Unsaturated Heterocyclic Systems. LIV. Photorearrangements of the Methyl-N-carbomethoxyazepines[1]

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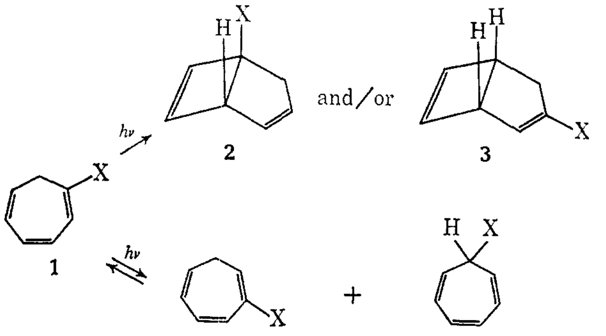
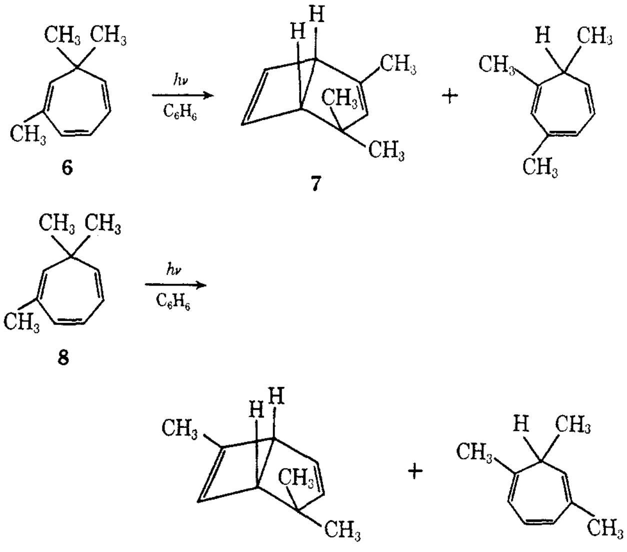
Irradiation of methanol solutions of 2-, 3-, and 4-methyl-N-carbomethoxyazepines (**10**, **14**, and **17**, respectively) with a Hanovia 450-W mercury arc under nitrogen through Pyrex yields in each instance a two-component mixture containing both possible bicyclic valence tautomers. All of the 2-carbomethoxy-2-azabicyclo[3.2.0]-hepta-3,6-dienes are primary photoproducts which may be considered to arise by disrotatory cyclization from the lowest lying excited states of the three azepines. Only in the case of **10** is product selectivity observed. The origin of this selectivity in terms of steric factors is discussed.

Irradiation of a number of conjugated medium-ring dienes and trienes in solution has been shown to give bicyclic structures which incorporate a cyclobutene ring, and the course of these reactions remains unaltered upon the introduction of heteroatoms into the ring system.[3] *A priori*, placement of a substituent at one of the vinyl carbons of a cyclic triene, *e.g.*, **1**, permits two competitive electrocyclic reactions which can lead to **2** and **3**. A. P. ter Borg[4,5] and Chapman[6] have shown that photoisomerizations of both 1- (**1**) and 7-substituted cycloheptatrienes (**5**) are complicated by 1,7-sigmatropic shifts of hydrogen, but nevertheless it is clear that the nature of the substituent exerts a substantial influence on the selectivity of formation of **2** and **3**. This effect appears to be chiefly electronic in nature.



1 **2** **3** **4** **5**

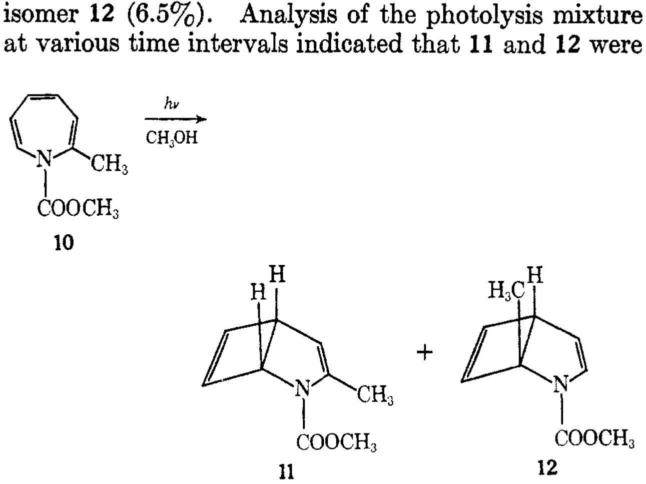
Jones has found that irradiation of 2,7,7- (**6**) and 3,7,7-trimethylcycloheptatriene (**8**) give **7** and **9**, respectively, together with products arising from 1,7 migrations of methyl and hydrogen.[7,8] In these cyclizations, a single isomer of the bicyclic product was formed in each case, indicating that the course of the isomerizations was controlled by steric interactions.



