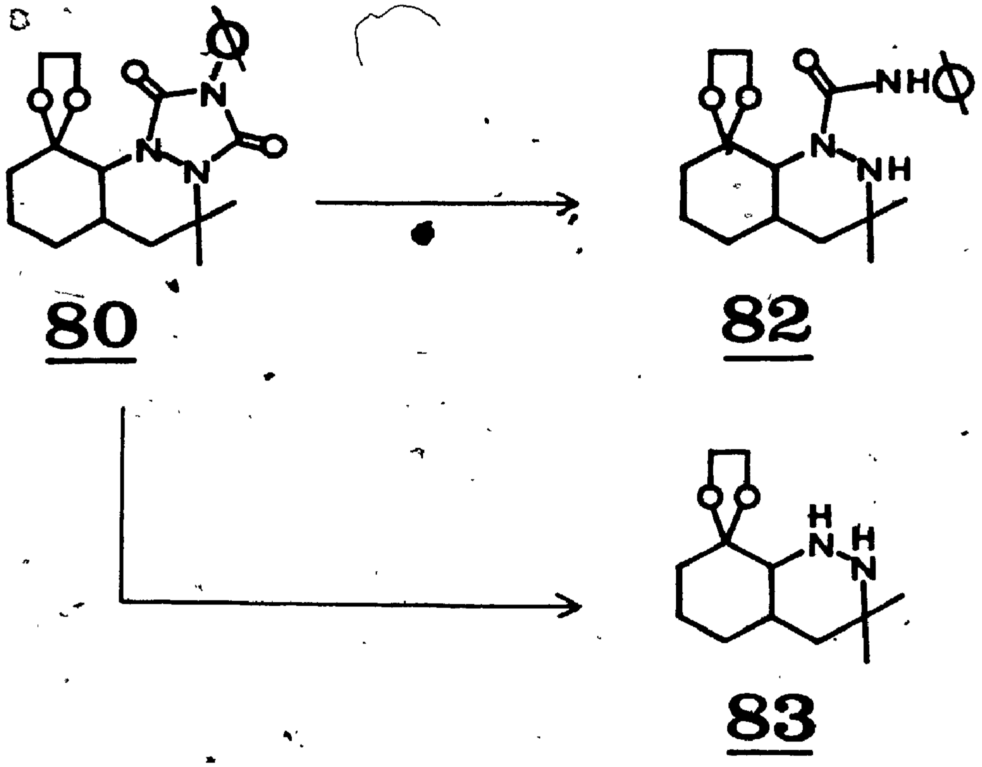
When the hydrolysis of 78 was conducted at a higher temperature (55°), a new methyl signal (1.27 ppm) appeared (other than those of 78 and 79) and no change in the methyl signals occured when the reaction mixture was exposed to air for one week. The new substance was probably not the required product (70). At still higher temperature (105°), the hydrolysis yielded an air-sensitive compound as the sole product. This was identified as 74 by comparison of its pmr spectrum with that of an authentic sample.

Because the direct approach to the generation of 70 by basic hydrolysis failed, an alternative approach was required.

APPROACHES USING A PROTECTED KETONE FUNCTION: 1) KETALIZATION

Ketones 56 and 61 were converted to the corresponding ethylene glycol ketals, 80 (mp 170-171.0°) and 81 (mp 137.5-139.5°), respectively. The ketals (80 and 81) showed a pair of methyl signals at 1.31 and 1.76, and 1.34 and 1.80 ppm, respectively. No other methyl signals were observed. This, and the sharpness of their melting points, implies that both are pure stereoisomers. The ketal 80 is a probably trans-fused diazadecalin, since it comes from a trans precursor 56. On the other hand, the stereochemistry of the ketal 81 is not known.

Basic hydrolysis of 80 using potassium hydroxide in aqueous methanol (refluxing conditions) gave 82 as the only product (reaction 34). Aniline was not detected at all. This substance, 82, mp 152.0-152.5°, had an NH



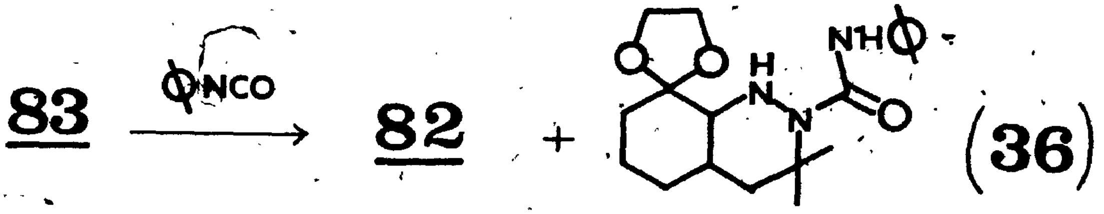
(34)

(35)

(4.35 ppm, a D_2O exchangable broad singlet, and 3350 and 3240 cm^{-1}) and an NHCO (8.70 ppm, a D_2O exchangable singlet and ν_{max} 1665 cm^{-1}). The continuing presence of the ethylene ketal (ca. 3.80 ppm, 4H) and the geminal methyl groups (0.97 and 1.14 ppm) were apparent. The structure 82 was assigned to this substance. The isomeric structure 84 (see reaction 36) could not be discarded at this stage. However, facts which justify this decision will be presented in a later section.

When the hydrolysis was performed at a higher temperature (150°) in an inert atmosphere, <u>82</u> was further hydrolysed to <u>83</u> and aniline (reaction 35). Compound <u>83</u>, being air-sensitive, the hydrolysis and isolation as well as the spectroscopic measurements had to be carried out either under nitrogen or under reduced pressure. Upon distillation of the aniline under reduced pressure, <u>83</u> was isolated as a colorless liquid. This substance did not have a carbonyl group and showed the expected spectroscopic properties for <u>83</u>: two deuterium exchangable NH protons at 3.7 ppm, and ν_{max} 3360, 3260 and 3180 cm^{-1} (73). The methine proton on carbon bearing nitrogen appeared at 2.63 ppm as a broad doublet (J=5.0 H_z). The ethylene ketal was still present (ca. 3.99 ppm, 4H). However, the appearance of the geminal methyl groups as a sharp singlet (1.14 ppm) was rather puzzling, since they were supposedly non-equivalent methyl groups. Hence, to confirm the structure, reaction with phenylisocyanate was carried out.

Addition of a degassed solution of phenylisocyanate to <u>83</u> under reduced pressure gave two products, their ratio being 1:2. The minor product was identified as <u>82</u> by comparison of its mp, ir and pmr spectra with those of an authentic sample obtained by hydrolysis of <u>80</u>. The major product showed a similar pmr spectrum to that of <u>82</u>: NH (a D_2O exchangable proton between 3.8 and 4.1 ppm), NHCO (a D_2O exchangable broad singlet at 8.87 ppm), ethylene ketal (3.8-4.1 ppm, 4H) and geminal methyl groups (1.47 and 1.58 ppm). The isomeric structure 84



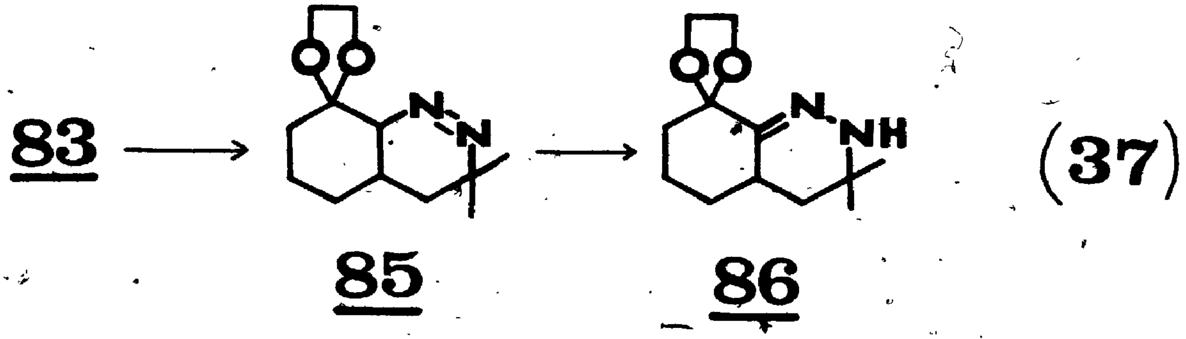
84

(36)

was assigned to this substance (reaction 36). The location of the CONHϕ group was clearly shown by the triplet nature (J=7.0 H_z) of the methine proton (3.21 ppm) on carbon bearing the NH group in 84, which became a doublet upon addition of D_2O. This requires that the other isomer be 82 as previously indicated.

The formation of both 82 and 84 from 83 strongly supported the structural assignment of 83. The sharp singlet of the geminal methyl groups observed in 83, therefore, must have been due to coincidental identity of chemical shift for the two methyl groups.

When a colorless degassed solution of a mixture of 83 and aniline was exposed to air, a yellow color developed immediately. The pmr spectrum of this yellow solution showed the appearance of a new pair of methyl signals (1.19 and 1.50 ppm) for 85 as well as the methyl signal of 83. When this solution was kept at room



temperature for one day, 83 disappeared completely and a new pair of methyl signals (those for 86) appeared at 1.06 and 1.11 ppm, those for 85 still being present. Their ratio (85/86) was 1:1. Similar results were obtained using oxygen instead of air.

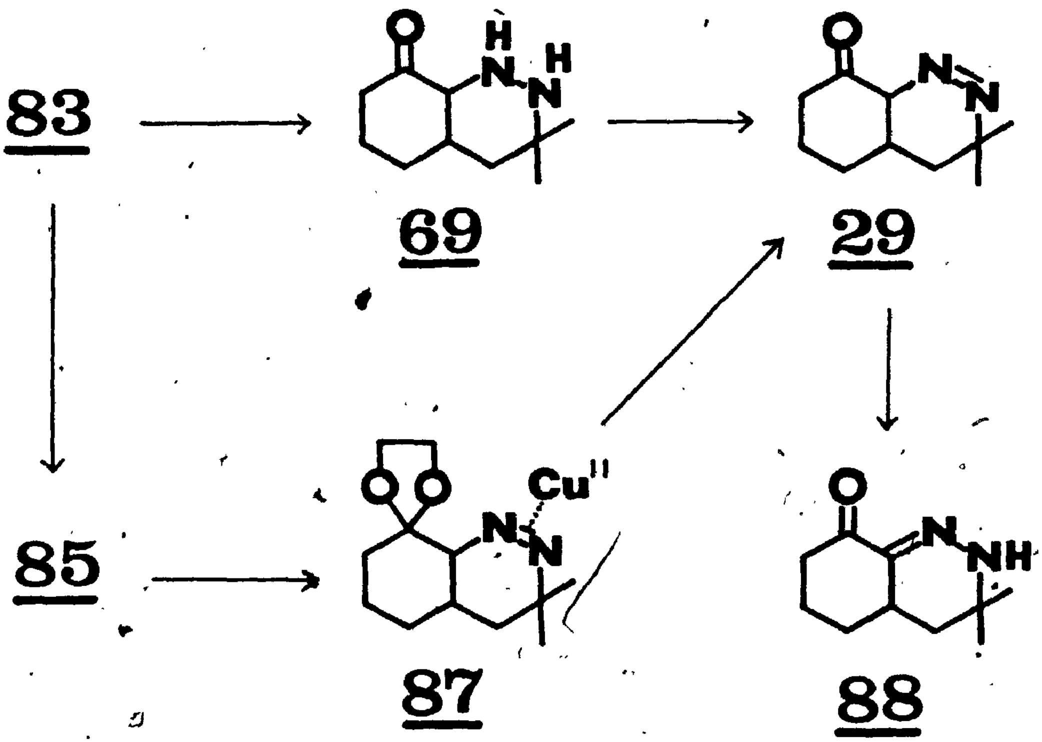
Hydrazines are known to give the corresponding azo compounds readily upon oxidation (55, 57). Facile isomerization of azo group to hydrazone by the action of acid, base or heat is also well-documented in the literature (55, 57, 74). For this reason, compounds 85 and 86 were assigned the structures indicated (reaction 37).

The above oxidation reactions did not provide an efficient route to 85; it was inevitably accompanied by 86. In order to obtain 85 cleanly and minimize the catalytic action of the base present, quick oxidation of 83 was required. This was achieved using mercuric oxide as the oxidant. Upon addition of mercuric oxide to a solution of 83 and aniline, 83 disappeared quickly (pmr spectrum) and 85 appeared without apparent contamination by 86. The aniline signals remained unchanged. Compound 85 showed nine protons between 1.1 and 2.0 ppm and five protons between 3.9 and 4.1 ppm, other than the methyl signals. The methine proton on carbon bearing the azo group was not apparent and was presumably beneath the signal of the ethylene ketal. All attempts to isolate this substance in its pure state were unsuccessful, because contamination with 86 took place during this isolation.

Compound 86 was also formed when 83 was subjected to preparative tlc in air. The isolated 86 was obtained as colorless crystals, mp 129.0-130.0°. The yield was 86%, based on the amount of 80 consumed. This substance showed the expected molecular ion peak at m/e 224 and had C=NNH (ν_{max} 1634 and 3300 cm^{-1}) (75). The broad signal of the NH appeared at 4.92 ppm and the uv absorption corresponding to the hydrazone was also observed at 213 nm (ε 4700) and 239 nm (ε 5100) (76).

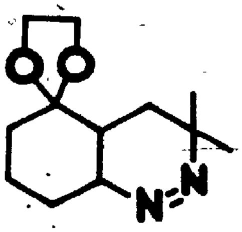
The approach to the synthetic target (29) from 83 requires the removal of the ketone protecting group. The hydrolysis of the ketal could be achieved, in principle, in two ways: direct hydrolysis of <u>83</u> leading to <u>69</u>, or hydrolysis of <u>85</u> after oxidation of <u>83</u>. The latter case

SCHEME 13



obviously requires suitable protection of the azo group, since <u>85</u> would immediately isomerize to <u>86</u> under the acidic conditions required for the hydrolysis. This protecting group would have to be removed under near neutral conditions in order to prevent the facile isomerization of <u>29</u> to <u>88</u> (Scheme 13). One possibility might be conversion of 85 to its cupric complex (87). The formation of this type of complex is well-illustrated in the literature (55, 56, 77) and such complexes regenerate the azo group upon treatment with a weak base (e.g., an amine) at low temperature.

However, this latter route to 29 was not attempted, because the isomeric azo compound 89 failed to give the

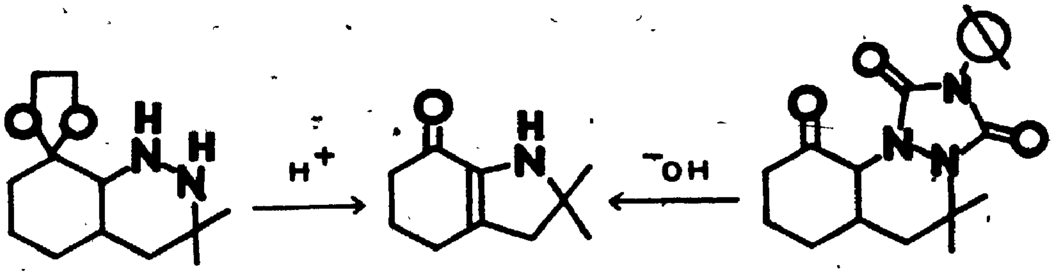


89

corresponding cupric complex upon treatment with cupric chloride (see later section). Therefore, the other route to 29, direct hydrolysis of 83, was investigated with the hope of obtaining 69, which could be easily converted to 29 under neutral conditions.

Upon acidic hydrolysis (HCl, 55°) in an inert atmosphere, 83 yielded a single compound. Unfortunately this product was not the hoped-for 69, but was identified as 71 by comparison of its pmr spectrum with that of an authentic sample obtained by basic hydrolysis of 56.

