Thermochemical Behavior of Conjugated *cis*-Bicyclo[5.1.0]octenones, *cis*- and *trans*-Bicyclo[5.2.0]non-2-en-4-ones, and Their Methylene Analogs

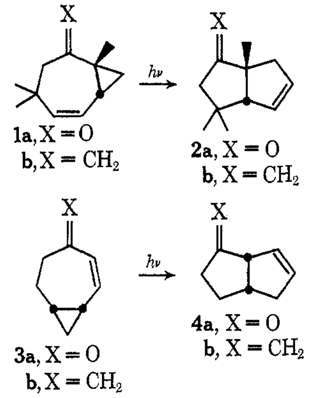
Leo A. Paquette,* Richard P. Henzel,[1] and Richard F. Eizember

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210

Received April 19, 1973

The pyrolysis of *cis*-bicyclo[5.1.0]oct-2-en-4-one (**3a**), *cis*-bicyclo[5.1.0]oct-5-en-2-one (**1a**), *cis*-bicyclo[6.1.0]-non-6-en-2-one (**25**), and their methylene derivatives has been studied in a flow system in the 300–600° range. Three major processes obtain, namely, 1,5-homodienyl hydrogen shift, ring contraction by 1,3 shift of the internal cyclopropane bond, and isomerization to a less strained bicyclic system by vinylcyclopropane rearrangement involving an external cyclopropyl bond. However, not all three structural types give evidence of totally similar chemical behavior and these differences are discussed. Thermal activation of *cis*- and *trans*-bicyclo[5.2.0]-non-2-en-4-one and their methylene analogs exhibit, in contrast, a major tendency for fragmentation with loss of ethylene. Bond relocation to afford [3.2.2] bicyclic products does operate in certain examples, but a stereochemical dependence is noted. Most interestingly, no 1,3 shift of the central cyclobutane bond was evidenced in any of the cases studied. This and other marked divergences in behavior between the vinylcyclopropane and vinylcyclobutane systems are presented in a mechanistic framework.

cis-Bicyclo[5.1.0]oct-5-ene derivatives **1** have been discovered to transmute to **2** upon irradiation, with vinylcyclopropane rearrangement occurring from the respective singlet states.[2] A formally analogous skeletal change takes place during photoexcitation of **3**, but the comparison is superficial since **3a** and **3b** preferably rearrange from their T_1 excited states.[2] Attempts to photoisomerize *cis*- and *trans*-bicyclo[5.2.0]non-2-en-4-one and their methylene derivatives have to date afforded polymeric materials, except in protic media where solvent incorporation occurs in some instances.[2] In connection with these photochemical studies on medium ring ketones and olefins possessing a double bond and a cyclopropane or cyclobutane ring in conjugation, we have examined the thermally induced transformations of such substrates for comparison purposes. Since vibrationally excited molecules rearrange, in general, *via* singlet biradical intermediates if concerted pathways are unavailable, it was the purpose of this investigation to determine the consequence of thermal activation on vinylcyclopropane and vinylcyclobutane systems incorporated into various medium ring frameworks.

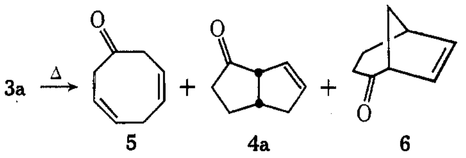


cis-Bicyclo[5.1.0]oct-2-enes 3a and 3b.—Pyrolysis of **3a** in a flow system for short contact times (≤3 sec) at reduced pressure and moderate temperatures (312–430°) resulted in rather efficient conversion to 3,6-cyclooctadienone (**5**, Table I). At more elevated temperatures, the quantities of **3a** and **5** in the pyrolysate were seen to decrease with attendant formation of significant quantities of ketones **4a** and **6**. As yet uncharacterized carbonyl compounds were also produced in less significant quantities at 470–530°.