6 **7** **8** **9**

The availability of a series of substituted 1H-azepines[9] has permitted us to examine the effect of methyl groups on the cause of photochemical electrocyclic reactions in these 8π-heterocyclic systems.

The 2-Methyl Derivative.—Irradiation of 2-methyl-N-carbomethoxyazepine (**10**) in dilute methanol solution for 2 hr gave a mixture which consisted of 2-carbomethoxy-3-methyl-2-azabicyclo[3.2.0]hepta-3,6-diene (**11**, 93.5%) and the corresponding 1-methyl isomer **12** (6.5%). Analysis of the photolysis mixture at various time intervals indicated that **11** and **12** were primary photoproducts and that neither bicyclic compound was noticeably destroyed upon continued irradiation. The assignments of structure to the photoproducts were based chiefly on spectral data, analysis of which was rendered particularly facile because of the extensively analyzed nmr spectrum of the parent



10 **11** **12**

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[1] For previous paper in this series, see L. A. Paquette, D. E. Kuhla, and J. H. Barrett, *J. Org. Chem.*, **34**, 2879 (1969).

[2] National Institute of Health Predoctoral Fellow, 1965–1968.

[3] See, for example, (a) L. A. Paquette and J. H. Barrett, *J. Amer. Chem. Soc.*, **88**, 1718 (1966); (b) L. A. Paquette, J. H. Barrett, R. P. Spitz, and R. Pitcher, *ibid.*, **87**, 3417 (1965); (c) L. A. Paquette, *ibid.*, **86**, 500, 4092 (1964); (d) L. A. Paquette, *Tetrahedron Lett.*, 2027 (1963), and references cited in these papers.

[4] A. P. ter Borg and H. Kloosterziel, *Rec. Trav. Chim.*, **84**, 241 (1965).

[5] A. P. ter Borg, E. Razenberg, and H. Kloosterziel, *Chem. Commun.*, 1210 (1967).

[6] G. W. Borden, O. L. Chapman, R. Swindell, and T. Tezuka, *J. Amer. Chem. Soc.*, **89**, 2979 (1967).

[7] L. B. Jones and V. K. Jones, *ibid.*, **90**, 1540 (1968).

[8] L. B. Jones and V. K. Jones, *ibid.*, **89**, 1880 (1967).

[9] L. A. Paquette, D. E. Kuhla, J. H. Barrett, and R. J. Haluska, *ibid.*, **34**, 2866 (1969).

bicyclic (**13**) (Table I).[3a] The nmr spectrum of **11** shows the C-methyl group at δ 2.04 indicative of its attachment to sp^2-hybridized carbon. H-3 in **13** resonates at approximately δ 6.56, and, since this absorption is absent in the spectrum of **11**, it follows that the ring substituent occupies this position. The remaining hydrogens appear as multiplets in the appropriate regions. In the spectrum of **12**, the methyl substituent is positioned at C-1 (δ 1.60).[10] The remaining bridgehead proton is seen as a somewhat broadened doublet at δ 3.26 while the vinyl protons take on the appearance characteristic of **13**. The mass spectra of **11** and **12** also confirm the assigned structures (see below).