(reaction 38). When the hydrolysis was conducted under



83 **71** **56** (38)

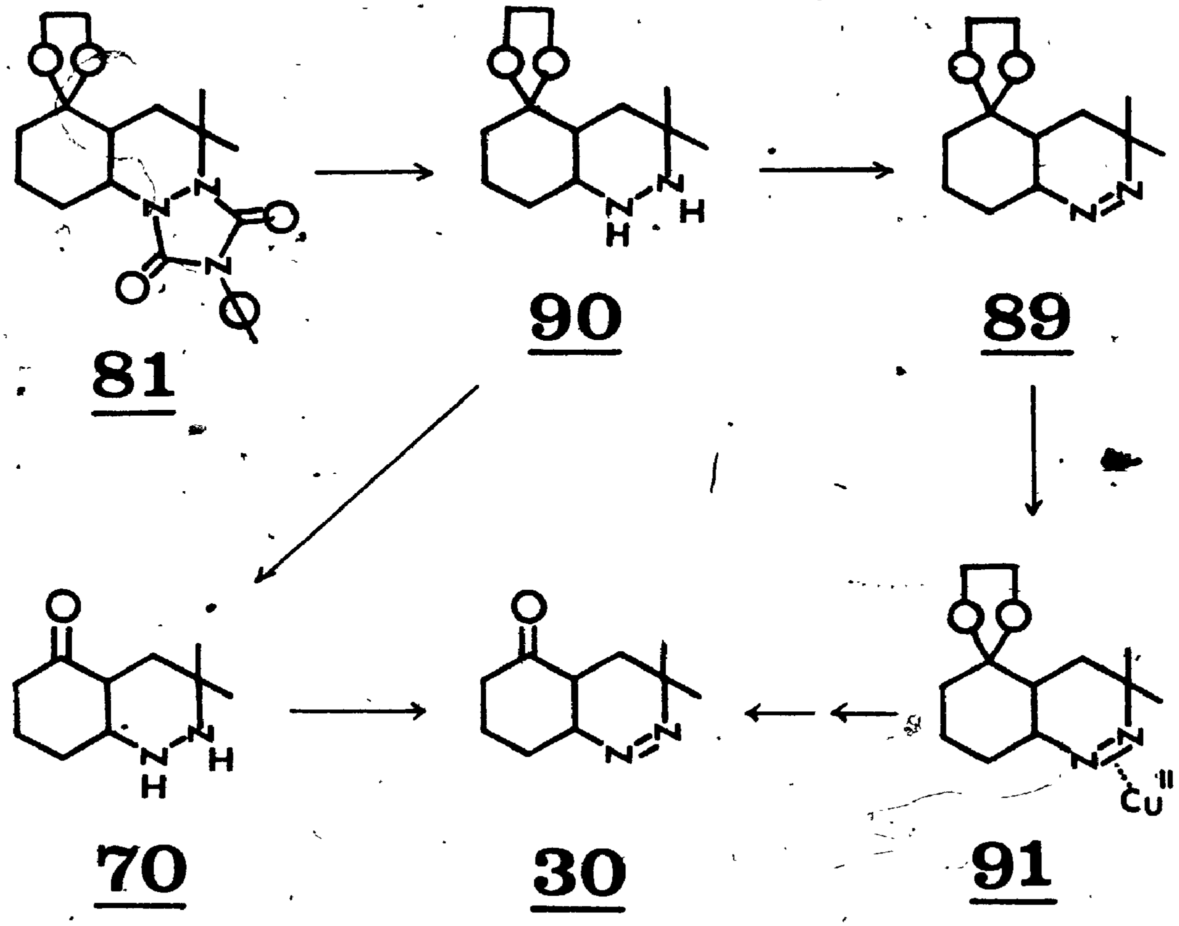
milder conditions (AcOH, 80-85°), the same product was obtained together with starting material. A similar rationale for the formation of 71 to that shown in Scheme 11 is probably applicable.

These results clearly indicated that 69, the direct precursor of the final target (29), could not be synthesized under acidic or basic conditions. The synthesis of the precursor had to be achieved under conditions as neutral as possible.

The synthetic work toward the azo-ketone 29 was stopped at this stage, and synthetic efforts were directed toward the other target, azo-ketone 30. The planned synthetic sequence was similar to that for the synthesis of 29 and is outlined in Scheme 14.

Basic hydrolysis (KOH, 150° under nitrogen) of

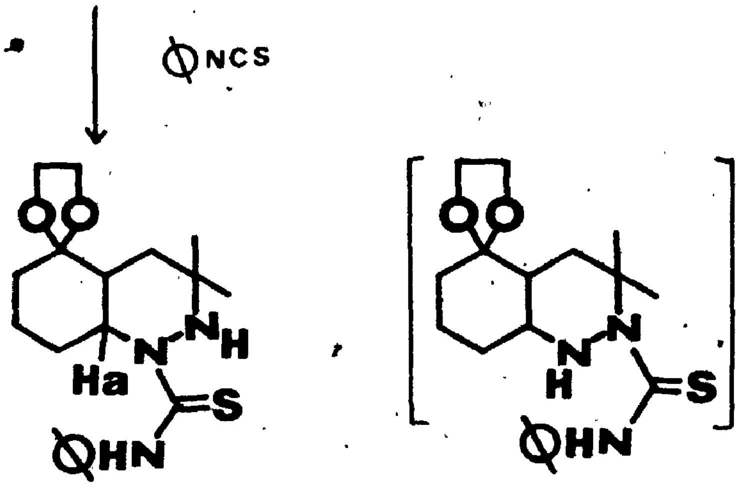
SCHEME 14



compound 81 gave 90 and aniline as the only products. The aniline was removed from the mixture by a series of vacuum distillations, to give 90 as colorless crystals, mp 70.0-71.0°. These crystals changed to a pale yellow liquid upon exposure to air. The physical constants for this air-sensitive compound were measured either under nitrogen or in degassed solvents. This substance had the expected spectral properties for 90: two NH groups (a broad singlet of two D_2O exchangable protons at 3.34 ppm, and ν_{max} 3200 cm^{-1}), and two methine protons which coupled mutually with J=5.0 H_z (2.05 ppm, a broad doublet of triplet with J=13.0, 5.0 and 5.0 H_z, and 2.91 ppm, a broad doublet of triplets with J=12.0, 5.0 and 5.0 H_z). The ethylene ketal appears at 3.90 ppm as a singlet and the geminal methyl groups at 1.05 and 1.13 ppm.

The hydrazine (90) reacted rapidly with phenylthioisocyanate to give a crystalline product (reaction 39). This substance, mp 225.0-226.0°, had a molecular ion peak (m/e 361) corresponding to 92 (or 93). The NH proton appeared

90



92 **93**

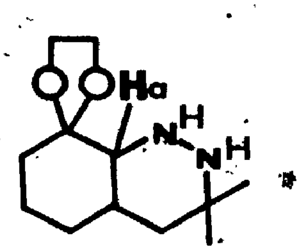
(39)

at 3.38 ppm as a singlet and the NHCS proton appeared at 9.74 ppm as a broad singlet. The two methine protons appeared at 2.24 and ca. 5.84 ppm and their mutual coupling constant was 5.2 H_z (by double irradiation). The presence of the geminal methyl groups (1.14 and 1.24 ppm), ethylene ketal (ca. 3.95 ppm, 4H) and aromatic protons (7.1-7.6 ppm, 5H) was apparent. The structural differentiation between 92 and 93 was achieved by comparing the chemical shifts (methyl groups and Ha) of the compounds which are listed in Table 1.

When the CONH group was α to the geminal methyl groups as in 84, the chemical shifts of the methyl groups (1.47 and 1.58 ppm) were much closer to those of 80 and 81 (1.31-1.80 ppm) than to those of 83 and 90 (1.05-1.14 ppm). In contract, the chemical shift of Ha (3.21 ppm) was rather close to those of 83 and 90 (2.91 ppm) than to those of 80 and 81 (4.35-4.45 ppm). The reversed situation was apparent when the CONH group was located β to the geminal methyl groups, as in 82. Here, the chemical shifts of the methyl groups (0.97 and 1.14 ppm) were in range similar to those of 83 and 90, while the chemical shift of Ha (4.64 ppm) was similar to those of 80 and 81. The fact that the phenythioisocyanate adduct (reaction 39) had Ha at ca. 5.58 and the methyl groups at 1.14 and 1.24 ppm, clearly implied therefore that this compound had structure 92 rather than 93. This conclusion

Table 1

(Chemical Shifts in ppm)



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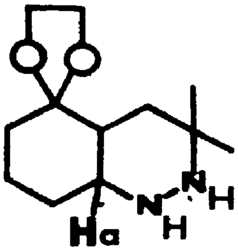

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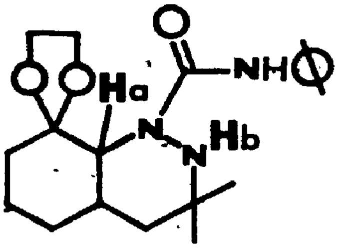
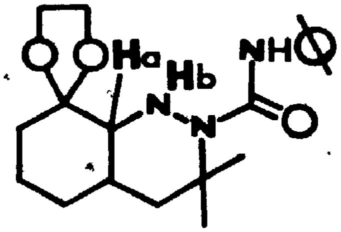


82

	83	90	82
Ha	2.91	2.91	4.64
Me	1.14 (6H)	1.05, 1.13	0.97, 1.14



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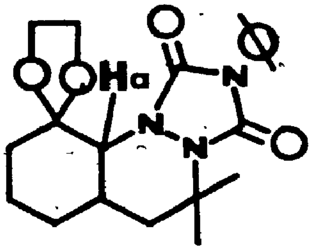

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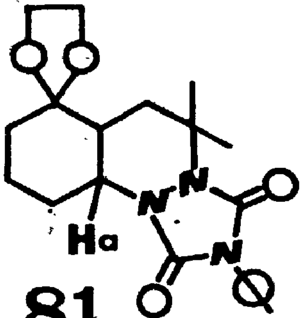
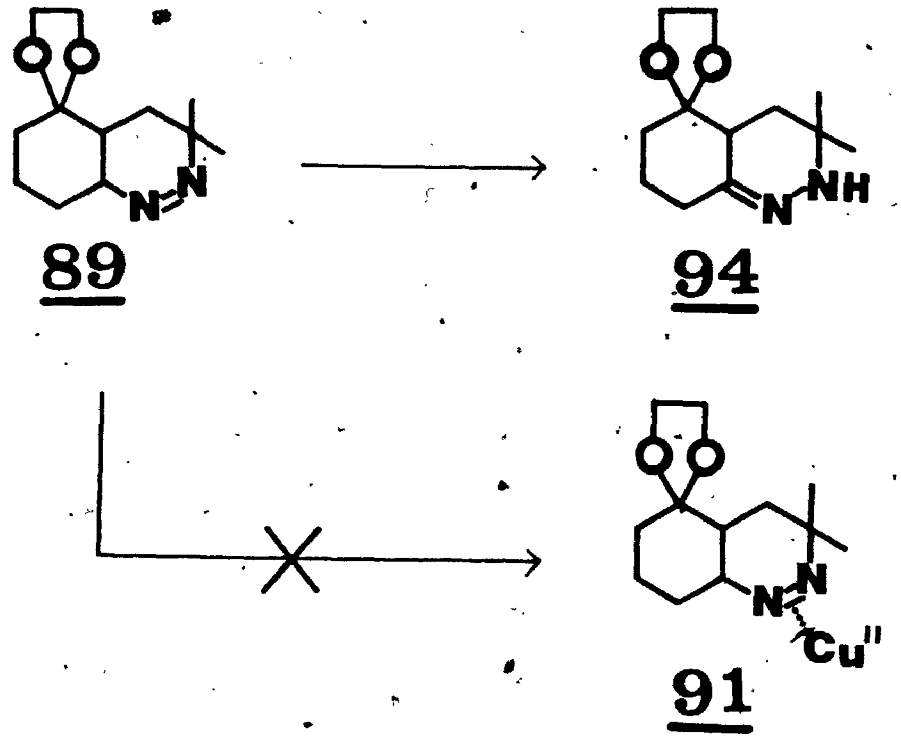


81

	84	80	81
Ha	3.21	4.35	4.45
Me	1.47, 1.58	1.31, 1.76	1.34, 1.80

was substantiated by the singlet nature of the NH proton (3.38 ppm).

Air oxidation of <u>90</u> slowly led to the formation of the corresponding azo compound (<u>89</u>). The same compound was rapidly formed when mercuric oxide was used as the oxidant. Upon distillation, compound <u>89</u> was isolated as pale yellow crystals. These crystals melted at 49.0-52.0° and rapid further heating (to ca. 120°) resulted in the



89 **94** (40)

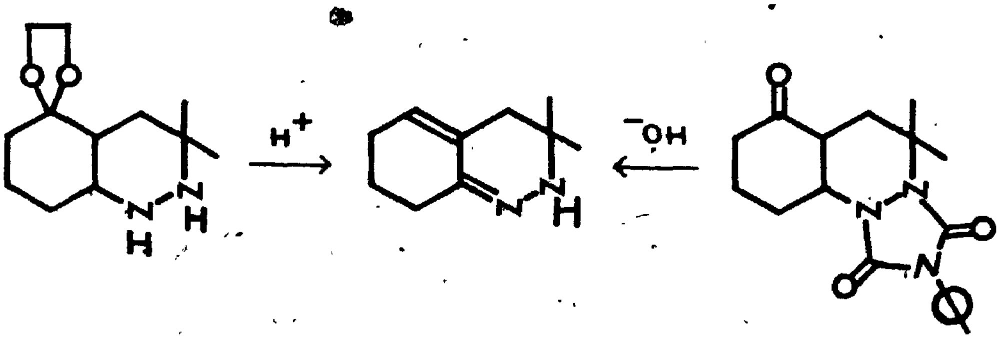
91 (41)

evolution of gas, presumably nitrogen. The mass spectrum did not show a molecular ion peak, presumably because of this facile elimination of nitrogen. This substance had uv absorption at 363 nm (ε 140) which is characteristic of an azo group contained in a six-membered ring (78).

The azo compound (89) was surprisingly resistant to isomerization to the corresponding hydrazone. Even in the presence of pyridine, it took about two months (at ca. -15°) to convert 60% of 89 to 94 (reaction 40). However, upon addition of p-toluenesulfonic acid at room temperature, the conversion was rapid. Compound 94, mp 119.0-120.5°, upon exposure to air, very slowly turned dark brown. The crystals had the expected molecular ion peak (m/e 224) and the characteristic absorption of a hydrazone group [at 211 nm (ε 3800) and 235 nm (ε 4700)] (76). Upon slow heating of 89 to above 120° (the change from 52° to 110° taking 20 minutes), there was no evolution of nitrogen, and it is presumed that rearrangement to the hydrazone 94 occured more rapidly.

The conversion of 89 to its cupric complex (91) was attempted (reaction 41), but instead of the expected red precipitate of the complex, the formation of a dark brown tar was observed. The reason for this is not clear at the present time.

Attempts to generate 70 (Scheme 14) by acidic hydrolysis of 90 were made. Upon Hydrolysis (HCl, room temperature under nitrogen) of 90, an air-sensitive compound was produced. This compound did not show the expected carbonyl group of 70 in its ir spectrum, and was identified (pmr, ir) as the conjugated hydrazone 74, previously obtained by basic hydrolysis of 61 (reaction 42). Compound 70 (or its equivalent compound 73) was probably



(42)

90 74 61

an intermediate in the formation of 74 in a mechanism similar to that in Scheme 12.

These results showed that compound 70, the direct precursor for the synthetic target (30) could not be generated under acidic or basic conditions. A protecting group which could be removed under neutral conditions was required.

APPROACHES USING A PROTECTED KETONE FUNCTION: 2) A PHOTOLABILE PROTECTING GROUP

The potential carbonyl group to be useful in the present synthesis must satisfy at least two conditions: the group must be stable under strongly basic conditions; and the conversion to carbonyl function must be achieved under neutral conditions. There are several functional groups known to fulfil these requirements. A few examples are shown in the following equations 43-45. Reactions 43 and 44 involve the use of oxidizing reagents, e.g., oxygen, triazolinedione (54) (≠) and mercuric chloride, in the carbonyl generation step, whereas reaction 45 does not. The use of oxidants, in the present system, is precluded because oxidation of a hydrazine to an azo compound is expected to be faster than that of an alcohol to a ketone. Rearrangement of the azo group to the hydrazone would

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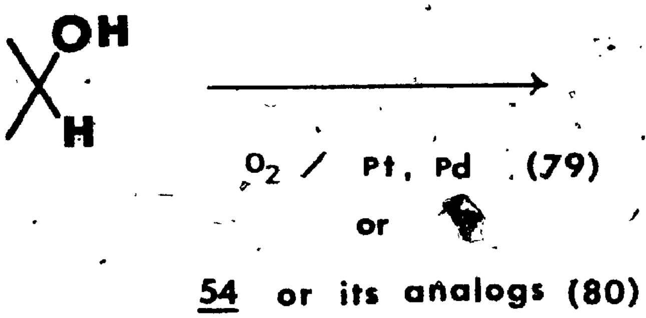
≠An attempted oxidation of alcohol 95 (see text) to ketone 61 using the triazolinedione was unsuccessful (see Experimental).



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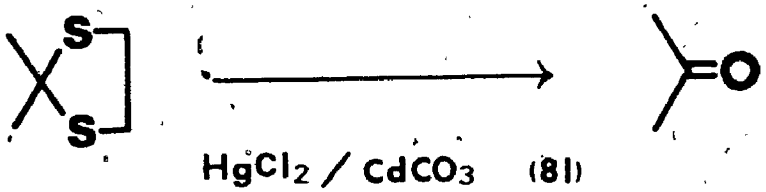

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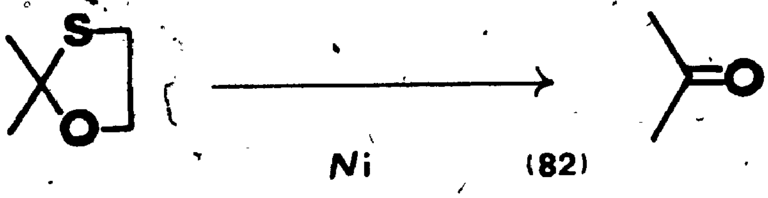
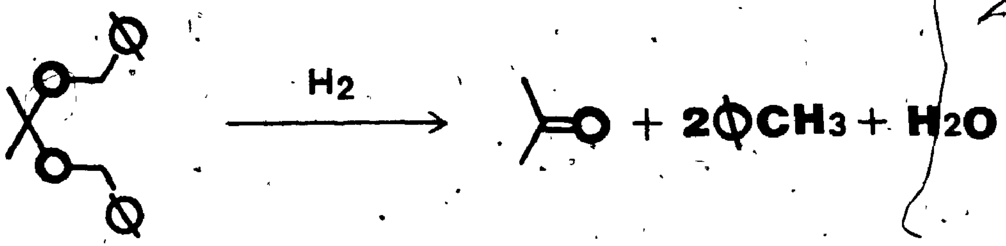


(45)

presumably follow rapidly. In reaction 45 which does not need any oxidant, the yield of ketone is variable and may be rather low (20-70%) (82).