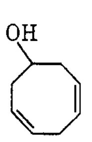
Table I

Pyrolysis of **3a** at Various Temperatures

Temp, °C	Pyrolysate composition, %: 3a	5	4a	6	Unknowns
312	78	22			
350	53	47			
390	10	89			1
432	10	85			5
470	5	71	8	11	5
530	12	42	18	21	7
600			51	24	25



Characterization of **5** and particularly its differentiation from the remaining five isomers of cyclooctadienone was achieved in the following way. Firstly, the ketone exhibited a nonconjugated carbonyl absorption in the infrared at 1720 cm^{-1} (neat) and only end absorption in the ultraviolet region. Hydrogenation proceeded with the uptake of 2 equiv of hydrogen to give uniquely cyclooctanone. Ultimate structural confirmation was achieved by sodium borohydride reduction to alcohol **7**, whose ir and nmr spectra were identical with those of an authentic sample.[3]



7

A possible unequivocal synthesis of **6** was suggested by the earlier work of Hall in which deamination of **8** was claimed to afford **9**.[4] However, repetition of

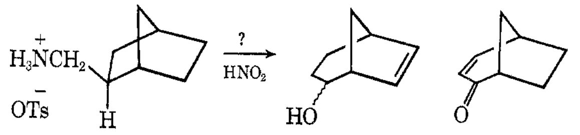
---

[1] National Science Foundation Graduate Trainee, 1970–1972.

[2] L. A. Paquette, G. V. Meehan, R. P. Henzel, and R. F. Eizember, *J. Org. Chem.*, **38**, 3250 (1973).

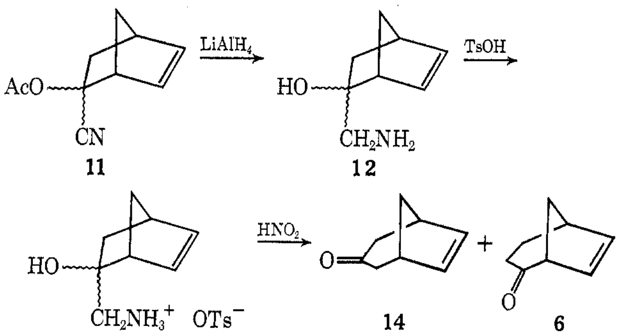
[3] P. Radlick and S. Winstein, *J. Amer. Chem. Soc.*, **86**, 1866 (1964). We thank Professor Radlick for making copies of these spectra available to us.

[4] H. K. Hall, *J. Amer. Chem. Soc.*, **82**, 1209 (1960).



8 **9** **10**

this reaction and oxidation of the resulting mixture of alcohols gave, in our hands, very complex mixtures which presumably contain the isomeric ketone **10** as the major component. To avoid the operation of multiple carbonium ion rearrangements such as take place during this Tiffeneau ring expansion, recourse was made to the Demjanov–Tiffeneau procedure. Accordingly, acetoxy nitrile **11**,[5] obtained by the Diels–Alder reaction of cyclopentadiene and α-acetoxyacrylonitrile according to Bartlett,[6] was reduced with lithium aluminum hydride and converted to the tosylate salt **13** in conventional fashion. Nitrous acid deamination led to a 45:55 mixture of **14** and **6** which was separated by preparative vpc methods. The less abundant isomer was identified by comparison of spectra and melting point with those of authentic material;[7] the major component proved identical with **6** in all respects.[8]



11 **12** **13** **14** **6**

Ketones **4a** and **6** were stable to the pyrolysis conditions. Interestingly, however, **5** undergoes partial reversion to **3a** and irreversible conversion to **4a** and **6** in the temperature range studied (Table II).