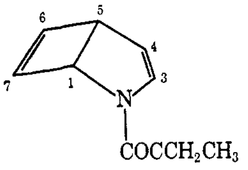

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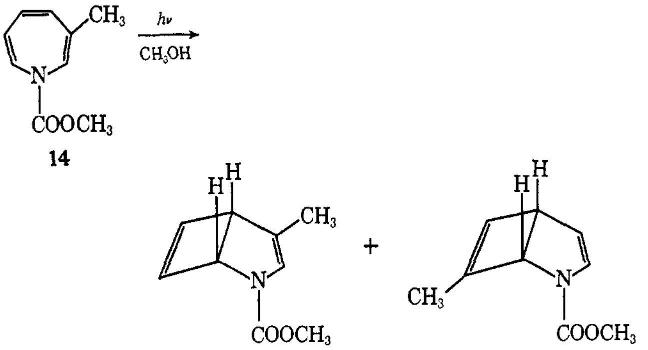
TABLE I

PROTON CHEMICAL-SHIFT VALUES FOR VARIOUS 2-CARBALKOXY-2-AZABICYCLO[3.2.0]HEPTA-3,6-DIENES

	δ units					
Compd	H-1	H-3	H-4	H-5	H-6	H-7
13	4.88	6.56	5.18	3.88	6.42	6.04
11	4.75	...	4.80	3.51	6.19	5.89
12	...	6.24	4.87	3.26	6.15	6.05
15	4.79	6.12	...	3.64	6.40	5.99
16	4.71	6.40	5.08	3.60	5.99	...
18	4.38	6.35	4.97	...	6.35	5.89
19	4.69	6.48	5.12	3.66	...	5.72

The 3-Methyl Derivative.—When a 3% methanol solution of 3-methyl-N-carbomethoxyazepine (**14**) was irradiated for 12 hr, there resulted the complete disappearance of **14** and the concomitant formation of two photoproducts at equal rates in a 1:1 ratio. There was no indication of product interconvertibility. Preparative scale vpc separation of the mixture afforded pure samples of valence tautomers **15** and **16**. The more rapidly eluted isomer was identified at 4-methyl-2-carbomethoxy-2-azabicyclo[3.2.0]hepta-3,6-diene (**15**). In agreement with this structure, the nmr spectrum of **15** exhibits methyl absorption at δ 1.65 (t, J = 1.5 Hz, allylic coupling to H-3) and lacks the peak characteristic of H-4 (usually found in its isomers at δ 4.8–5.1). The bicyclic skeleton and the location of the methyl substituent on the five-membered ring were confirmed by mass spectral analysis.

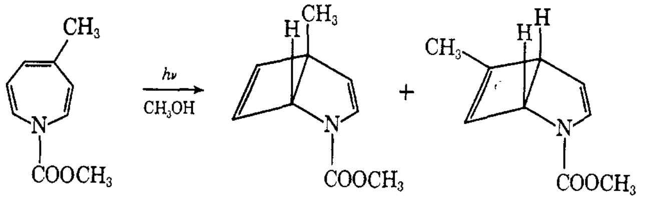


14 **15** **16**

The nmr spectrum of photoproduct **16** shows a methyl group on a double bond (δ 1.68). The vinyl protons appear as the expected broadened multiplets with the peak due to the proton at position 7 being absent. The multiplets attributable to H-6 and H-5 appear to be somewhat simplified (relative to the absorptions in **13**) by virtue of the introduction of the methyl group at C-7.

The 4-Methyl Derivative.—Irradiation of a 4% solution of **17** in anhydrous methanol was found to result in the total consumption of starting azepine during 12 hr. After careful removal of solvent, the resulting two-component product mixture was subjected to preparative vpc. The first fraction was found to be the 5-methyl derivative **18** (δ_{CH_3} 1.30), whereas the more slowly eluted substance was the 6-methyl isomer **19** (δ_{CH_3} 1.72). The ratio of **18**:**19** was 1.5:1.

It should be noted that all six possible monomethyl derivatives of 2-carbomethoxy-2-azabicyclo[3.2.0]hepta-3,6-diene have now been isolated. Comparison of the derived nmr spectra of these isomeric bicyclic heterocycles (Table I) provides a source of internal consistency for the experimental observations and structural assignments.



17 **18** **19**

Mass Spectral Studies.—The x-methyl-2-carbomethoxy-2-azabicyclo[3.2.0]hepta-3,6-dienes are rapidly oxidized upon exposure to air.[11] When handled or stored in an inert atmosphere, however, the pure substances appeared to be stable for a period of a few days. In all six cases, mass spectral analysis gave evidence of abundant molecular ion (m/e 165) formation (Table II).