For these reasons two new kinds of carbonyl protecting groups (equations 46 and 47) were devised. In addition a recently developed protecting group by Hebert and Gravel (equation 48) (83) was considered.

The first is simply an application of the well-known facile hydrogenolysis of benzylic ethers (84). The second is an application of the well-known photo-type II



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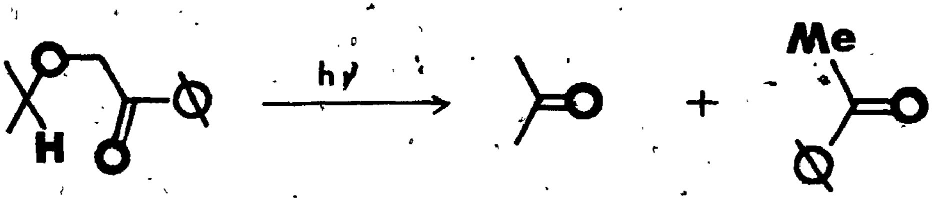

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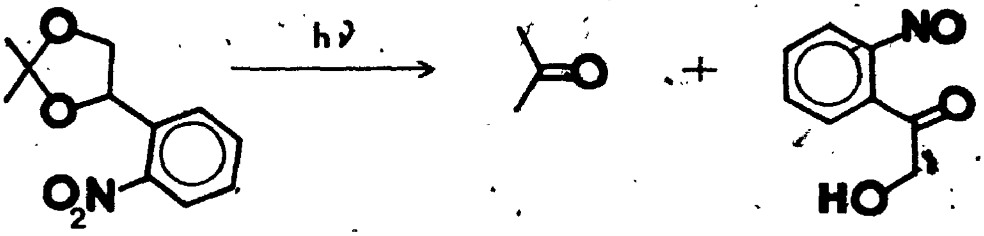
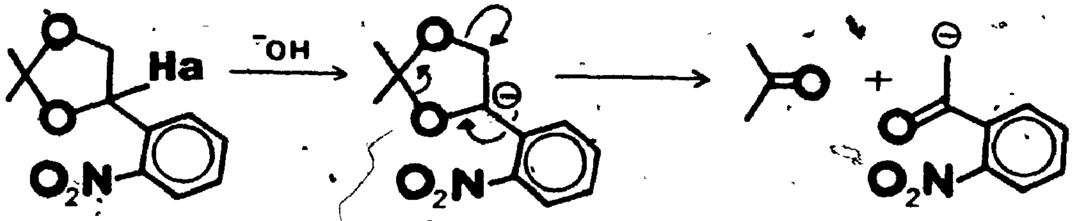


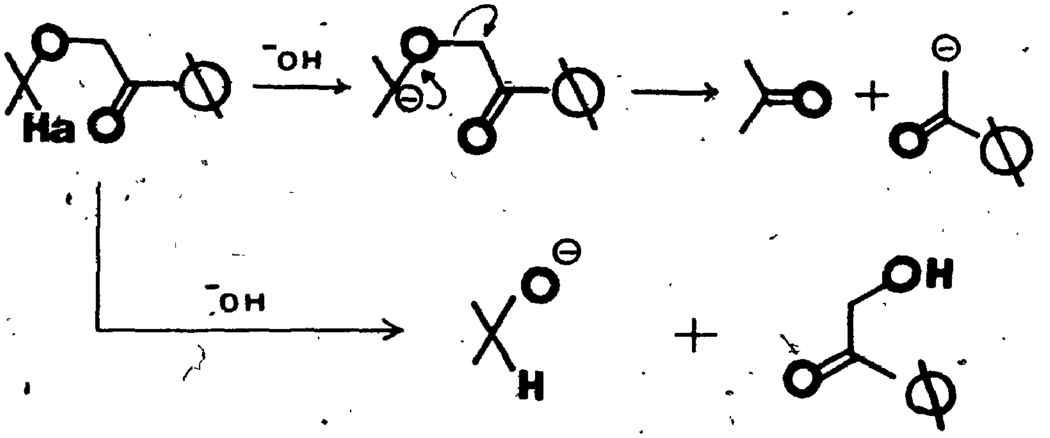
(48)

cleavage of phenyl ketones (34, 85). The third is mechanistically similar to the second since it involves r-hydrogen abstraction by a photo-activated functional group.

However, the hydrogenolysis may introduce a real possibility of competitive hydrogenolysis of the N-N bond of the hydrazine (86). The third reaction carries the danger of reaction of the hydrazine with the photo-formed nitroso group (87). It is also possible that the protecting group would not survive the strongly basic conditions required, because of elimination process shown in reaction 49. The α-alkoxyacetophenone (equation 47) could also suffer possible cleavages (equations 50 and 51) under these conditions. However, the danger seems less



(49)



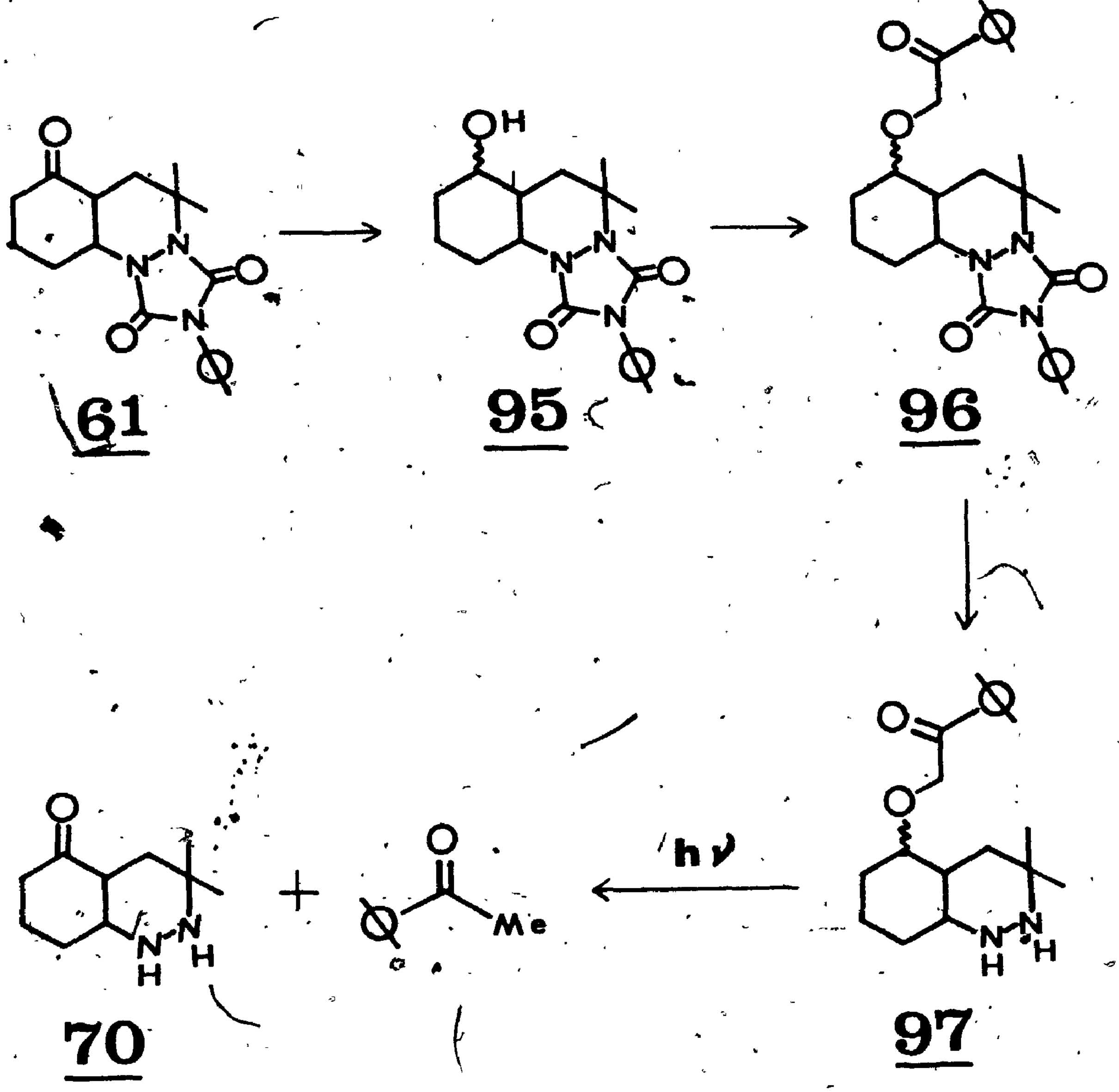
(50)

(51)

than that of the former case, because the acidity of Ha is lower in the acetophenone (reaction 50), and because the alkoxide anion is a relatively poor leaving group (reaction 51). One obvious problem is that the Type II process is not a clean reaction, but is often accompanied by the formation of cyclobutanol derivatives (34, 85). There appears to be some control over the incursion of this reaction since it is disfavoured in certain solvents

(88). The planned synthetic scheme is illustrated in Scheme 15.

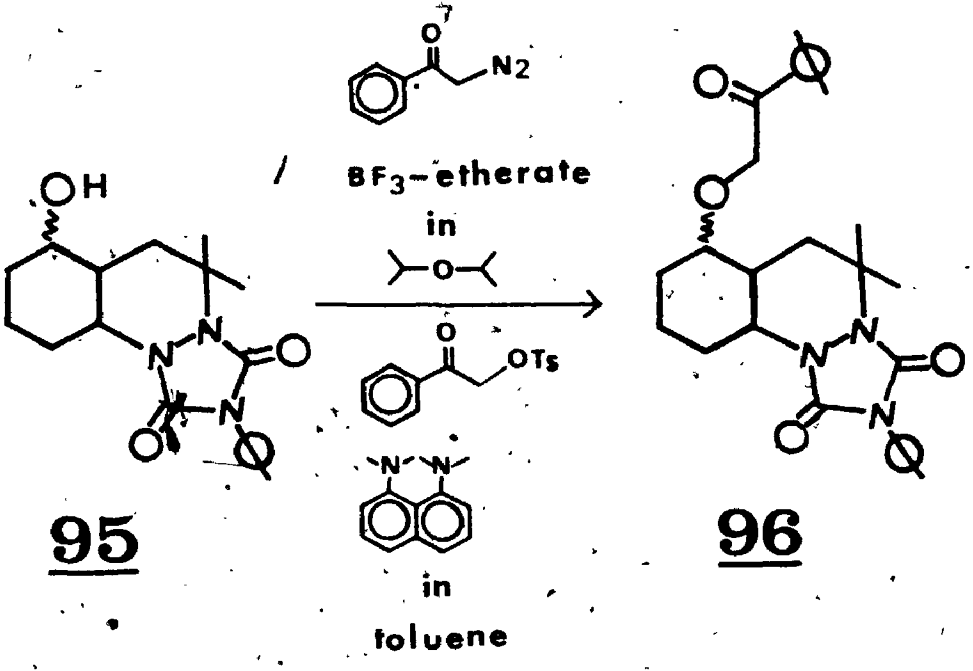
SCHEME 15



Upon sodium borohydride reduction, ketone 61 yielded alcohol 95, mp 153.0-154.0°. This substance showed the bands of the expected hydroxyl group (ν_{max} 3600 and 3460 cm^{-1}) and the urazole group (ν_{max} 1770 and 1710 cm^{-1}). This substance showed only one pair of the methyl groups in the pmr spectrum and the sharp melting point, implying that this was one of the two possible stereoisomeric alcohols and not a mixture.

Generally, when an α-alkoxyacetophenone is prepared from the corresponding alcohol and α-diazoacetophenone, a large excess of the alcohol is used in order to increase the yield (89). For the preparation of 96, only small amounts of alcohol 95 were available and therefore it was critical to find the optimum reaction conditions. A reasonably satisfactory procedure was found using diazoacetophenone and, in addition another, using α-tosyloxylacetophenone (reaction 52). Following these procedures, only equivalent amounts of alcohol 95 were required to produce 96 in ca. 65% yield. When in the first reaction ether or dioxane was used instead of diisopropyl ether as the solvent, the major product was not 96, but instead alkylation of the alcohol by the oxonium cation (produced from the ether) predominated. In the second reaction, if phenacyl bromide or chloride was used instead of tosyloxylacetophenone, it was found, as reported by others (90), that far less satisfactory results were obtained.

Compound 96 was thus obtained as colorless crystals, mp 58.5-60.0° and showed the expected molecular ion peak (m/e 448). The methylene protons on the carbon bearing the ether oxygen appeared as a AB quartet at 4.68 and 4.85



95

96

(52)

ppm (J=17.0 H_z). The methine protons, α to the ether group and α to the urazole, appeared at 3.56 and 4.16 ppm, respectively. The presence of the urazole moiety was apparent (ν_{max} 1765 and 1705 cm^{-1}).

This substance was subjected to basic hydrolysis (KOH, 100°, 37 hours) under nitrogen in order to obtain the corresponding hydrazine (97). Unfortunately, under the hydrolysis conditions, a mixture of products including aniline was obtained. The complexity of the reaction mixture was most likely due to two competing processes: cleavage of the ether linkage (as already shown in equation 50); and bimolecular condensation of the α-alkoxyl acetophenones (96 and 97) under the basic conditions. That such was occuring was suggested by the high (1:9) ratio of the benzoyl methylene to all aromatic protons in the pmr spectrum.

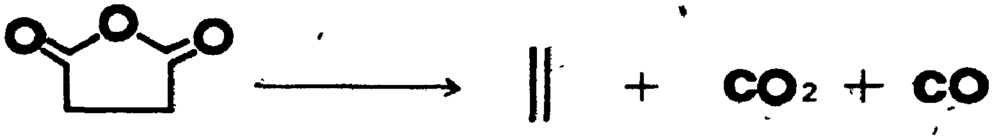
The use of the photo-labile protecting group, therefore, necessitates the generation of the hydrazine group in 97 under mild conditions. The use of the thiaurazole could allow this, but the possibility has not been tested.

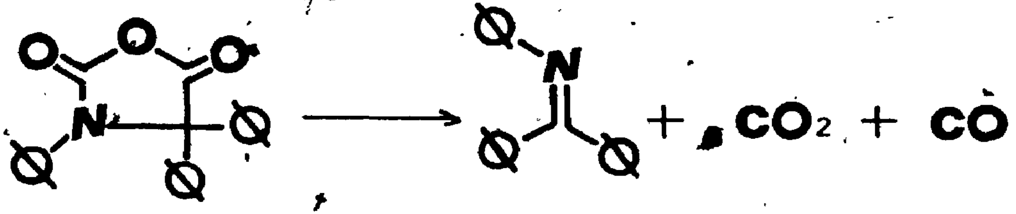
PHOTOLYSES OF THE THIAURAZOLE (78): ATTEMPTED SYNTHESIS OF THE AZO-KETONE (30)

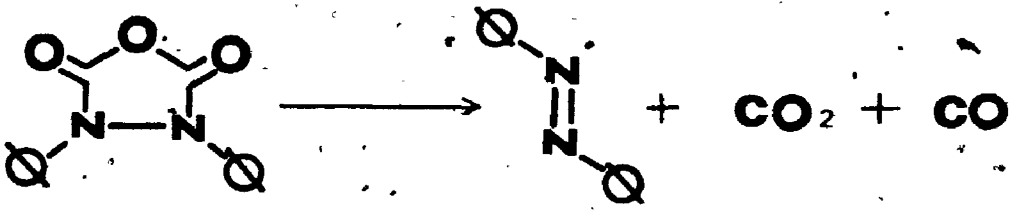
Since all acid and base induced reactions had failed, an attempt was made to find a photochemical way of generating the azo compound.

Acid anhydrides and its analogues are known to undergo photochemical degradation, and a few examples are illustrated in equations 53 (91), 54 and 55 (92). The present synthetic intermediates (56, 61 and 78) have similar structural features and, if similar photochemical degradations take place, the desired azo-ketones (29 and 30) may be obtained directly from these intermediates.