$$\mathbf{3a} \overset{\Delta}{\rightleftarrows} \mathbf{5}$$

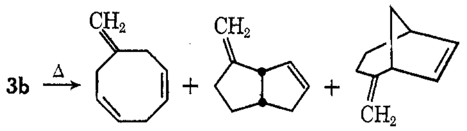
TABLE II
PYROLYSIS OF 5 AT VARIOUS TEMPERATURES

	Pyrolysate composition, %				
Temp, °C	**5**	**3a**	**4a**	**6**	Unknown
352	93	5			2
390	92	7			1
470	64	5	9	13	8

When related diene **3b** was heated under analogous conditions, similar thermal interconversions were observed (Table III). In this instance, rearrangement to bicyclic isomers occurred at somewhat lower temperatures than in the case of **3a**. The nmr spectrum of **15** shows many similarities to that of **5** and, in particular, reflects the symmetry inherent in the molecule. Its catalytic hydrogenation afforded only methylcyclooctane. Authentic **16** was synthesized by the action of methylenetriphenylphosphorane on **6**.

TABLE III
PYROLYSIS DATA OF 3b AT VARIOUS TEMPERATURES

	Pyrolysate composition, %				
Temp, °C	**3b**	**15**	**4b**	**16**	Unknown
365	88	11	0.5	0.5	
405	61	35	2	1	1
450	35	52	8	5	1
495	8	24	39	27	2
530	6	18	42	31	3
575		3	54	40	3



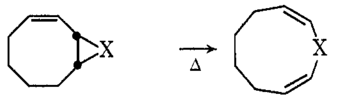
15 **4b** **16**

As revealed by the data in Table IV, 7-methylene-1,4-cyclooctadiene (**15**) also exists in thermal equilibrium with **3b** and is isomerized to **4b** and **16**. The latter two hydrocarbons proved stable over the entire range of temperatures examined.

TABLE IV
PYROLYSIS DATA OF 15 AT 455°

	Pyrolysate composition, %				
Temp, °C	**15**	**3b**	**4b**	**16**	Unknown
455	69	21	5	4	1

That electrocyclic opening of the cyclopropane ring in **3a** and **3b** which gives rise to **5** and **15**, respectively, follows a precedented 1,5-homodienyl hydrogen shift pathway elucidated initially by Doering[10] and Winstein,[11] and generalized in a number of subsequent investigations.[12–15] For example, to the extent that 9-substituted *cis*-bicyclo[6.1.0]non-2-ene derivatives carry no endo substituent at C_9 (*i.e.*, **17a–d**), concerted 1,5-hydrogen migration seemingly operates and the involvement of the unfavorable "saddle" conformation (**19**)



17a, $X = CH_2$[10,12]

b, $X = C{<}^{\mathrm{CH_2OH}}_{\mathrm{H}}$[13]

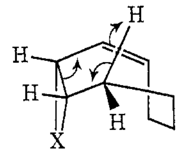
c, $X = O$[14]

d, $X = C{=}CH_2$[15]

e, $X = C{<}^{\mathrm{H}}_{\mathrm{CH_2OH}}$[13]

f, $X = CBr_2$[16]

18



19

---

(5) Previously reported to consist of 75% exo acetate and 25% endo acetate: W. L. Dilling, R. D. Kroening, and J. C. Little, *J. Amer. Chem. Soc.*, **92**, 928 (1970).

(6) P. D. Bartlett and B. E. Tate, *J. Amer. Chem. Soc.*, **78**, 2473 (1956).

(7) N. A. LeBel and R. N. Liesemer, *J. Amer. Chem. Soc.*, **87**, 4301 (1965).

(8) Subsequent to our completion of this synthesis, LeBel[9] has described a more lengthy and involved route to this ketone. Although their reported ir and nmr spectra compare very closely with those of our material, their cited melting point (65–81°) indicates the obtention of a less pure sample by these workers.

(9) N. A. LeBel, N. D. Ojha, J. R. Menke, and R. J. Newland, *J. Org. Chem.*, **37**, 2896 (1972).