TABLE II

MASS SPECTRAL DATA FOR THE x-METHYL-2-CARBOMETHOXY-2-AZABICYCLO[3.2.0]HEPTA-3,6-DIENES

Compd	m/e (% relative abundance)
11	39 (30), 44 (20), 51 (17), 52 (15), 53 (21), 59 (29), 65 (43), 77 (21), 78 (23), 79 (20), 80 (13), 91 (23), 92 (11), 94 (61), 104 (31), 105 (18), 106 (61), 132 (16), 133 (55), 138 (11), 139 (100), 140 (10), 165 (52).
12	39 (29), 50 (11), 51 (18), 52 (11), 53 (16), 59 (20), 63 (10), 65 (51), 77 (22), 78 (23), 79 (19), 80 (13), 91 (18), 94 (42), 104 (25), 105 (15), 106 (100), 107 (11), 132 (15), 133 (43), 139 (53), 165 (52).
15	39 (50), 32 (21), 50 (21), 51 (43), 52 (31), 53 (34), 59 (29), 63 (15), 65 (21), 77 (60), 78 (34), 79 (51), 80 (20), 91 (21), 94 (66), 103 (23), 106 (100), 133 (23), 139 (71), 165 (57).
16	39 (58), 42 (19), 50 (17), 51 (34), 52 (21), 53 (25), 54 (12), 55 (14), 59 (31), 63 (13), 65 (11), 77 (58), 78 (25), 79 (48), 80 (51), 81 (16), 91 (13), 104 (19), 106 (87), 125 (100), 133 (13), 165 (47).
18	39 (11), 44 (13), 50 (11), 51 (19), 52 (16), 53 (11), 59 (11), 77 (29), 78 (19), 79 (28), 91 (25), 94 (19), 104 (24), 105 (14), 106 (64), 132 (57), 133 (100), 134 (12), 139 (33), 165 (47).
19	39 (29), 44 (40), 50 (10), 51 (18), 52 (14), 53 (12), 59 (23), 63 (10), 65 (10), 77 (27), 78 (15), 79 (24), 80 (34), 91 (23), 104 (27) 106 (38), 125 (100), 132 (43), 133 (85), 134 (12), 165 (34).

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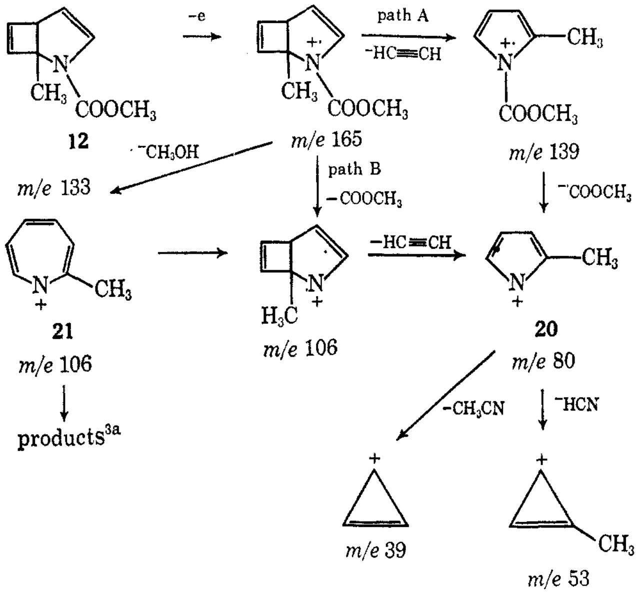
(10) It seems likely that this methyl chemical shift is a result of deshielding by the neighboring urethan function. Compare the values for δ_{CH_3} displayed by the other bicyclic isomers.

(11) This property precluded combustion analysis.

The principal fragmentation mode of the bicyclic valence tautomers was expected[3a] to be the loss of C-6 and C-7 and their attached substituents as an acetylene derivative, and this was generally observed (path A). Thus, peaks corresponding to M − HC≡CH (*m/e* 139) are clearly seen in the spectra of **11**, **12**, **15**, and **18**, whereas the molecular ions of **16** and **19** fragment with the ejection of neutral propyne and formation of an ion with *m/e* 125. The base peaks in the spectra of **12** and **15** are located at *m/e* 106, indicating that loss of the carbomethoxyl residue (path B) is particularly favored in these instances. In actuality, path B appears to compete favorably with path A in the decomposition of most of these compounds. Convincingly, the various differences and similarities serve to provide firm additional support for the nmr-based structural assignments. Scheme I depicts the proposed fragmentation pathway for **12**.