The uv absorption spectra of 56 and 61 are similar, both having strong absorption at 216-217 nm (ε 15500-16800), while that of 78 is slightly red shifted [223 nm (ε 5500)]. Since a convenient light source was available

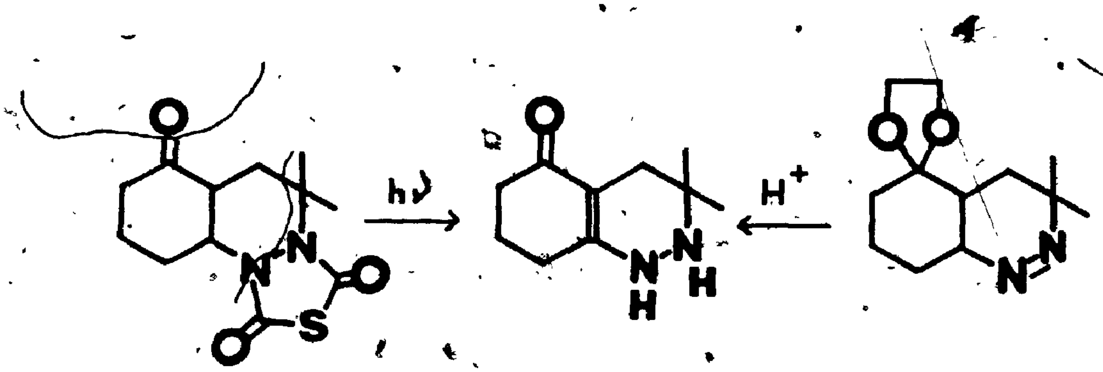

(53)


(54)


(55)

with λ_{max} 254 nm, the latter compound was chosen for irradiation. This compound had, at 254 nm, a larger absorption coefficient (ε 2200) as against ε 300 for the former compounds.

A degassed solution of <u>78</u> in acetonitrile-d_3 was irradiated in a quartz tube at ca. 7° for 53 hours. During the irradiation, colorless crystals appeared and accumulated on the reaction wall. The collected crystals, mp 202.0-204.0°, had a molecular ion peak (m/e 180) corresponding to the desired product (<u>30</u>), but did not show the expected saturated carbonyl group. Instead, this substance showed absorptions at 3400 and 1590 cm^{-1},



78 98 89

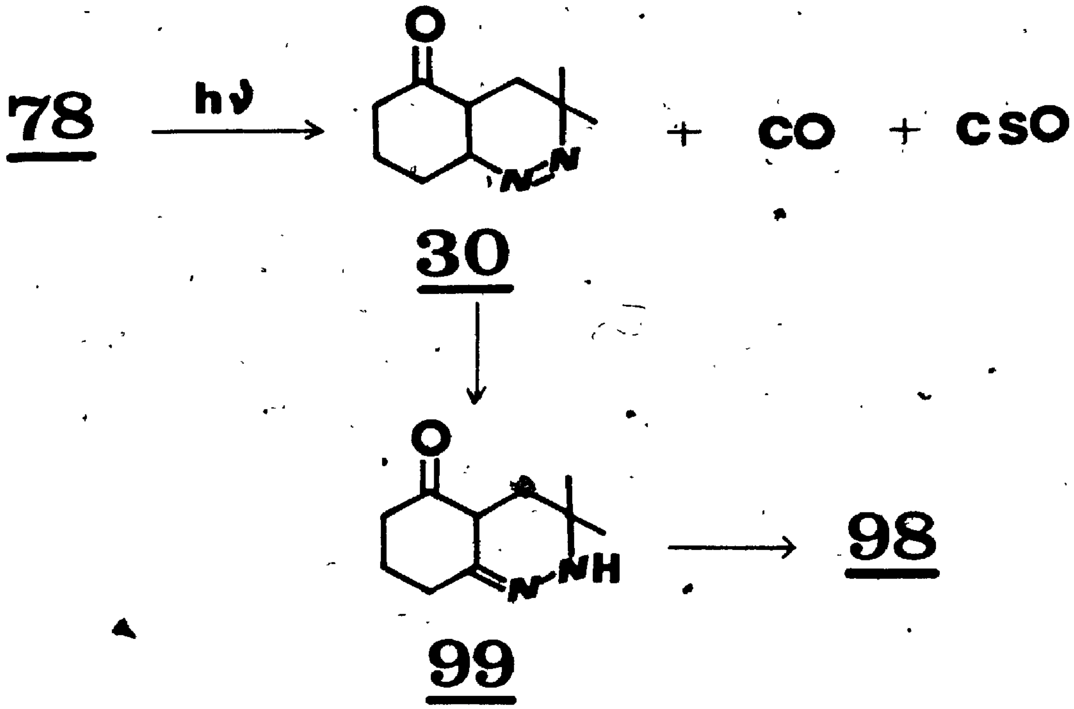
(56)

and at 223 nm (ε 1400) and 301 nm (ε 13000). These absorptions are similar to those of known β-amino-α,β-unsaturated ketones (93). The geminal methyl groups appeared as a sharp singlet (1.07 ppm), implying the existance of a plane of symmetry in this substance. Based on these data, the structure 98 was assigned to the product (reaction 56). The same substance was readily obtained when 89 was hydrolysed by acid.

When the irradiation was conducted in methylene chloride-d_2 at -78°, the same compound (98) was formed as the only product.

These results implied that the desired product (30) was formed, but, under the photolysis conditions, further transformation to 99, thence to 98 took place (Scheme 16). This type of photochemical isomerization of azo compounds to hydrazones has analogies in the literature

SCHEME 16



(94). Although the mechanism is presently not well-understood (44), there is a possibility that the isomerization is catalysed by acidic impurities which might have been present in the reaction system or produced during irradiation. If one could prevent this isomerization, the azo product (30) might be obtained, or, more likely, photochemical nitrogen elimination in 30 may take place. The latter process should lead directly to the formation of the HT-biradical (28) in its singlet state, if the excitation be direct or singlet-sensitized; or in its triplet state, if the reaction be triplet-sensitized. The latter biradical is the final target of the present synthesis.

Although the photochemical lability of such azo groups as that in 30 has been investigated using the azo-ketal 89 (see below), the irradiation conditions, under which the isomerization (30 to 99) could be surpressed, have not yet been found.

When a degassed solution of 89 in methylene chloride-d_2 was irradiated (Pyrex) for 15 hours at ca. -20°, isomerization of 89 to the corresponding hydrazone (94) again took place instead of the expected nitrogen elimination. This isomerization was accelerated when the irradiation was carried out at 0° in the presence of a trace of aniline (40 minutes). The results may well be due to the basic impurity (aniline) and/or some acidic impurities produced in the photolysis, perhaps from the solvent.

An attempt to eliminate nitrogen from 89 was undertaken using the photochemical sensitizer, acetone. Irradiation (Pyrex) of a degassed solution of 89 in acetone-d_2 (at -78°) for 24 hours led neither to the elimination of nitrogen nor to the isomerization to the hydrazone (94): only starting material was recovered. This was not investigated further.

Further investigations are clearly needed.

EXPERIMENTAL : PART TWO

GENERAL

Ir spectra were measured on Beckman IR-20A infrared spectrophotometer. Uv spectra were taken on Cary Recording Spectrophotometer. Pmr spectra were taken on Varian T-60 or HA-100 instruments with TMS as internal standard. Chemical shifts are reported in ppm unit and coupling constants (Hz) correspond to apparent splittings. Mass spectra and precise mass measurements were carried out on Varian M-66 spectrometer. Tlc and preparative tlc were performed using Silica Gel GF-254 (Merck) and for column chromatography Silica Gel 60 (Merck) was used, unless otherwise specified. Irradiations were carried out using a Hanovia 450 W medium pressure mercury lamp, unless otherwise mentioned. Melting points were measured on Reichert hot stage and are uncorrected. In the following description, isolation generally means extraction, washing, drying and distillation.

Preparation of 3-Isobutoxycyclohex-2-en-1-one (40)

Keton 40 was prepared following the general method reported by Eschenmoser et al for preparing 2-methyl-3-isobutoxycyclohex-2-en-1-one (61).

A mixture of 1,3-cyclohexanedione (10.1 g; Aldrich, 97% pure), isobutanol (20.0 ml), benzene (70 ml) and p-toluenesulfonic acid (p-TsOH) (0.5 g) was refluxed for 15 hours. During this time, water was removed continuously using a Dean — Stark apparatus. The reaction mixture, after cooling to room temperature, was poured into an ice-cold saturated solution of sodium bicarbonate. Isolation gave 40 as a slightly colored liquid, bp 102-103°/0.5 mm (13.9 g; 94%). This liquid was pure (pmr) and used without further purification.

Preparation of Isobutenyl Bromide

Isobutenyl bromide was prepared from 1,2-dibromo-2-methylpropane, following the procedure of Braude and Evans (95).

A solution of potassium hydroxide (58.0 g) in ethylene glycol (140 ml) was placed in a distillation apparatus equipped with a dropping funnel. To the well-stirred heated solution (140-150°) was added dropwise under nitrogen 1,2-dibromo-2-methylpropane (181.0 g). A distillate of bp 90-95° (116.5 g) was collected in an ice-cooled receiver. The distillate was washed successively with ice-cold aqueous sodium carbonate, dried ($CaCl_2$ and redistilled (nitrogen) to give isobutenyl bromide as a colorless liquid (86.2 g; 76%) bp 91.0-99.0°. [Lit. bp 91-92° (96), 90-91° (97), and 92° (95)].

Preparation of 3-Isobutenylcyclohex-2-en-1-one (31)

3-Isobutenylcyclohex-2-ene-1-one (31) was prepared following the general procedure of Normant (60).

Magnesium (48.5 g) and isobutenyl bromide (1.5 g) in 1.5 ml tetrahydrofuran (distilled over sodium) were placed in a flask under nitrogen. As soon as the reaction started (aided by a piece of iodine), a solution of isobutenyl bromide (26.5 g) in dry tetrahydrofuran (40 ml) was slowly added to the mixture. After the addition, the reaction mixture was cooled in ice and diluted with dry ether (20 ml, distilled over sodium). To this ice-cooled, well-stirred mixture, was added dropwise under nitrogen a solution of ketone 40 (13.9 g) in dry ether (25 ml). The reaction mixture was then allowed to warm to room temperature and stirred for 5 hours. The reaction mixture was then cooled in ice and acidified to pH3 (5% sulfuric acid). Isolation gave ketone 31 as a pale yellow liquid, bp 91-96°/0.8 mm (10.9 g; 88%). [Lit. bp 87°/0.7mm (60)].

Preparation of 4-Phenyl-1,2,4-triazoline-3,5-dione (54)

4-Phenyl-1,2,4-triazoline-3,5-dione (54) was prepared following the method of D. R. Arnold (98).

To a slurry of 4-phenylurazole in dioxane (400 ml) was added dropwise at room temperature with vigorous stirring t-butylhypochlorite (13.5 g, Frinton). The reaction mixture turned red immediately. After complete addition of the t-butylhypochlorite (30 minutes), the red solution was stirred another 20 minutes, then, filtered to remove the unreacted 4-phenylurazole. The dioxane was removed under reduced pressure (40-45°) and under nitrogen. The residue consisted of red crystals which were then sublimed (55-60°/10^{-2} mm) to give the triazolinedione 54, mp 170-179° with decomposition.

Preparation of Adduct 55

To a magnetically-stirred solution of 3-isobutenylcyclohex-2-en-1-one (435 mg) in benzene (70 ml) was added under nitrogen a few mg of the triazolinedione (54). The solution immediately turned red. The red colour of the dienophile was discharged within a few seconds. The addition of 54 was continued until the red color persisted for 2 hours (ca. 510 mg). Methanol was then added to the mixture and the solvents were evaporated to give colored crystals. Upon crystallization from a mixture of methylene chloride and ether, colorless crystals (696 mg), mp 150.0-153.0°, were collected. The mother liquor gave additional material (75 mg) upon addition of n-pentane (total yield, 82%). Adduct 55 of this purity was used for preparing ketone 56. Recrystallized material (twice, CH_2Cl_2/ether) had: ir ($CHCl_3$) 1774, 1742, 1710, 1600, 1500 and 1420 cm^{-1}; λ_{sh}^{MeOH} 215 nm (ε 17400), (max) 282 (360), (sh) 260 (570) and (sh) 266 (490); pmr ($CDCl_3$) δ 1.42 (s, 3), 1.71 (s, 3), 5.02 (d, 1, J=2.0 Hz), 5.38 (broad s, 1) and 7.3-7.6 (m, 5); mass spectrum (70 eV) m/e 325 (base peak), 310, 282, 118, 83, 73 and 58.

Anal. Calcd for $C_{18}H_{19}N_3O_3$: C, 66.44; H, 5.89; N, 12.92. Found: C, 66.15; H, 5.83; N, 12.75.

Preparation of Ketone 56

Adduct 55 (267 mg) in ethanol (70 ml) was hydrogenated for 2 days (atmospheric pressure, room temperature) over 5% Pd/c (39 mg). Filtration and evaporation of the reaction mixture gave slightly colored crystals, which upon recrystallization (CH_2Cl_2/ether), yielded ketone 56 as white crystals (243 mg; 91%), mp 185.0-187.0° (dec.). Ketone 56 had: ir ($CHCl_3$) 1770, 1710, 1580, 1510 and 1430 cm^{-1}; λ_{max}^{MeOH} 217 nm (ε 15500), 294 (40), (sh) 259 (280) and (sh) 266 (190); pmr ($CDCl_3$) δ 1.37 (s, 3), 1.75 (s, 3), 4.78 (d, 1, J=6.2 Hz) and 7.3-7.7 (m, 5); mass spectrum (70 eV) m/e (rel intensity) 327 (100), 312 (3), 299 (4), 284 (24), 178 (7), 165 (13), 151 (6), 137 (9), 123 (12), 122 (24), 119 (13), 107 (8), 91 (7), 81 (10), 67 (15) and 55 (9).

Anal. Calcd for $C_{18}H_{21}O_3N_3$: C, 66.03; H, 6.47; N, 12.84. Found: C, 66.20; H, 6.50; N, 12.89.

Preparation of 2-Isobutenyl-3-methoxycyclohex-2-en-1-one (14)

To a magnetically stirred solution of cyclohexane-1,3-dione (5.56 g) and sodium methoxide in methanol (sodium, 1.15 g, and methanol, 200 ml), was added dropwise at 0° under nitrogen a solution of isobutyraldehyde (freshly distilled under nitrogen) in dry methanol (100 ml, dried over type 3A molecular sieves). After the addition was over, the mixture was refluxed under nitrogen for one hour, and the methanol and excess isobutyraldehyde were distilled off under nitrogen (85°/water pump pressure), leaving a pale brown solid as residue. This solid, after drying (85°/10^{-2} mm for 5 hours), was washed three times with a mixture of dry ether and dry benzene (1:1), and again dried (65°/0.4 mm). A suspension of the solid in dry ether (400 ml) was treated with a stream of dry hydrochloric acid (gas) for one hour, while being stirred vigorously by a mechanical stirrer. The suspended solid gradually dissolved during the bubbling, and was replaced by a colorless precipitate (mainly NaCl). The reaction mixture was filtered and the solvent was immediately evaporated (45°/water pump pressure) to give a yellow liquid, to which benzene (20 ml) was added and then evaporated to remove any hydrochloric acid remaining. The addition and evaporation process was repeated three times. The liquid, thus obtained, was a complex mixture of products (by pmr), enedione 42 predominating: pmr spectrum of 42 ($CDCl_3$) δ 1.09 (d, 6, J=6.0 Hz) and 7.15 ppm (d, 1, J=10.0 Hz). This product mixture was kept under nitrogen at room temperature for 16 hours. By that time, the bulk of the enedione 42 had been converted to a hydroxydienone 43 (pmr): pmr of 43 ($CDCl_3$); δ 1.50 (d, 3, J=1.0 Hz), 1.80 (d, 3, J=1.0 Hz), 5.53 (septet, 1, J=1.0 Hz) and ca. 7.5 ppm (broad s, 1,exchanged with D_2O). The signals of the other products remained unchanged. This mixture was immediately treated with ca. 5-fold excess diazomethane in ether (ca. 300 ml), and kept at 0° for 5 hours. Evaporation of the ether and excess diazomethane gave a slightly colored liquid (6.075 g), which showed one major spot on tlc (benzene and ethylacetate, 1:2). Upon preparative tlc (benzene and ethylacetate, 3:4), the compound corresponding to the major spot was isolated as a liquid (3.00 g). This was compound 44 (> 95% pure by pmr) and used for preparations of 32 and 60 without further purification. Analytical sample of 44 was prepared as follows. Preparative tlc was repeated (n-pentane/ether, 7:5) and the lower half of the band of 44 was collected. Bulb to bulb distillation (50°/<10^{-3} mm) of this liquid gave colorless crystals, which were sublimed (room temperature/<10^{-3} mm) to give material of mp 42.0-44.0°. Methoxydienone 44 had: ir (CCl_4) 1660, 1605, 1360, 1290 and 1240 cm^{-1}; λ_{max}^{MeOH} 224 nm (ε 12700) and 275 (12200); pmr

(CDCl$_3$) δ 1.47 (d, 3, J=1.2 Hz), 1.84 (d, 3, J=1.2 Hz), 3.78 (s, 3) and 5.65 (septet, 1, J=1.2 Hz), δ 5.65 proton coupled with δ 1.47 and δ 1.84 protons with J=1.2 Hz (double irradiation); mass spectrum (70 eV) m/e (rel intensity) 180 (67), 165 (100), 149 (73) and 55 (40).