(10) W. von E. Doering and W. R. Roth, *Angew. Chem.*, **75**, 27 (1963); *Angew. Chem., Int. Ed. Engl.*, **2**, 115 (1963).

(11) D. S. Glass, J. Zirner, and S. Winstein, *Proc. Chem. Soc.*, 276 (1963); P. Radlick and S. Winstein, *J. Amer. Chem. Soc.*, **85**, 344 (1963).

(12) D. S. Glass, R. S. Boikess, and S. Winstein, *Tetrahedron Lett.*, 999 (1966).

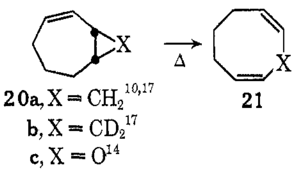
(13) D. L. Garin, *J. Amer. Chem. Soc.*, **92**, 5254 (1970).

(14) J. K. Crandall and R. J. Watkins, *Tetrahedron Lett.*, 1717 (1967).

(15) P. Radlick, W. Fenical, and G. Alford, *Tetrahedron Lett.*, 2707 (1970).

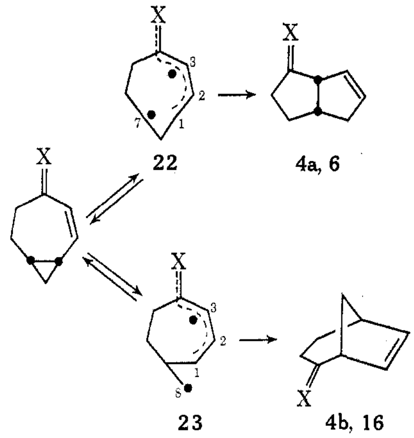
has been strongly implicated.[11,12] When attainment of this conformation is inhibited for steric reasons, as in the case of **17e** and **17f**, this rearrangement pathway is not followed.[13,16]

The less flexible *cis*-bicyclo[5.1.0]oct-2-ene systems (**20**) find it more energetically demanding to attain the requisite favored conformation and, although they do undergo bond reorganization to **21**, isomerization is less facile. Energies of activation for several rearrangements of this type have been determined and those associated with **17a** (E_a = 31.4 kcal/mol[12]) and **20a** (E_a = 38.6 kcal/mol[17]) illustrate the point clearly. In a number of examples, as in the present situation, this 1,5-hydrogen shift has been found to be reversible, the equilibrium lying heavily in favor of the monocyclic valence isomer. In flow systems such as the one employed herein, equilibrium is not achieved and, consequently, the data in Tables I–IV serve only as an indication of relative stabilities.



The current situation is further complicated at the more elevated temperatures by the incursion of two additional reactions, both of which are of the vinylcyclopropane–cyclopentene type. That these pathways are encountered only upon considerable thermal activation is consistent with the higher activation energies generally observed for such rearrangements (45–55 kcal/mol).[18] Were orbital symmetry factors in control of these 1,3 shifts a [$_\pi 2_a$ + $_\sigma 2_s$] or [$_\pi 2_s$ + $_\sigma 2_a$] process would necessarily operate. These transformations would give either a trans-fused [3.3.0] bicyclic containing a cis double bond or a cis-fused product containing a trans double bond. Neither of these results because of prohibitive strain, and biradicals are assumed to intervene.

The data require that the cyclopropane ring in **3a** and **3b** undergo homolytic scission in two ways in competitive fashion.[19] Rupture of the internal cyclopropane bond leads to **22**, which may return to starting material by C_1–C_7 bonding or proceed to **4a** or **6** upon C_3–C_7 bond formation. Similarly, biradical **23** can experience reclosure to the [5.1.0] bicyclic or cyclization to **4b** or **16**. The formation of comparable amounts of both product types may signal control of reactivity by a composite of conformational, steric, and electronic effects. It will be seen below that this apparently delicate balance of factors which exists with *cis*-bicyclo[5.1.0]oct-2-enes may be readily disrupted.