SCHEME I



Loss of methanol from the molecular ion would also seem to be facile in a number of examples; where this is a major process, an intense peak at *m/e* 133 is seen. Of the many lower molecular weight product ions, the majority can be construed as arising from intermediate ions such as **20**, **21**,[9] or the nonmethylated counterpart of **20**. The ions of mass 39 and 53, for example, are very probably due to the cyclopropenyl cation and its methyl homolog, respectively.[12]

Discussion

Woodward–Hoffmann orbital symmetry arguments for electrocyclic reactions indicate that cyclobutene production very likely occurs by disrotatory motion of π orbital envelopes in the lowest lying excited state. In monosubstituted N-carbomethoxyazepines, however, two different disrotatory cyclizations are possible. The ratio of primary photoproducts from the irradiation of such substituted 1H-azepines reveals the influence exerted by the R group upon the two competitive electrocyclic processes. The irradiation of **10** was seen to be quite selective, leading to **11** and **12** in a ratio of 14:1; the 3-methyl isomer (**14**) gave **15** and **16** in equimolar quantities; lastly, photolysis of **17** afforded **18** and **19** in a ratio of 1.5:1.

Of the two possible 2-azabicyclo[3.2.0]hepta-3,6-dienes derivable from **10**, that in which the ring methyl substituent occupies the more congested angular position (**12**) is produced only in low yield, indicating dominant steric effects in this reaction. On this basis, the observation that **14** produces both possible valence tautomers (**15** and **16**) in equal amounts is not unanticipated, since the photoisomers are not expected to differ measurably in strain energy. Significantly, however, the 4-methyl function in **17** does not exert an overwhelming directive influence on the course of the photoreaction, despite the fact that in **18** the alkyl group is located at an angular position.

It appears, therefore, that the presence of a methyl group at an angular position does not alone constitute a significantly strong deterrent to product formation. Rather, the selectivity noted in the cyclization of **10** is rationalized on the basis of serious nonbonded interactions between the methyl group and the rather bulky substituent on nitrogen (subject, of course, to pyramidal inversion) as disrotation leading to **12** begins. Such repulsive forces, which are absent in the alternative electrocyclization, are apparently sufficient to cause the preferred formation of **11**. As noted earlier, steric factors also seem to control the valence isomerization of *x*,7,7-trimethylcycloheptatrienes.[7,8] In contrast, the photorearrangements of **14** and **17** are not affected by nonbonded interactions and selectivity is not observed. These results are congruent with HMO calculations which indicate no preference for the competitive cyclizations in the absence of polarizable substituents.[8]

Experimental Section[13]

Irradiation of 2-Methyl-N-carbomethoxyazepine (**10**).—A solution of 4.31 g (0.026 mol) of **10**[9] in 350 ml of methanol was irradiated at room temperature under a nitrogen atmosphere with an immersion type Hanovia 450-W lamp equipped with a Pyrex filter. The progress of the reaction was followed by vpc.[14] After 2 hr, the azepine had completely reacted and the solvent was removed under reduced pressure at 25°. The remaining light yellow liquid was found to be a two-component mixture (ratio of 14:1, vpc analysis). Vacuum distillation gave 3.49 g (81%) of pale yellow liquid, bp 46–48° (0.05 mm); the ratio of components was unaltered. Preparative scale vpc[14] at 130° cleanly separated the two photoproducts. The most rapidly eluted material proved to be **11** (93.5%), ir $\nu_{max}^{CCl_4}$ 1721 cm^{-1}; the minor product was 12 (6.5%), ir $\nu_{max}^{CCl_4}$ 1718 cm^{-1}.

Irradiation of 3-Methyl-N-carbomethoxyazepine (**14**).—A solution of 1.25 g (7.56 mmol) of **14**[9] in 350 ml of methanol was irradiated as above. After 12 hr, vpc analysis indicated the absence of **14** and the presence of two photoproducts in equal amounts. The reaction mixture was concentrated *in vacuo* at 25° and the residue was distilled to give 1.02 g (81.5%) of a mixture of **15** (50%) and **16** (50%). Preparative scale vpc[14] at 115° afforded pure samples of the two bicyclic valence tautomers.