For $C_{11}H_{16}O_2$, m/e 180.1130 (calcd 180.1149).

When the mixture of hydroxy-dienone 43 and other products was subjected to preparative tlc (benzene/ether, 1:1), two major by-products of the condensation reaction were isolated as colorless crystals: compounds 45 and 46. Neither 42 nor 43 were isolated.

Compound 45 was recrystallized (n-pentane/ether), 98.0-98.5°C: ir (CHCl$_3$) 1668, 1617, 1379, 1172, 1128 and 952 cm^{-1}; λ_{max}^{MeOH} 232 nm (ε 21500) and 292 (5150); pmr (CDCl$_3$) δ 0.72 (d, 6, J=7.0 Hz), ca. 1.7 (doublet of septet, 1, J=3.5 for d and J=7.0 Hz for heptet), 3.84 (broad d, 1, J=3.5 Hz), δ ca. 1.7 proton coupled with δ 0.72 protons (J=7.0 Hz) and with δ 3.84 proton (J=3.5 Hz) (double irradiation); mass spectrum (70 eV) m/e (rel intensity) 218 (18) and 217 (100).

Compound 46 was recrystallized (C[illegible]Cl$_2$/ether), mp 189.0-190.0°: ir (CHCl$_3$) ca. 2600 (broad), 1590, 1381, 1369 and 1190 cm^{-1}; λ_{max}^{MeOH} 261 nm (ε 25000); pmr 0.80 (d, 6, J=6.0 Hz), 2.80 (doublet of heptet, 1, J=11.5 for d and J=6.0 Hz for heptet), 2.89 (d, 1, J=11.5 Hz), ca. 11.85

(broad, 1, exchanged with D_2O) and 12.85 (s, 1, exchanged with D_2O); mass spectrum (70 eV) m/e (rel intensity) 278 (20), 236 (14) and 235 (100).

Reactions of Hydroxy dienone 43

Hydroxy dienone 43 was not isolated in the pure state. Crude hydroxy dienone 43, used in the following reactions, was prepared following the method described for the preparation of methoxydienone 44.

i) Formation of Oxygen-adduct 47

When crude hydroxy ketone 43 (ca. 50 mg, liquid) was kept in contact with air (room temperature/overnight), colorless crystals appeared. These crystals were collected and recrystallized (n-pentane/ether) to give the oxygen-adduct 47, mp 153.5-155.0°. This substance was stable under acidic (benzene-p-TsOH refluxing) and basic (basic alumina) conditions, and showed a positive iodide test. Upon treatment with triphenylphosphine, 47 gave a mixture of products. Oxygen-adduct 47 had: ir ($CHCl_3$) 3600, 1695, 1645, 1275, 1185, 1170 and 975 cm^{-1}; λ_{max}^{MeOH} 227 nm (ε 7000); pmr ($CDCl_3$) δ 1.31 (s, 3), 1.44 (s, 3), ca. 3.8 (broad s, 1, exchanged with D_2O) and 6.56 (s, 1); mass spectrum (70 eV) m/e (rel intensity) 198 (28), 169 (27), 166 (100), 155 (50), 151 (56), 139 (46), 127 (25), 111 (71), 99 (48), 83 (68), 72 (52) and 55 (57).

Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found C, 60.87; H, 7.21.

The oxygen-adduct 47 was also formed when a solution of crude hydroxyketone 43 in air-saturated $CHCl_3$ was kept (in the dark) at −20° for a week.

ii) Rearrangement to Enone 48

When a degassed pmr solution (10^{-4} mm by freeze-thaw cycles) of crude hydroxy ketone 43 was kept at room temperature for two weeks, oxygen-adduct 47 was not formed at all, rather ca. half of 43 was converted to enone 48. The latter was isolated by preparative tlc (n-pentane/ether, 1:3) as a slightly colored liquid. This liquid changed to colorless crystals upon the following purifications: bulb to bulb distillation (50°/0.2 mm), preparative tlc (n-pentane/ether, 1:1) and a series of bulb to bubl distillation (50°/0.02 mm), successively. These colorless crystals of enone 48 melted at ca. room temperature. Enone 48 had: ir (CCl_4) 1655, 1635, 1400, 1370, 1269, 1170, 1058 and 999 cm^{-1}; λ_{max}^{MeOH} 271 nm (ε 15000); pmr ($CDCl_3$) δ 1.41 (s, 6), 1.85-2.15 (m, 2), 2.25-2.45 (m, 4) and 2.60 (t, 2, J=1.6 Hz); mass spectrum (70 eV) 166 (90), 151 (100), 138 (23), 123 (21), 110 (15) and 95 (37).

For $C_{10}H_{14}O_2$: m/e 166.0988 (calcd 166.0993).

The enone 48 was also formed during bulb to bulb distillation (120°/0.3 mm) of crude hydroxyketone 43.

LAH Reduction of Methoxydienone 44 (66, 99)

To a stirred mixture of lithium aluminium hydride (95 mg) in dry ether (30 ml) was added dropwise at 0° a solution of methoxydienone 44 (446 mg) in dry ether (15 ml). After completion of the addition (10 minutes), the reaction mixture was kept stirring for 15 minutes at 0°. Methanol (2 ml) was added to the mixture to destroy the excess reducing reagent. Then, the mixture was acidified to pH4 with an ice-cooled solution of 10% hydrochloric acid. The reaction mixture was immediately extracted with ether (four times). Isolation gave a liquid (340 mg). This showed three spots on tlc (benzene/ether, 7:1). The corresponding products were collected by preparative tlc (benzene/ether, 10:1): in order of decreasing Rf value, 2-isobutenylcyclohex-2-en-1-one (32) as a colorless liquid (224 mg), diene-alcohol 49 as a slightly colored liquid (66 mg) and oxygen-adduct 47 as crude crystals (30 mg). The crystals showed an identical pmr spectrum to that of an authentic sample.

The liquid (32) was distilled (bulb to bulb, 60°/0.8 mm) and the distillate was used for spectral measurements. Compound 32 had: ir ($CHCl_3$) 1665 (strong), 1446, 1431, 1383, 1363, 1328, 1174, 1113 and 978 cm^{-1}; $\lambda_{max}^{n\text{-pentane}}$ 212 nm (ε 17800), 269 (3700), (sh) 329 (8[illegible] ca. 342 (65), ca. 357 (30) and ca. 375 (10); pmr (CDCl$_3$) δ 1.69 (d, 3, J=1.5 Hz), 1.81 (d, 3, J=1.5 Hz), ca. 2.0 (m, 2), ca. 2.4 (m, 4), 5.88 (octet, 1, J=1.5 Hz) and 6.72 (dt, 1, J=4.5, 4.5 and 1.5 Hz), δ 5.88 proton coupled with δ 1.69 and 1.81 protons and with δ 6.72 proton (J=1.5 Hz) (by double irradiation); mass spectrum (70 eV) m/e (rel intensity) 150 (100), 135 (35), 122 (21), 117 (11), 107 (25), 93 (19), 91 (19), 79 (39) and 77 (21).

For $C_{10}H_{14}O$: m/e 150.1048 (calcd 150.1044).

The enol 49 was distilled (bulb to bulb, 50°/0.7 mm): ir (CHCl$_3$) 3600, 3420, ca. 2960, 1645, 1440, 1380, 1220, ca. 1040, 980, 950, and 915 cm^{-1}; λ_{max}^{MeOH} 232 nm (ε 9600); pmr (CDCl$_3$) δ 1.77 (broad s, 6) 1.5-2.8 (m, 6), 4.06 (m, 1) and ca. 5.64 (m, 2); mass spectrum (70 eV) m/e (rel intensity) 152 (100), 137 (27), 134 (53), 119 (87), 109 (76), 106 (88), 105 (29), 97 (71), 95 (36), 93 (78), 91 (86), 84 (54), 81 (50), 79 (56) and 77 (54).

For $C_{10}H_{16}O$: m/e 152.1217 (calcd 152.1200).

The amount of lithium aluminium hydride, used in the reduction of 44, had pronounced effects on the product radio (32/49). On the other hand, the combined yield (32 + 49) was not affected to any major extent (70∿80%) using molar equivalent ratios of LAH/44 of 2.65 (7.3), 4.30 (3.4) and 14.30 (1.8) [32:49 ratios in parentheses].

When the reduction was conducted at the temperature of refluxing ether, compound 32 was not formed at all (by tlc and nmr). Instead, one of the major products was diene 50. This substance was isolated by preparative tlc (benzene/ether, 6:1) of the product mixture (at least four products by tlc), and purified by bulb to bulb distillation (60°/0.5 mm). Compound 50 had: ir (CCl_4) 1250 cm^{-1}; pmr ($CDCl_3$) δ 1.75 (broad s, 6), 3.30 (s, 3) and 5.56 (broad s, 1); pmr (70 eV) m/e (rel intensity) 166 (21), 1[illegible]1 (24), 134 (100), 119 (85), 106 (79), 93 (44) and 91 (65).

Diels-Alder Reaction of Methoxy Dienone 44 and Triazolinedione 54

Methoxydienone 44 obtained from 1,3-cyclohexanedione (2.78 g) following the method previously described and the crude product was used for the following reaction.

To the solution of 44 in benzene (30 ml) were added small portions of triazolinedione 54 until the solution remained red. Evaporation of the solvent gave a yellow liquid which upon column chromatography (benzene and ether, 1:1) yielded adduct 60 (colorless crystals) (1.46 g). After recrystallization (EtOH), this had a mp 141.0-142.5°: ir ($CHCl_3$) 1775, 1718, 1650, 1500 and 1415 cm^{-1}; λ_{max}^{MeOH} 218 nm (ε 26000), (sh) 260 (250) and (sh) 266 (190); pmr ($CDCl_3$) δ 1.47 (s, 3), 1.88 (s, 3), 3.32 (s, 3), ca. 3.6 (m, 1), 6.45 (s, 1) and ca. 7.4 (m, 5); mass spectrum

(70 eV) m/e (rel intensity) 355 (100), 340 (15), 324 (53), 323 (25), 308 (17), 180 (24), 179 (20), 165 (28), 149 (21), 119 (8) and 55 (5).

Anal. Calcd for $C_{19}H_{21}O_4N_3$: C, 64.21; H, 5.96; N, 11.83. Found: C, 64.35; H, 5.90; N, 11.84.

Hydrogenation of Adduct 60: Compounds 63 and 64

Adduct 60 (116 mg) was hydrogenated (room temperature, atmospheric pressure) in ethanol (40 ml) for 4 hours, over 5% Pd/c (14 mg). Filtration and evaporation yielded a colorless liquid, which upon standing changed partially into colorless crystals. The crystals (38 mg; 32%) were collected and had, after recrystallization (ethanol and a mixture of CH_2Cl_2/ether, successively), a mp 223.0-224.5°. This substance was methoxyketone 63: ir ($CHCl_3$) 1758, 1710, 1595, 1495, 1445, 1405, 1270, 1150, 1140, 1105 and 1055 cm^{-1}; λ_{sh}^{MeOH} 217 nm (ε 13800), (sh) 255 (290), 260 (320) and 266 (310); pmr ($CDCl_3$) 1.33 (s, 3), 1.83 (s, 3), 3.18 (s, 3) and ca. 7.4 (broad s, 5); mass spectrum (70 eV) m/e (rel intensity) 357 (16), 326 (7), 325 (8), 218 (100), 181 (67), 119 (9). 56 (29) and 55 (11).

Anal. Calcd for $C_{19}H_{23}O_4N_3$: C, 63.85; H, 6.48; N, 11.76. Found: C, 63.79; H, 6.36; N, 11.69.

Upon preparative tlc (benzene/ether, 2:1), the mother liquor yielded enone 64 as colorless crystals (59 mg: 56%); recrystallization (a mixture of EtOH/ether and ethanol, successviely) gave material with mp 162.0-163.0°: ir ($CHCl_3$) 1778, 1725, 1650, 1615, 1500, 1410, 1380, 1370 and 1290 cm^{-1}; λ_{sh}^{MeOH} 215 nm (ε 5800), and (max) 301 (13000); pmr ($CDCl_3$) δ 1.59 (s, 6), ca. 2.1 (m, 2), ca. 2.45 (m, 2), 2.51 (t, 2, J=2.0 Hz), 3.25 (tt, 2, J=5.5 and 2.0 Hz) and 7.45 (s, 5), δ 3.25 protons coupled with δ 2.51 protons (J=2.0 Hz), δ 2.51 protons coupled with δ 2.18 protons (J=5.5 Hz) (double irradiation); mass spectrum (70 eV) m/e (rel intensity) 325 (100), 310 (10), 282 (21), 206 (15), 191 (35), 164 (30), 150 (20), 149 (14), 135 (12), 119 (13), 91 (11) and 55 (9).

Anal. Calcd for $C_{18}H_{19}N_3O_3$: C, 66.44; H, 5.89; N, 12.92. Found: C, 66.28; H, 6.06; N, 12.76.

Hydrogenation of Adduct 60: Compound 61

Adduct 60 (174 mg) was hydrogenated (room temperature, atmospheric pressure) in ethanol (60 ml) and pyridine (3 drops) for 55 hours over 5% Pd/c (18 mg). Filtration and evaporation gave a mixture (171 mg) of at least four products (by pmr). Upon addition of methanol the liquid partially crystallized (65 mg: 41%). The crystals, ketone 61, after recrystallization (CH_2Cl_2/ether), had mp 185.0-187.5°: ir ($CHCl_3$) 1770, 1711, 1505, 1420, 1275 and 1200 cm^{-1}; λ_{max}^{MeOH} 216 nm (ε 16800), (sh) 260

(270), (sh) 266 (180) and (max) 300 (40); pmr ($CDCl_3$) δ 1.38 (s, 3), 1.80 (s, 3), 3.00 (dt, 1, J=13.5, 5.0 and 5.0 Hz), 4.46 (m, 1) and 7.3-7.5 (m, 5); mass spectrum (70 eV) m/e (rel intensity) 327 (100), 312 (19), 216 (43), 193 (10), 178 (8), 151 (32), 150 (10), 124 (14), 119 (15), 97 (10) and 55 (13).

Anal. Calcd for $C_{18}H_{21}O_3N_3$: C, 66.03; H, 6.47; N, 12.84. Found: C, 65.95; H, 6.61; N, 12.62.

Enone 64 from Methoxyketone 63

A solution of methoxyketone 63 in benzene (10 ml) was refluxed overnight in the presence of a few mg of p-toluenesulfonic acid. During the refluxing, methanol was removed continuously using a Dean-Stark apparatus. To the cooled solution was added a mixture of anhydrous sodium carbonate (30 mg) and magnesium sulfate. Filtration and evaporation gave colorless crystals (34 mg: 97%), showing a single spot corresponding to enone 64 on tlc (benzene/ether, 3:2). The pmr spectrum was also identical to that of enone 64, obtained by hydrogenation of adduct 60.

Hydrogenation of Enone 64

Enone 64 (36 mg) was hydrogenated (room temperature, atmospheric pressure) in ethanol (13 ml) for 35 hours over 5% Pd/c (4 mg). Filtration and evaporation gave a mixture

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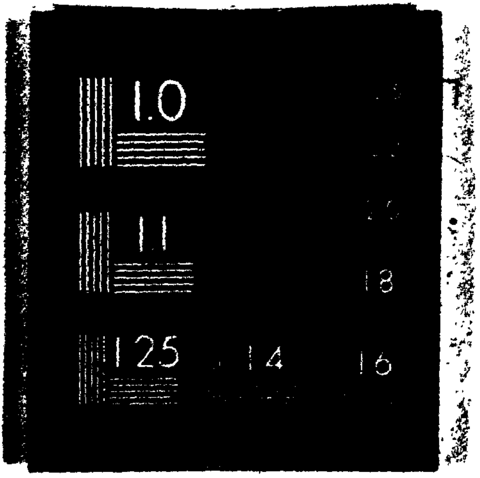

ARC - 374

of products as a liquid (31 mg), which, upon addition of ether, yielded colorless crystals (14 mg: 39%) of ketone 61.

Diels-Alder Reaction of Dienone 32 and Triazolinedione 54

To a magnetically stirred solution of dienone 32 (224 mg) in benzene (25 ml) were added small portions of triazolinedione 54 until the solution remained red. Upon completion of this addition, the solution was stirred for a further 2 hours. Then ethanol (2 ml) was added to the mixture. Evaporation of the solvents yielded crude crystals, which, after recrystallization (EtOH), gave adduct 62 as colorless crystals (423 mg: 87%), mp 157.0-159.5°. Adduct 62 had: ir ($CHCl_3$) 1774, 1710, 1645, 1505, 1420, 1370 and 1270 cm^{-1}; λ_{max}^{MeOH} 220 nm (ε 18000); pmr ($CDCl_3$) δ 1.60 (s, 3), 1.68 (s, 3), ca. 3.15 (m, 1), 4.45 (broad ddd, 1, J=11.0 5.0, 2.5 Hz), 6.34 (d, 1, J=2.5 Hz) and ca. 7.4 (m, 5), δ 4.45 proton coupled with δ 6.34 proton and with δ ca. 3.15 proton (J=2.5 and 5.0 Hz, respectively) (double irradiation); mass spectrum (70 eV) m/e 325 (base peak), 310, 191 and 150.

Hydrogenation of Adduct 62

Adduct 62 (484 mg) was hydrogenated (room temperature, atmospheric pressure) in a mixture of ethanol (90 ml) and pyridine (5 drops) for 36 hours, over 5% Pd/$BaCO_3$

(62 mg). Filtration and evaporation yielded crude crystals, which, upon recrystallization (EtOH), gave white crystals (451 mg: 93%), mp 184.0-186.0°. The latter was identified as ketone 61 by comparison with an authentic sample (tlc and pmr).

When the reaction was carried out in the absence of pyridine, the yield of 61 decreased to ca. 70%. The yield of 61 also decreased (to 50∿60%) if 5% Pd/C was used as the catalyst instead of 5% Pd/$BaCO_3$.

Basic Hydrolysis of Ketone 56

Ketone 56 (100 mg) was placed in a glass tube which contained lithium hydroxide (50 mg) in methanol (3 ml) and water (1.5 ml). A slow stream of nitrogen, passed over Catalyst 3R-11 (BASF), was bubbled into the solution (25 minutes, 0°), and the glass tube was then sealed. The sealed tube was heated at 105° for 18 hours. During the heating, the solution turned pale yellow. The tube, after being allowed to cool to room temperature, was cooled in dry ice and opened. The contents were immediately poured into a separatory funnel which contained methylene chloride (ca. 20 ml), water (ca. 20 ml) and several pieces of dry ice. The chilled methylene chloride layer was quickly separated after vigorous shaking. Quick isolation (avoiding air) gave a brown liquid. A specimen for pmr spectrum prepared under reduced pressure (5×10^{-3} mm) using degassed solvent ($<10^{-3}$ mm by freeze-thaw cycles) showed only one sharp singlet (1.23 ppm) in methyl region. Signals for aromatic protons were also observed. The latter were identified as those due to aniline by comparison with a pmr of an authentic sample of aniline. The high field signal was attributed to the methyl groups of compound 71. The pmr (≠) and ir of 71, obtained by subtracting the aniline signals, are: pmr ($CDCl_3$) δ 1.23 (s, 6), 1.2-2.6 (m, 8) and ca. 3.7 (broad s, 1, exchanged with D_2O); ir ($CDCl_3$) 1655 (strong) and 1603 cm^{-1}.

Tlc (benzene/ether) of the mixture showed one major spot other than that of aniline together with at least four minor spots. Separation of the major component by preparative tlc (ether) was unsuccessful.

Attempts to obtain pure 71 by distillation (up to 120°/$<10^{-3}$ mm) were also unsuccessful.

When the hydrolysis was carried out at 70° (12 hours), the product mixture showed five methyl signals (1.1-1.6 ppm) other than those of starting material (56), and aniline was not detected. At 140° (29 hrs), three methyl signals (1.1-1.5 ppm) other than that of 71 were observed together with the signals of aniline.

≠The identical pmr spectrum was obtained in a separate experiment where all the isolation processes were conducted either in a nitrogen box or under reduced pressure ($<5\times10^{-3}$ mm).

When lithium hydroxide was substituted with potassium hydroxide, the same results were obtained.

Basic Hydrolysis of Ketone 61

Ketone 61 (54 mg) was placed in a glass tube which contained a potassium hydroxide (20 mg) solution in methanol (2 ml) and water (1 ml). A small stream of nitrogen, passed over Catalyst R3-11 (BASF), was bubbled through the solution (30 minutes at 0°) and the tube was sealed immediately. The sealed tube was heated at 110-115° for 84 hours. The solution remained colorless during the heating (≠). The reaction tube, after cooling to room temperature, was cooled in dry ice, opened and immediately transferred into a funnel which contained a well-mixed mixture of methylene chloride (ca. 20 ml), water (ca. 20 ml) and several pieces of dry ice. Extraction, evaporation of the solvent (room temperature) gave a very slightly colored liquid. The pmr of the liquid (kept under reduced pressure, 2×10^{-2} mm) showed a sharp singlet (1.09 ppm) in methyl region. Aromatic protons were also observed. The latter was identified as those of aniline by comparison with an authentic sample. The former was identified as hydrazone 74 by comparison with a pmr spectrum of an authentic sample prepared by acid

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≠When nitrogen directly from a cylinder (L-grade, Liquid Air Ltd.) was used the solution turned brown during the heating.

hydrolysis of 90. No sign of a third product was detected.

When the hydrolysis was conducted at 75° (2 days), neither 74 nor aniline were formed, but a new compound, probably 68, appeared. This material was not isolated, but showed the following pmr ($CDCl_3$): δ 1.47 (s, 6), 6.80 (t, 1, J=4.0 Hz) and 7.33 (broad s, 5).

Attempted Diels-Alder Reaction between Dienone 31 and Thiadiazolinedione 75

Dienone 31 (130 mg) and 1,3,4-thiadiazolidine-2,5-dione 75 (60 mg) was dissolved in a mixture of THF (1.5 ml), dimethylformamide (1.0 ml) and acetic acid (0.2 ml). The mixture was cooled to -78° and stirred magnetically. Lead tetraacetate (400 mg) was added to the solution and the solution was stirred at -78° for 7 hours. Ethylene glycol (0.2 ml) was then added to the reaction mixture and the mixture was allowed to warm up to room temperature. Examination of the product (tlc, pmr spectrum) showed it to be essentially starting material.

Diels-Alder Reaction between Dienone 32 and Thiadiazolinedione 75

Adduct 77 was prepared following the general procedure of Corey (72) using thiadiazolinedione 75. Dienone 32 (500 mg) and 1,3,4-thiadiazolidine-2,5-dione (550 mg) were dissolved in a mixture of tetrahydrofuran

(6 ml), dimethylformamide (4 ml) and acetic acid (0.8 ml). The magnetically stirred mixture was cooled in a dry ice-acetone bath and lead tetraacetate (2.4 gr) was added. The mixture was stirred at -78° for 3 hours. Ethylene glycol (2.5 ml) was then added and the reaction mixture was allowed to warm gradually to room temperature. The mixture was poured into water (100 ml) and extracted with methylene chloride. The extract was washed with a saturated sodium carbonate solution and dried over cotton wool. Evaporation of the solvent gave a colored liquid. The tlc of the liquid showed three major spots corresponding to dienone <u>32</u>, adduct <u>77</u> and an unidentified product, in order of decreasing Rf value. Upon addition of ethanol, the liquid gave colorless crystals (582 mg) of adduct <u>77</u>. The crystals, after recrystallization (EtOH) had mp 159.5-160.0°: ir (KBr) 1700, ca. 1650, 1460, ca. 1250, 1180, 1090, and 908 cm^{-1}; λ_{max}^{MeOH} 223 nm (ε 5900); pmr ($CDCl_3$) δ 1.50 (s, 3), 1.80 (s, 3), 4.81 (ddd, 1, J=11.5, 5.0 and 2.0 Hz) and 6.16 (d, 1, J=2.0 Hz), δ 4.81 proton coupled with δ 6.16 proton with J=2.0 Hz (double irradiation); mass spectrum (70 eV) m/e (rel intensity) 267 (15), 266 (100), 191 (62), 164 (19), 150 (47), 149 (17), 135 (30), 122 (22), 107 (15), 79 (40) and 77 (24).

For $C_{12}H_{14}O_3N_2S$ m/e 266.0715 (calcd 266.0725).

Hydrogenation of Adduct 77

A solution of adduct 77 (264 mg) in a mixture of methanol (100 ml) and pyridine (2 drops) was subjected to hydrogenation (room temperature/atmospheric pressure) over 5% Pd/C (348 mg). The reaction was stopped after 6 days, although starting material still remained on tlc (benzene/ether, 3:2). The product, upon preparative tlc (benzene/ether, 20:3), gave ketone 78 as a colorless liquid (179 mg) and starting material as colorless crystals (24 mg). The former, upon addition of ether, gave colorless crystals. These crystals were recrystallized (CH_2Cl_2, ether and petrol ether, 30-60°), mp 124.0-125.0°: ir (KBr) 1710, 1680, 1470, 1400, 1250, 1210, 1170, 1110 and 1000 cm^{-1}; λ_{max}^{MeOH} 223 nm (ε 5500); pmr ($CDCl_3$) δ 1.41 (s, 3), 1.81 (s, 3), 2.95 (broad dt, 1, J=14.0, 5.0 and 5.0 Hz) and 4.73 (m, 1), δ 2.95 proton coupled with δ 4.73 proton with J=5.0 Hz (double irradiation); mass spectrum (70 eV) m/e (rel intensity) 269 (14), 268 (96), 208 (15), 193 (12), 152 (84), 124 (36), 112 (29), 109 (21), 97 (100), 95 (21), 84 (32) and 81 (29).

For $C_{12}H_{16}O_3N_2S$ m/e 268.0862 (calcd 268.0881).

Basic Hydrolysis of Ketone 78

i) at 105°

Keton 78 (29 mg) was placed in a glass tube, together with potassium hydroxide (45 mg), methanol (2 ml) and water (1 ml). The glass tube was sealed after bubbling a small stream of nitrogen, passed over Catalyst R3-11 (BASF), through the mixture for 25 minutes at 0°. The sealed tube was heated at 105° for 22 hours. After cooling in dry ice, the tube was opened and the contents were transferred into a separatory funnel which contained a mixture of methylene chloride, water and several pieces of dry ice. Quick extraction and evaporation gave a slightly colored liquid. Upon addition of undegassed solvent for pmr the liquid gave a dark yellow solution. The pmr showed an identical spectrum to that of Compound 74 obtained by acidic hydrolysis of hydrazine 90.

ii) at Room Temperature

Ketone 78 (42 mg) was dissolved in a solution which contained lithium hydroxide (20 mg), tetrahydrofuran and water. The mixture was stirred magnetically under nitrogen and kept at room temperature for 2 hours. The reaction mixture (colorless) was poured into water (15 ml) and extracted with methylene chloride, to give only a trace of slightly colored oil. The water layer was acidified with acetic acid until pH 5 and re-extracted with methylene chloride. Evaporation of the solvent gave a slightly colored liquid (34 mg). The pmr spectrum of the liquid showed no signals of the starting material, but showed the following signals which were assigned as those of compound 79: ($CDCl_3$) δ 1.2-2.7 ~~(m, 8),~~ 1.53

(s, 6), 6.88 (t, 1, J=4.0 Hz) and ca. 8.2 (broad, 1). This substance was not investigated further.

iii) at 55°

A mixture of ketone 78 (24 mg), lithium hydroxide (54 mg), tetrahydrofuran (2 ml) and water (2 ml), was heated at 55° in a sealed tube (under nitrogen) for 2 days. Isolation of the product gave a mixture of 79/78 and an unknown substance (stable under air) in roughly equal amounts. The material was not further investigated.

Preparation of Ketal 80

A mixture of ketone 56 (1.566 g), ethylene glycol (1.250 g) and p-TsOH (0.115 g) in benzene (150 ml) was refluxed (40 hours) in a flask equipped with a Dean—Stark apparatus. After cooling to room temperature, sodium carbonate (ca. 3 g) was added, followed by isolation to give crystalline residue. This was recrystallized (CH_2Cl_2/ether) to yield ketal 80 (1.614 g; 91%), mp 170.0-171.0°.

Ketal 80 had: ir ($CHCl_3$) 1760, 1700, 1603, 1502, 1420, 1290, 1275, 1150, 1025 and 950 cm^{-1}; λ_{max}^{MeOH} 217 nm (ε 16500), (sh) 259 (310) and (sh) 266 (180); pmr ($CDCl_3$) δ 1.31 (s, 3), 1.76 (s, 3), ca. 2.5 (m, 2), 3.6-4.0 (m, 4), 4.35 (d, 1, J=4.5 Hz) and 7.2-7.5 (m, 5), δ 4.35 proton coupled with one of δ ca. 2.5 protons with J=4.5

Hz (double irradiation); mass spectrum (70 eV) m/e (rel intensity) 371 (100), 356 (5), 283 (11), 270 (10), 119 (14), 99 (38), 86 (13) and 55 (11).

Anal. Calcd for $C_{20}H_{25}O_4N_3$: N, 11.31. Found: N, 11.26.

Preparation of Ketal 81

A solution of ketone 61 (133 mg) in a mixture of benzene (10 ml) and ethylene glycol (150 mg), was refluxed overnight in the presence of p-toluenesulfonic acid (20 mg). During the refluxing, a Dean — Stark apparatus was used to remove water. After cooling, anhydrous sodium carbonate (ca. 200 mg) was added; filtration and evaporation then yielded a liquid. Upon preparative tlc (n-pentane/ether, 1:1), the liquid gave ketal 81 as white crystals (149 mg). This substance had, after recrystallization (ether/n-pentane), a mp 137.5-139.5° and showed: ir (CCl_4) 1782, 1713, 1502, 1412, 1332 and 1108 cm^{-1}; λ_{max}^{MeOH} 217 nm (ε 16000), (sh) 260 (260) and (sh) 266 (180); pmr ($CDCl_3$) δ 1.34 (s, 3), 1.80 (s, 3), 1.3-2.0 (7), 2.25 (dt, 1, J=5.0, 5.0 and 12.5 Hz), 3.95 (s, 4), 4.45 (m, 1) and 7.2-7.6 ppm (m, 5); mass spectrum (70 eV) m/e (rel intensity) 371 (100), 356 (13), 195 (60) and 99 (19).

Basic Hydrolysis of Ketal 80: Formation of Compound 82

A solution of ketal 80 (50 mg) and potassium hydroxide (250 mg) in methanol (3 ml) and water (2 ml) was refluxed under nitrogen for 3 days. Isolation gave 82 as white crystals (48 mg), which showed a single spot on tlc (benzene and ether; 3:1). After recrystallization (ethanol/ether) the material had mp 152.0-152.5°; ir (KBr) 3350, 3240, 1665, 1586, 1526, 1437, 1215, 1160 and 1028 cm^{-1}; pmr ($CDCl_3$) δ 0.97 (s, 3), 1.14 (s, 3), ca. 3.80 (m, 4), 4.35 (broad s, 1, exchangable with D_2O), 4.64 (d, 1, J=6.0 Hz), 6.8-7.7 (m, 5) and 8.70 (broad s, 1, exchangable with D_2O); mass spectrum (70 eV) m/e (rel intensity) 346 (22), 345 (100), 330 (21), 226 (27), 211 (24) and 166 (17).

When the hydrolysis was stopped after 24 hour-refluxing, a mixture of 82 and the starting material (80) was obtained in the ratio of 4 to 3.

Basic Hydrolysis of Ketal 80: Formation and Oxidation of Hydrazine 83

Ketal 80 (41 mg) was in a glass tube containing a solution of potassium hydroxide (30 mg), methanol (2 ml) and water (1 ml), and was deoxygenated by passing nitrogen (0°, 25 minutes). The tube was then sealed and heated at 150° for 36 hours. After cooling to room temperature and then in dry ice the tube was opened and the contents were transferred into a separatory funnel which contained a mixture of methylene chloride, water and several pieces of dry ice. The latter mixture had been previously shaken for 5 minutes. The chilled methylene chloride extract was immediately passed through cotton wool and the solvent was evaporated at 35° to give a colorless liquid. This was immediately degassed ($<10^{-3}$ mm) and the pmr solution (colorless) was prepared on a vacuum line using degassed solvent (5×10^{-3} mm). The pmr showed a sharp singlet (1.14 ppm) for the methyl groups of 83 and no other methyl signals were observed. The sealed pmr tube was opened and, after a slow stream of oxygen was bubbled through the solution (5 minutes), it was resealed. As soon as the oxygen was introduced, the solution turned yellow. The pmr (30 minutes after the introduction of oxygen) showed the appearance of a pair of methyl signals (1.19 and 1.50 ppm) of equal intensity beside the sharp singlet of 83. The signals were attributed to those of the azo compound 85. The ratio (83/85) was ca. 5:1. The ratio was reversed to ca. 1:4 when the pmr solution was kept for 12 hours (room temperature). At the same time, a small pair of methyl signals started appearing at 1.06 and 1.11 ppm and an unidentified methyl signal also appeared at 1.19 ppm. The former signals were believed to be those of the hydrazone 86. After a total of 31 hours exposure to the oxygen, the methyl signals corresponding to 83 and 85 had disappeared completely and only those corresponding to 86 and the unidentified product remained. The aniline signals remained unchanged during the transofmrations. Similar results were obtained when air was used as oxidant instead of oxygen.

In a similar separate experiment, a degassed pmr solution (colorless) of 83 (and aniline) was prepared. Upon addition of mercuric oxide (ca. 20 mg), the color of the solution immediately changed to a reddish brown. The pmr mixture, after shaking 5 minutes (room temperature) showed a complete disappearance of 83 and the quantitative formation of 85. There were no other methyl signals nor was any change in the signals of aniline observed. The solution was filtered through a celite layer (CH_2Cl_2) and the solvent was immediately evaporated (room temperature). The pmr of the residual brown oil showed not only 85 but also 86, their ratio (85/86) being ca. 3:1. After 6 hours (room temperature), 85 disappeared completely, whereas 86 remained. No methyl signals other than those of 86 were observed.