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(12) For a discussion of the mass spectra of pyrroles, see H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1967, pp 596–614.

(13) The nmr spectra were determined with Varian A-60 or A-60A spectrometers. The mass spectra were measured with an AEI MS-9 instrument at an ionizing energy of 70 eV. Infrared spectra were determined with a Perkin-Elmer Model 237 spectrometer fitted with a sodium chloride prism.

(14) A 5 ft × 0.25 in. aluminum column packed with 20% SF-96 on 60–80 mesh Chromosorb W at 157° was employed in conjunction with a Varian-Aerograph A-90P3 instrument.

The more rapidly eluted product proved to be **15**, ir $\nu_{max}^{CCl_4}$ 1706 cm^{-1}; the second substance was identified as **16**, ir $\nu_{max}^{CCl_4}$ 1715 cm^{-1}.

Irradiation of 4-Methyl-N-carbomethoxyazepine (**17**).—A solution of 1.50 g (9.1 mmol) of **17**[9] in 350 ml of methanol was irradiated as described for **10** for 12 hr. The reaction mixture was concentrated and samples of **18** (60%, ir $\nu_{max}^{CCl_4}$ 1712 cm^{-1}) and **19** (40%, ir $\nu_{max}^{CCl_4}$ 1712 cm^{-1}) were collected by gas chromatography[14] at 110°.

Registry No.—**11**, 20628-97-1; **12**, 20628-98-2; **13**, 20628-99-3; **15**, 20629-00-9; **16**, 20629-01-0; **18**, 20629-02-1; **19**, 20629-03-2.

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Unsaturated Heterocyclic Systems. LV. Cycloaddition Reactions of Derivatives of 1H-Azepine[1]

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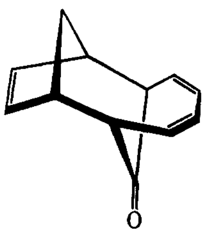
The cycloadditions of N-substituted azepines to various dienophiles and dienes have been studied. With tetracyanoethylene, the azepines add as 1,4-dienes without prior valence bond isomerization; however, a directional specificity is observed with the monomethyl ring substituted examples. With N-phenylmaleimide, there is again evidenced 1,4 addition to the seven-membered ring, the stereochemical outcome (*endo*) being in agreement with orbital symmetry considerations. In the case of isobenzofurans, $(4 + 2)\pi$ cycloaddition to the 4,5 bond of the azepines occurs. Significantly, the stereochemistry of these reactions is likewise *endo*. 2,5-Dimethyl-3,4-diphenylcyclopentadienone functions in a similar fashion. Therefore, this kinetic preference for addition to the double bond of the azepine ring most remote from the nitrogen atom does not appear to be dependent on the electronic characteristics of the 4π donor. These results indicate that the 1H-azepine nucleus is unique in its capability to undergo thermally induced cycloaddition reactions without recourse to prior valence tautomerism.

A common and fundamental property of conjugated medium-ring polyenes is their capability for cycloaddition. Frequently, however, addition of a dienophile to a cyclic polyolefin eventuates in Diels–Alder $[(4 + 2)\ \pi]$ reaction with the valence tautomer of the triene or tetraene system. Thus, cyclooctatetraenes (**1**), azacyclooctatetraenes (**2**), cycloheptatrienes (**3**), and oxepins (**4**) yield tricyclic adducts formally derived from bicyclo[4.2.0]octatriene,[3] 7-azabicyclo[4.2.0]octatriene,[4] norcaradiene,[5] and benzene oxide[6] intermediates, respectively. The reported exceptions to this general trend appear to be tropone (**5**),[7] certain tropolones and their ethers,[7] and 1H-azepines (**6**).[8] This difference in behavior is understandable in view of the facility with which **1**–**4** equilibrate with their valence tautomers and the contrasting difficulty presumably experienced by **5**[9] and **6**[10] to attain a similar rapid equilibrium with their bicyclic forms. Cycloaddition to the diene tautomers is kinetically preferred because of the favorable increase in coplanarity of the four participating π orbitals in these structures.