Compound 85 had the following pmr signals ($CDCl_3$): δ 1.1-2.0 (m, 9), 1.19 (s, 3), 1.50 (s, 3) and 3.9-4.1 ppm (m, 5).

Isolation and Characterization of the Hydrazine 83

A mixture of hydrazine 83 and aniline was prepared from ketal 80 (54 mg), following the method previously described. The mixture was distilled at room temperature ($<10^{-3}$ mm) overnight to yield colorless crystals in a receiver cooled in an acetone-dry ice bath. The crystals melted when they were allowed to warm up to room temperature, and the pmr spectrum showed the signals of aniline. When the distillation temperature was raised to 60° ($<10^{-3}$ mm), another colorless liquid (hydrazine 83) was collected in the second cooled receiver. The liquid was sealed in the receiver under reduced pressure and transferred into a nitrogen-filled box where the samples for ir and mass spectra were prepared. A degassed carbon tetrachloride ($<10^{-3}$ mm by freeze-thaw cycles) was used as the ir solvent. A pmr solution was prepared under reduced pressure ($<10^{-3}$ mm) using degassed solvent (5×10^{-3} mm).

Hydrzine 83 had: ir (CCl_4) 3360, 3260, 3180, 1450, 1367, 1170, 1140, 1110, 1090, 1060 and 959 cm^{-1}; pmr ($CDCl_3$) δ 1.14 (s, 6H), 1.05-2.40 (m, 9H), 2.63 (broad d, 1, J = 5.0 Hz), ca. 3.7 (broad s, 2, exchangable with D_2O) and ca. 3.99 (m, 4); mass spectrum (70 eV) m/e (rel intensity) 227 (11), 226 (100), 211 (65), 181 (13), 166 (58), 165 (24), 139 (52), 125 (54), 112 (79) and 99 (58).

For $C_{12}H_{22}O_2N_2$ m/e 226.1660 (calcd 226.1680).

Reaction of Hydrazine 83 with Phenyl Isocyanate

A mixture of hydrazine 83 and aniline was prepared from ketal 80 (100 mg) following the method previously described. To the mixture, a degassed solution (5×10^{-3} mm) of phenyl isocyanate (72 mg) in chloroform (2 ml) was added under reduced pressure ($<10^{-3}$ mm) and the system was sealed, and kept at room temperature (24 hours). During this time colorless crystals appeared in the solution. The solvent and the excess phenyl isocyanate were then evaporated, to give colorless crystalline residue which showed three distinctive spots (under uv) on tlc (benzene and ethyl acetate; 3:1). The crystals partially dissolved in chloroform and the insoluble crystals were collected (40 mg) and identified as N,N'-diphenyl urea by comparison with an authentic sample (tlc and ir). This substance showed a spot corresponding to the spot with the highest Rf value on the original tlc. The chloroform-soluble part showed two major spots. Upon preparative tlc, (benzene and ethyl acetate, 5:1) the corresponding two fractions were obtained, the higher Rf being 40 mg and the other 21 mg. The latter was identified, after recrystallization (methanol/water), as compound 82 by comparison (mp, ir, pmr and tlc) with an authentic sample obtained by basic hydrolysis of 80.

The former fraction was purified by preparative tlc (benzene and ether, 3:1) and recrystallized (ethanol) to give compound 84, mp 149.0-150.0°: pmr ($CDCl_3$) δ 1.47 (s, 3), 1.58 (s, 3), 1.2-2.0 (m, 8), ca. 2.15 (m, 1) 3.21 (broad t, 1, J=7.0 Hz), 3.8-4.1 (m, 5), 6.8-7.5 (m, 5) and 8.87 ppm (broad s, 1). δ 8.87 proton exchanged with D_2O, 5 protons (3.8-4.1 ppm) decreased to 4 under D_2O and at the same time the broad triplet (3.21 ppm) changed to a broad doublet (J=7.0 Hz).

Acidic Hydrolysis of Hydrazine 83

A mixture of ketal 80 (34 mg), potassium hydroxide (60 mg), methanol (2 ml) and water (1 ml) was reacted in a sealed tube as described previously. After the hydrolysis was over, the sealed tube was cooled in dry ice, opened and allowed to warm to 0° under nitrogen. To the solution, concentrated hydrochloric acid was added drop by drop to pH 2 and the reaction system was sealed under nitrogen, passed over Catalyst 3R-11 (BASF), and kept at 55° overnight. The solution remained colorless. The sealed reaction system was then cooled to -78° (dry ice) and opened. The contents were immediately transferred into a separatory funnel which contained a mixture of methylene chloride, water and several pieces of dry ice. Quick isolation yielded a yellow oil. When the oil was dissolved in undegassed pmr solvent ($CDCl_3$), the color changed to brown. The pmr showed a mixute of 71 and aniline; the spectrum was identical to that obtained from the basic hydrolysis of ketone 56.

Under milder conditions the hydrolysis of 83 was incomplete (AcOH/80-85°) or did not occur (AcOH/55° or HCl/room temperature).

Isolation and Characterization of Hydrazone 86

A mixture of hydrazine 83 and aniline was prepared from ketal 80 (188 mg) as described previously. The tlc (ether) of the mixture showed in air a long tailing spot and a spot corresponding to aniline. The former, upon preparative tlc (ether), was separated to give crude colored crystals (99 mg) of hydrazone 86 (86% yield based on the amount of ketal 80 used). Sublimation (70-95°/ $2x10^{-2}$ mm) of the crystals yielded yellowish crystals (90 mg) which were recrystallized (ether/n-pentane) to give colorless crystals (22 mg), showing a single spot on tlc (ether). The pmr spectrum of the crystals was measured and the crystals recovered from the pmr measurement were sublimed twice at $75-80^{o}/5x10^{-2}$ mm. The sublimed crystals melted at 129.0-130.0° and had: ir (CCl_4) ca. 3300, 1634, 1435, 1382, 1367, 1197, 1172, 1060, 1035 and 912 cm^{-1}; λ_{max}^{MeOH} 213 nm (ϵ 4700) and 239 (5100); pmr ($CDCl_3$) δ 1.06 (s, 3), 1.11 (s, 3), ca. 2.35 (m, 1), 3.7-4.2 (m, 4) and 4.92 (broad, 1, exchanged with D_2O); mass spectrum (70 eV) m/e (rel intensity) 224 (61), 209

(48), 195 (16), 181 (83), 165 (21), 152 (46), 139 (21), 137 (100), 109 (15), 99 (67), 95 (18) and 86 (38).

For $C_{12}H_{20}O_2N_2$ m/e 224.1503 (calcd 224.1524).

Basic Hydrolysis of Ketal 81: General Observations

Ketal 81 (127 mg) was placed in a glass tube which contained a solution of potassium hydroxide (392 mg) in methanol (4 ml) and water (1.5 ml). A small stream of nitrogen, passed over Catalyst R3-11 (BASF), was bubbled through the solution for 35 minutes at 0° and the glass tube was immediately sealed and heated at 150° for 23 hours, the solution remaining colorless. After cooling, the tube was further cooled in dry ice, opened and the contents were immediately transferred into a separatory funnel which contained a mixture of water (20 ml), methylene chloride (20 ml) and several pieces of dry ice (≠). The products were extracted three times (CH_2Cl_2). The combined, chilled extract was quickly passed through cotton wool and evaporated (35°) to give a slightly colored liquid (94 mg), which was kept under vacuum (2×10^{-2} mm) at -15° until use.

Using ca. 40 mg of the liquid, a pmr solution was prepared under nitrogen. It showed a pair of methyl

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≠When the extraction was done without using dry ice (0°-room temperature), some portion of the product (90) was oxidized to 89 during the isolation.

signals of equal intensity (1.05 and 1.13 ppm), a sharp singlet for -OCH_2CH_2O- (3.90 ppm) as distinct peaks as well as the low field signals for aromatic protons. The latter was identified as those due to aniline, by comparison with pmr of an authentic sample. The former signals were assigned as those due to product 90. No sign of the presence of a third product was detected, since total integration of protons was in agreement with 22 protons for 90 and 7 protons for aniline, the ratio (90/aniline) being 1.36:1. The yield of 90 was calculated to be 94% based on the ratio and weight of the product mixture.

The products, recovered from the pmr solution, were kept at -15° overnight exposed to air. Then the pmr of the products were remeasured under nitrogen, showing a decrease in the intensity of the methyl signals of 90 and the appearance of a new pair of methyl signals (1.25 and 1.44 ppm) which were assigned as those due to compound 89. No change in signals for aniline was observed. The ratio (90/89) was ca. 3:1. The ratio did not change nor did new signals appear, when the solution was kept under nitrogen for 4 days (-15°). But the ratio changed to 3:2, when a small stream of air was bubbled through the pmr solution (30 minutes at 0°). Further change in the ratio to ca. 3:4 was observed after bubbling with oxygen (24 hours at 0°). The oxygen stream was shut off and excess mercuric oxide (50 mg) was added to the solution. The mixture was stirred at room temperature for 5 minutes. The pmr showed a complete disappearance of compound 90 and a full appearance of 89. Aniline still remained unchanged. The mixture was poured into water and extracted with methylene chloride. The pmr spectrum of the residue, obtained by evaporation of the solvent, showed no change in the signals of 89 and of aniline. When the pmr solution was kept under air for 2 months at -15°, the pmr showed the appearance of another new pair of methyl signals (1.05 and 1.13 ppm), and a decrease in intensity of the methyl signals for compound 89. The ratio was 3:2. The new compound (94) completely replaced compound 89 when small crystals of p-toluensulfonic acid were added to the solution and this solution kept at room temperature for 1 day.

The rest of the initial product mixture (ca. 5.4 mg) was dissolved in ether (15 ml), saturated with air, and kept overnight at -15°. Then products were isolated by removing the ether. The pmr spectrum showed two pairs of methyl signals, corresponding to products 90 and 89 in the ratio of ca. 1:6. The signals of aniline remained unchanged. The products, recovered from the pmr measurement, were immediately subjected to a bulb to bulb distillation (room temperature/0.02 mm): for 12 hours, to give a distillate and a residue. The former consisted of a mixture of colorless crystals and a colorless liquid, which were collected in a receiver, cooled in acetone-dry ice. But upon exposure to air, the colorless mixture gradually turned to a pale yellow liquid. The pmr spectrum of the air-exposed distillate showed aniline as the major product and 90 and 89 as the minor products (the ratio 90/89 was ca. 1:3). The latter residue was a light brown liquid, and its pmr showed only compounds 90 and 89 in the ratio of ca. 6:1, with no trace of aniline. The mixture, recovered after the pmr measurement, was treated with a mixture of mercuric and mercurous chloride in water, giving a very dark brown tar.

Isolation and Characterization of Hydrazine 90

A mixture of ketal 81 (54 mg), KOH (80 mg), methanol (3 ml) and water (1.5 ml) was reacted following the previously described procedure to give a slightly colored mixture of substance 90 and aniline. The products were immediately placed in a bulb to bulb distillation apparatus, which consisted of a series of four receiving bulbs. The products were distilled at 65° ($5\text{x}10^{-3}$ mm) into the first bulb which was cooled by acetone, leaving a trace of yellow liquid as the residue. Under the same conditions, the colorless distillate was redistilled from the first to the second bulb; the latter was in turn cooled by acetone, yielding a colorless distillate. The bulbs were wrapped with dry ice and sealed in between them by flame. Repeat of the distillation (45°/<10^{-3} mm) from the second into the third bulb, cooled in acetone, gave colorless crystals, some of which were sublimed at room temperature (<10^{-3} mm) to the acetone-cooled fourth bulb (12 hours) in order to make sure all aniline was removed from the residual colorless crystals in the third bulb. The residual crystals (compound 90) in the third bulb were sealed under the reduced pressure, transferred into a nitrogen-filled dry box. In the box , the sample for ir was made using degassed carbontetrachloride (10^{-4} mm by freeze-thaw cycles) and the samples for a mass spectrum and mp measurement were sealed in capillary tubes under the nitrogen.

The pmr solution (separate preparation) was prepared on a vacuum line by mixing 90 and degassed solvent (10^{-4} mm by freeze-thaw cycles).

Compound 90 had: mp 70.0-71.0°; ir (CCl_4) 3200, 2960, 1260, 1100 and 1082 cm^{-1}; pmr ($CDCl_3$) δ 1.05 (s, 3), 1.13 (s, 3), 2.05 (broad dt, 1, J=13.0, 5.0 and 5.0 Hz), 2.91 (broad dt, 1, J=12.0, 5.0 and 5.0 Hz), 3.34 (broad s, 2) and 3.90 (s, 4), δ 3.34 protons exchanged with D_2O, δ 2.05 proton coupled with δ 2.91 proton with J=5.0 Hz (double irradiation); mass spectrum (70 eV) m/e (rel intensity) 227 (13), 226 (100), 212 (13), 211 (95), 183 (28), 181 (36), 112 (49), 99 (88), 98 (50) and 86 (54).

For $C_{12}N_{22}O_2N_2$ m/e 226.1655 (calcd 226.1680).

Isolation and Characterization of Azo Compound 89

Ketal 81 (47 mg), KOH (65 mg), methanol (2 ml) and water (1 ml) were heated in a sealed tube following the usual procedure, to give a mixture of compound 90 and aniline. To the products were added mercuric oxide (ca. 100 mg) and methylene chloride (3 ml) and the mixture was stirred for 15 minutes at room temperature. The mixture was then filtered through a sintered glass funnel to remove excess mercuric and mercurous oxides. The filtrate was evaporated under reduced pressure at room temperature to remove aniline, giving a pale yellow liquid. Distillation of the liquid (48-50°/<10^{-3} mm; 8 hours) yielded a small amount of a pale yellow liquid as distillate in a receiver cooled in acetone, while the bulk of the liquid remained as the residue. Upon cooling to -15°, this distillate gave pale yellow crystals of compound 89. Upon rapid heating, the crystals melted at 43-48° and further rapid heating to ca. 120° resulted in nitrogen evolution. When heated slowly (the change from 52° to 110° taking 20 minutes), they melted at 49.0-52.0° and no nitrogen evolution was observed, even above 140°. The crystals were used for ir, uv and mass spectra measurements. The rest of the crystals were combined with the distillation residue (which showed same tlc as the distillate) and its pmr was measured. Compound 89 had: ir (CCl_4) 2950, 1466, 1293, 1098, 1030, 941 and 914 cm^{-1}; λ_{max}^{MeOH} 363 nm (ε 140); pmr ($CDCl_3$) δ 1.25 (s, 3), 1.44 (s, 3), 2.37 (m, 1), 3.92 (broad s, 4) and 4.40 (m, 1), δ 2.37 proton coupled with δ 4.40 proton (double irradiation); mass spectrum (70 eV) m/e (rel intensity) 112 (58), 99 (100) and 86 (26).

Isolation and Characterization of Hydrazone 94

A mixture of compound 89 and aniline was prepared, following the method previously described, from ketal 81 (48 mg), KOH (68 mg), methanol (2 ml) and water (1 ml). The mixture was dissolved in methylene chloride (ca. 3 ml) and a catalytic amount of p-toluenesulfonic acid was added to the solution. The solution was stirred under nitrogen at room temperature for 2 hours. Extraction (CH_2Cl_2) and evaporation gave a slightly colored liquid, a mixture of compound 94 and aniline. In order to remove the aniline, distillation was performed at 60° (<10^{-3} mm) to give a mixture of colorless cyrstals and yellow liquid as the distillate, collected in an acetone-cooled receiver. Upon redistillation of this mixture (80°/<10^{-3} mm) were obtained colored crystals as the distillate and colorless crystals as the residue. The latter, compound 94, melted at 119.0-120.5° and was used immediately for the spectroscopic measurements. Compound 94, upon exposure to air, very slowly turned yellow, then dark brown. Compound 94 had: ir (CCl_4) 3370, 2960, 2890, 1450, 1169, 1139 and 1080 cm^{-1}; λ_{max}^{MeOH} 211 nm (ϵ 3800), 235 (4700); pmr ($CDCl_3$) δ 1.05 (s, 3), 1.13 (s, 3), ca. 1.1-2.9 (9) and ca. 3.95 (m, 5). δ ca. 3.95 (5H) changed to ca. 3.95 (4H) under D_2O; mass spectrum (70 eV) m/e (rel intensity) 225 (8), 224 (61), 209 (22), 152 (24), 99 (100), 96 (29) and 86 (26).

For $C_{12}H_{20}O_2N_2$ m/e 224.1500 (calcd 224.1524).