More recently, several reports concerning the cycloaddition of cyclic trienes to suitable dienes in a $(6 + 4)\pi$ reaction have appeared. Thus, tropone (**5**) condenses readily with cyclopentadiene to give **7**,[11] whereas both **5** and cycloheptatriene add to 2,5-dimethyl-3,4-diphenylcyclopentadienone to afford **8a** and **8b**, respectively.[12] Orbital symmetry considerations indicate that such reactions, if effected with heat, may be concerted and should exhibit a preference for *exo* addition



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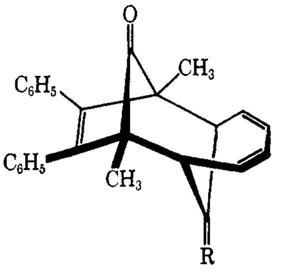

8a, R = O
b, R = H_2

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[1] For previous paper, see L. A. Paquette and D. E. Kuhla, *J. Org. Chem.*, **34**, 2885 (1969).

[2] National Institutes of Health Predoctoral Fellow, 1965–1968.

[3] For a review, consult G. Schröder, "Cyclooctatetraene," Verlag Chemie, Weinheim/Bergstr., Germany, 1965.

[4] L. A. Paquette and T. Kakihana, *J. Amer. Chem. Soc.*, **90**, 3897 (1968).

[5] (a) K. Alder and G. Jacobs, *Chem. Ber.*, **86**, 1528 (1953); (b) M. J. Goldstein and A. H. Gervitz, *Tetrahedron Lett.*, 4417 (1965); (c) G. H. Wahl, Jr., *J. Org. Chem.*, **33**, 2158 (1968).

[6] (a) E. Vogel, R. Schubart, and W. A. Böll, *Angew. Chem. Intern. Ed. Engl.*, **3**, 510 (1964); (b) E. Vogel, E. A. Böll, and H. Günther, *Tetrahedron Lett.*, 609 (1965).

[7] (a) T. Nozoe, T. Mukai, K. Takase, and T. Nagase, *Proc. Jap. Acad.*, **28**, 477 (1962); *Chem. Abstr.*, **48**, 2678 (1954); (b) J. Meinwald, S. L. Emerson, N. C. Yang, and G. Buchi, *J. Amer. Chem. Soc.*, **77**, 4400 (1955); (c) O. L. Chapman and D. J. Pasto, *ibid.*, **81**, 3696 (1959); (d) T. Nozoe, T. Mukai, T. Nagase, and Y. Toyooka, *Bull. Chem. Soc. Jap.*, **33**, 1147 (1960); (e) J. Ciabattoni, J. E. Crowley, and A. S. Kende, *J. Amer. Chem. Soc.*, **89**, 2778 (1967); (f) Y. Kitahara, I. Murata, and T. Nitta, *Tetrahedron Lett.*, 3003 (1967); (g) S. Ito, H. Takeshita, Y. Shoji, Y. Toyooka, and T. Nozoe, *ibid.*, 3215 (1968).

[8] (a) J. E. Baldwin and R. A. Smith, *J. Amer. Chem. Soc.*, **87**, 4819 (1965); (b) A. S. Kende, P. T. Izzo, and J. E. Lancaster, *ibid.*, **87**, 5044 (1965).

[9] Valence tautomerism of a tropone or tropolone would lead to an energetically unfavorable cyclopropanone derivative.

[10] (a) L. A. Paquette, D. E. Kuhla, J. H. Barrett, and R. J. Haluska, *J. Org. Chem.*, **34**, 2866 (1969); (b) L. A. Paquette, D. E. Kuhla, and J. H. Barrett, *ibid.*, **34**, 2879 (1969); (c) L. A. Paquette, J. H. Barrett, and D. E. Kuhla, *J. Amer. Chem. Soc.*, **91**, 3231 (1969).

[11] (a) R. C. Cookson, B. V. Drake, J. Hudec, and A. Morrison, *Chem. Commun.*, 15 (1966); (b) S. Ito, Y. Fujise, T. Okuda, and Y. Inoue, *Bull. Chem. Soc. Jap.*, **39**, 1951 (1966).

[12] R. B. Woodward and K. Houk, unpublished work cited by R. B. Woodward, "Aromaticity," Special Publication No. 21, Chemical Society (London), 1967, pp 242–246.