Reaction of Hydrazine 90 with Phenyl Thioisocyanate

A mixture of hydrazine 90 and aniline was prepared, by the general method, from ketal 81 (50 mg), KOH (200 mg), methanol (2 ml) and water (1 ml). The aniline was distilled off (room temperature/$2x10^{-3}$ mm for 12 hours) from the mixture. The pmr of the residue using air-saturated solvent showed the methyl signals for compound 90 as well as 89 in the ratio of ca. 5:1. This pmr solution was diluted with undegassed methylene chloride (3 ml), and phenyl thioisocyanate (80 mg) was added under reduced pressure to the diluted solution. The mixture was stirred (room temperature) overnight. Then the solvents and excess phenyl thioisocyanate were evaporated at room temperature ($<10^{-3}$ mm), yielding a slightly colored liquid, which upon addition of ethanol (1 ml) gave compound 92 as colorless crystals (16 mg). The product, after pmr spectral measurement, was recrystallized (EtOH) and had mp 225.0-226.0 °: ir (KBr) 3287, 3230, 3174, 2950, 1600, 1591, 1526, 1445, 1377, 1349, 1276, 1205, 1190, 1095 and 1085 cm^{-1}; pmr ($CDCl_3$) δ 1.14 (s, 3), 1.24 (s, 3), 2.24 (dt, 1, J=12.8, 5.2 and 5.2 Hz), 3.38 (s, 1), ca. 3.95 (m, 4), ca. 5.84 (m, 1), 7.1-7.6 (m, 5) and 9.74 (broad s, 1), δ 2.24 proton coupled with δ ca. 5.84 proton (J=5.2 Hz, double irradiation); mass spectrum (70 eV) m/e (rel intensity) 361 (41), 225 (23), 210 (100), 204 (15), 135 (24) and 99 (54):

Acidic Hydrolysis of Hydrazine 90: General Observations

Ketal 81 (75 mg) was reacted in a sealed tube with KOH (222 mg) in methanol (3 ml) and water (1 ml) as described previously. The sealed tube was opened at -78°, immediately placed under nitrogen, and the solution allowed to warm to 0°. To the solution was added concentrated hydrochloric acid drop by drop until the solution reached pH 2. Then the solution was sealed under nitrogen in a glass tube and heated at 70-80° for 7 hours. The reaction tube was allowed to cool to room temperature and then cooled to 0°. The tube was opened and the contents were immediately poured into a mixture of methylene chloride, water and several pieces of dry ice. The water layer was basified using sodium carbonate until pH 10. Quick extraction (methylene chloride, three times) and evaporation

(20°/water pump pressure) yielded a slightly colored liquid, a mixture of compound 74 and aniline. When a solution of the mixture for pmr spectrum was prepared using air-saturated solvent, there developed immediately a yellow color. The pmr spectrum showed, besides the signals for aniline, one sharp methyl signal at 1.09 ppm and a multiplet at 5.65 ppm, their relative integration being 6:1. Distillation (25°/10^{-2} mm) of the yellow liquid, recovered from the pmr tube and dried, gave first a colorless liquid and then colorless crystals as the distillate, leaving colored crystals as the residue. The liquid distillate consisted of aniline and 74 (pmr). The crystalline distillate, upon exposure to air, turned immediately into yellow crystals and, subsequently into an organge liquid. This liquid showed at least seven methyl signals other than that of 74. Signals for aniline were also detected. The colored residue of the distillation, which had been kept under vacuum (10^{-2} mm), was sublimed to give colorless crystals (hot air gun/10^{-3} mm). The latter was dissolved in a degassed solution of $CDCl_3$ and TMS (degassed to 10^{-3} by freeze and thaw cycles) under vacuum (10^{-3} mm), and sealed in a pmr tube. The solution was colorless. The pmr showed no detectable aniline signals, but solely those of 74. The tube was opened under nitrogen, phenyl thioisocyanate (ca. 50 mg) was added to the solution, and the tube was resealed under nitrogen. The pmr showed very slow appearance of a new methyl signal at 1.80 ppm and a concomitant disappearance of the methyl signal of 74. The ratio, after two weeks at room temperature, was ca. 3:1. All attempts to isolate the new compound by distillation and preparative tlc were unsuccessful.

Oxidation of 74 using mercuric oxide did not give clear results, a complex mixture of products being formed.

Compound 74 was also prepared under milder conditions; using a few drops of concentrated hydrochloric acid at room temperature for 3 days. But when acetic acid was used (60-65° for 2 hours), no formation of 74 was observed, starting material being recovered.

Isolation and Characterization of Hydrazone 74

A mixture of compound 74 and aniline was prepared from ketal 81 (57 mg) following the procedure described previously. The mixture was placed in a bulb to bulb distillation apparatus, which had three receiving bulbs and a branch connected to a uv cell between the second and third bulbs. The third bulb was connected with a cold finger trap (dry ice/acetone). Distillation of the liquid (room temperature/$<10^{-3}$ mm) gave a colorless liquid in the first bulb, cooled in acetone. In the cold finger, bulk of aniline was trapped as colorless crystals, which melted during warming to room temperature. The distillation flask, which contained the residue, was removed from the first bulb by sealing in between them. The distillate in the first bulb was redistilled (room temperature/$<10^{-3}$ mm) into the second bulb which was cooled by acetone. The distillate was colorless crystals of 74 which did not melt at room temperature. The residue in the first bulb was also colorless crystals of 74. The latter was sealed under reduced pressure from the distillation system and used for mp, ir and mass spectra measurements. The samples for mp and mass spectrum were prepared under nitrogen. The sample for ir spectrum was also prepared under nitrogen using degassed carbontetrachloride.

The bulk of the crystals in the second bulb were sublimed into the third bulb in acetone (55-60°/$<10^{-3}$ mm). The second bulb and the uv cell were detached from the third bulb by sealing. The uv sample of 74 was prepared under vacuum by introducing degassed n-pentane into the uv cell and the second bulb which contained the residual white crystals of 74. The sample was colorless and the uv spectrum was run immediately. The pmr spectrum was obtained from a separate experiment. Compound 74 had mp 54.0-56.0°: ir (CCl_4) 3340, 3260, 2920, 1430, 1380, 1364, 1249, 1190, 1060 and 990 cm^{-1}; pmr ($CDCl_3$) 1.09 (s, 6), 5.65 (m, 1); mass spectrum (70 eV) m/e (rel intensity) 165 (7), 164 (32), 150 (10) and 149 (100); λ_{max}^{MeOH} 225 and 287 nm.

For $C_{10}H_{16}N_2$ m/e 164.1307 (calcd 164.1313).

Acidic Hydrolysis of Azo Compound 89

Azo compound 89 (aniline free) was prepared from purified 90 which, in turn, was prepared from ketal 81 (47 mg) as described previously. This compound was treated with a catalytic amount of p-toluenesulfonic acid in methanol (2 ml) and water (1 ml). The azo compound 89 was immediately transformed into hydrazone 94 (tlc). The reaction mixture was heated under nitrogen at 60° for 22 hours and then at 80° for 5 hours. By this time tlc (ether/ethanol, 95:5) showed the appearance of a polar compound 98 as the sole product. The mixture was poured into water and extracted (CH_2Cl_2). The extract, after washing (H_2O) and drying (cotton wool), was evaporated to give a trace of colored crystals. The water layer was further extracted (CH_2Cl_2), to yield a trace of colorless crystals. The latter was identified as compound 98 by comparison with ir of an authentic sample obtained by photolysis of 78.

Reduction of Ketone 61 with Sodium Borohydride

Keton 61 (474 mg) was dissolved in methanol (40 ml) under refluxing conditions. The solution was then cooled in ice and sodium borohydride (90 mg) was added to the magnetically stirred solution. Tlc of the solution, after 10 minutes at 0°, showed the complete disappearance of starting material. A dilute solution of hydrochloric acid was added to the solution. Extraction (CH_2Cl_2), drying ($MgSO_4$) and evaporation gave a colorless oil. Upon addition of ethanol, the liquid gave colorless crystals (405 mg) of alcohol 95. A pmr spectrum of the mother liquor showed not only the methyl signals of 95, but also another pair of methyl signals at 1.25 and 1.78 ppm. The recrystallized (EtOH) alcohol 95 had mp 153.0-154.0°: ir ($CHCl_3$) 3600, 3460, 1770, 1710, 1505, 1425, 1290, 1190, 1065 and 1005 cm^{-1}; pmr ($CDCl_3$) 1.32 (s, 3), 1.78 (s, 3), 1.2-1.8 (m, 8), 2.3 (broad s, 1, D_2O exchangable), 2.44 (m, 1), 3.73 (m, 1), 4.13 (m, 1) and 7.2-7.5 (m, 5); mass spectrum (70 eV) m/e (rel intensity) 329 (100), 314 (15), 178 (30), 135 (21), 119 (21) and 108 (21).

Attempted Oxidation of Alcohol 95 with Triazolinedione 54

Alcohol 95 (34 mg) was dissolved in benzene (1 ml) and triazolinedione 54 (16 mg) was added to the solution. The mixture was stirred at room temperature under nitrogen for 24 hours. Methanol (2 ml) was then added to the solution, which had been remaining red, to destroy the oxidant. The solvents were evaporated to yield a yellow liquid. The pmr of the liquid showed no signals corresponding to the expected ketone 61. The major component was starting material.

Preparation of Phenacyl Derivative 96

i) using α-Tosyloxyacetophenone

A mixture of alcohol 95 (88 mg), α-toxyloxyacetophenone (144 mg), 1,8-bis-(dimethylamino)-naphthalene (55 mg) and toluene (3 ml) was placed in a sealed tube under nitrogen and heated at 120° for 4 days. Upon cooling the solution separated into two layers. The top layer was a yellow solution in which were suspended a few colorless crystals. The bottom layer consisted of brown crystals. The sealed tube was opened after being cooled in dry ice. The crystals were removed by filtration and the solvent was evaporated from the filtrate to give a brown oil. The oil was partially soluble in a mixture of methylene chloride and ether. The soluble part was separated and its tlc showed three major spots, corresponding to α-tosyloxylacetophenone, phenacyl derivative 96 and alcohol 95, in order of decreasing Rf value. Upon preparative tlc, 96 and 95 were isolated as a yellow liquid (72 mg), and as slightly colored crystals (26 mg), respectively. Distillation of the liquid was attempted at 125°/10^{-2} mm, without success. It was then dissolved in boiling cyclohexane and the soluble part was separated (from the insoluble part). After evaporation of the solvent and preparative tlc (alumina, ether), the very slightly colored liquid obtained was distilled (200°/5×10^{-3} mm) in a bulb to bulb apparatus to give a colorless viscous liquid. When this liquid was placed under reduced pressure (room temperature/10^{-2} mm) for a week, it crystallized (mp 58.5-60.0°). Phenacyl derivative <u>96</u> had: ir (CH_2Cl_2) 1765, 1705, 1600, 1510, 1410 and 1125 cm^{-1}; pmr ($CDCl_3$) δ 1.35 (s, 3), 1.80 (s, 3), 2.71 (m, 1), 3.56 (m, 1), 4.16 (m, 1), 4.68 (d, 1, J=17.0 Hz), 4.85 (d, 1, J=17.0 Hz), ca. 7.4 (m, 8) and ca. 7.9 (m, 2); mass spectrum (70 eV) m/e (rel intensity) 448 (29), 447 (100), 432 (7), 357 (12), 329 (12), 327 (24), 312 (15), 292 (10), 216 (29), 178 (31), 151 (17), 135 (49), 119 (37), 108 (58), 105 (49), 93 (21), 91 (34), 81 (23) and 77 (28).

ii) <u>using α-Diazoacetophenone</u>

Alcohol <u>95</u> (55 mg) was dissolved in diisopropyl ether (7 ml) under refluxing conditions, and a small drop of BF_3-etherate was added to the solution. To the magnetically stirred solution was added dropwise a solution of diazoacetophenone (25 mg) in diisopropyl ether (1 ml), over a 5 hour period. When ca. three quarters of the solution had been added, brown tars started appearing on the reaction wall. The tars prevented the function of the magnetic stirrer in the later stages of the reaction. The reaction was stopped 3 hours after the final portion of the diazoacetophenone solution was added. Evaporation of the solvent gave a dark brown liquid. Tlc (benzene and ether, 1:1) of the liquid showed three major tailing spots together with several minor spots. One of the major spots, corresponding to pheacyl derivative 96, was separated as a colorless liquid (29 mg) by preparative tlc (benzene and ether, 10:7). Alcohol 95 (27 mg) was also recovered from the tlc. The phenacyl derivative 96, thus obtained, had an identical pmr as that obtained previously using α-tosyloxylacetophenone.

Basic Hydrolysis of Phenacyl Derivative 96

Phenacyl derivative 96 (57 mg) was placed in a glass tube which contained a mixture of potassium hydroxide (90 mg), methanol (2 ml) and water (1.3 ml). A small stream of nitrogen, passed over Catalyst R3-11 (BASF), was bubbled through the solution for 30 minutes at 0° and the glass tube was sealed immediately. The sealed tube was heated at 100° for 37 hours and then cooled in dry ice. The contents were immediately transferred into a separatory funnel which contained a well-stirred mixture of methylene chloride, water and several pieces of dry ice. Quick extraction with the chilled methylene chloride and evaporation of the solvent (room temperature/water pump pressure) yielded a pale yellow liquid. The liquid was immediately placed under reduced pressure (10^{-3} mm). A solution for pmr of the liquid was prepared on a vacuum line by mixing with degassed solvent (10^{-3} mm by freeze and thaw cycles). The pmr spectrum showed a complex mixture which did not contain starting material. The pheacyl group appeared to have been essentially destroyed.

Photolysis of Ketone 78

A degassed solution ($6x10^{-5}$ mm by freeze-thaw cycles) of ketone 78 (39 mg) in acetonitrile-d_3 (0.25 ml) was prepared in a quartz pmr tube and irradiated in a Rayonet reactor at 7-8° using 254 nm light. After 6 hours of irradiation, colorless crystals started appearing on the reaction wall. The irradiation was stopped after total 53-hour-irradiation, because the wall was, by that time, covered with the colorless crystals. The solution, originally colorless, was yellow. The pmr tube was opened and the contents were transferred into a flask rinsing with methylene chloride. Evaporation of the solvents gave colored crystals. The pmr spectrum of the crystals showed a sharp methyl singlet of compound 98 as well as the methyl signals of the starting material. The ratio (98/78) was ca. 3 to 1. The crystals were recrystallized twice (acetonitrile) to prepare 98, mp 202-204.0°: ir (CH_2Cl_2) 3400, 1590, 1485, 1465, 1390, 1380, 1185 and 1140 cm^{-1}; λ_{max}^{MeOH} 223 nm (ε 1400) and 301 (13000); pmr ($CDCl_3$) 1.07 (s, 6); mass spectrum (70 eV) m/e (rel intensity) 181 (12), 180 (100), 165 (71), 163

(21), 150 (22), 135 (51), 124 (81) and 79 (58).

For $C_{10}H_{16}ON_2$ m/e 180.1255 (calcd 180.1262).

Compound 98 was also formed when a degassed solution of ketone 78 in methylene chloride-d_2 was irradiated (λ_{max} 254 nm) at -78°. No other product was detected (by pmr).

Photolysis of Azo Compound 89

i) in $CDCl_3$

Azo compound 89 was prepared, by the method previously described, from hydrazine 90 which was in turn prepared from ketal 81 (36 mg). It was contaminated with a small amount of aniline (the distillation of aniline was not complete) (pmr). A degassed sample ($5x10^{-3}$ mm by freeze-thaw cycles) of 89 (and a trace of aniline) was prepared in a pmr tube (Pyrex) and the tube was sealed. The solution was pale yellow.

Upon irradiation at 0°, the color of the solution gradually changed to a deeper yellow. After 30 minutes of irradiation, ca. 70% of 89 was transformed in[illegible] hydrazone 94, and, 10 more minutes later, the only substance detected was 94 other than a trace of aniline.

ii) in CD_2Cl_2

Purif[illegible] hydrazine 90 was obtained from ketal 81

(39 mg) following the method previously described. The hydrazine 90 was reacted with mercuric oxide (35 mg) in CD_2Cl_2 (0.3 ml, passed through Na_2CO_3 layer) to give, after a filtration through a sintered glass (fine) funnel, a pmr solution of 89 in CD_2Cl_2, which was pale yellow. The pmr sample (Pyrex) was degassed to $<10^{-3}$ mm by freeze-thaw cycles, and showed no presence of aniline. Upon irradiation at -18∿-30° for 15 hours about a third of 89 was transformed to hydrazone 94. No sign of any other product was observed.

iii). in Acetone-d_6

Azo compound 89 was prepared from purified hydrazine 90, which was in turn prepared from ketal 81 following the method previously described. To make sure there was no aniline present, the azo compound 89 was placed in a distillation apparatus ($35°/<10^{-3}$ mm) for 4 hours to remove any volatile impurity. The residue was a pale yellow liquid, which was extracted with n-pentane/water. The solvent was evaporated and the residue was dried under reduced pressure (room temperature/$<10^{-3}$ mm). The pmr of a degassed solution ($<10^{-3}$ mm by freeze-thaw cycles) of the dried residue in acetone-d_6 (0.2 ml) showed only the signals corresponding to 89. When this sample (in the Pyrex pmr tube) was irradiated at -78° for 24 hours, no change in the pmr signals was observed.

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