***cis*-Bicyclo[5.1.0]oct-5-enes 1a and 1b and Their [6.1.0] Bicyclic Homologs.**—When **1a** was heated at 500° for ≤3 sec in the flow system, a product mixture composed of **1a** and **2a** (ratio 3:1) was obtained (95% mass balance). An increase in temperature to 550° under the same conditions led to greater than 98% conversion to **2a**. At 600°, no **1a** remained and **2a** was the only volatile product isolated (50% yield). A point of interest was the observation that hydrocarbon **1b** likewise rearranges exclusively to **2b** but with a facility greater than its ketone counterpart. At 500°, for example, the clear pyrolysate consisted of 20% of **1b** and 80% of **2b** (85% mass balance). At 550°, vpc analysis of the reaction mixture showed it to be free of any unrearranged **1b**.

To extend the range of these transformations and demonstrate the general nature of the vinylcyclopropane rearrangement leading to ring-contracted (n − 2) products, the present work was broadened to include **25** and **26**. *cis*-Bicyclo[6.1.0]non-6-en-2-one (**25**) was synthesized in 80% yield from 2,4-cyclooctadien-1-one (**24**)[20] by reaction with dimethyloxosulfonium methylide. The spectral properties of **25** and methylene derivative **26** which are detailed in the Experimental Section serve to establish their gross structure. Pyrolysis of **25** at 600° resulted in only 10% conversion to a single isomeric product subsequently shown to be **27** on the basis of spectra and hydrogenation to *cis*-bicyclo[4.3.0]nonan-2-one (**29**).[21] At more elevated temperatures (Table V), the conversion to **27** could be enhanced somewhat. At 700°, however, significant competitive decomposition began to set in. By way of contrast, **26** underwent 98% conversion to **28** at 600° (92% mass recovery). The structure assigned to the product diene was confirmed by hydrogenation to **31** and independent synthesis of this same hydrocarbon from **29** (see scheme).

TABLE V

PYROLYSIS OF **25** AT VARIOUS TEMPERATURES

	Pyrolysate composition, %		
Temp, °C	**25**	**27**	Unknowns
600	90	10	
650	67	33	
700	70	17	13

The greater ease of rearrangement of **1a** and **1b** relative to **25** and **26** is not reconcilable with the increased conformational flexibility of the [6.1.0] bicyclics. Past experimental experience provides evidence that less sterically constrained systems generally rearrange more smoothly, particularly when a concerted migration is

---

(16) M. S. Baird, D. G. Lindsay, and C. B. Reese, *Chem. Commun.*, 784 (1968).

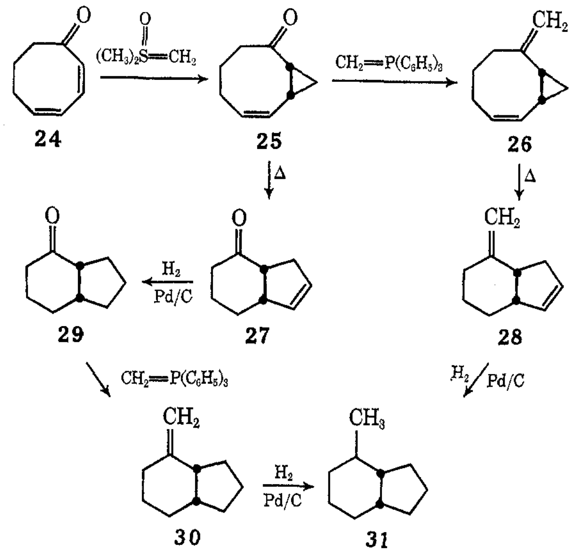
(17) W. Grimme, *Chem. Ber.*, **98**, 756 (1965).

(18) W. von E. Doering and E. K. G. Schmidt, *Tetrahedron*, **27**, 2005 (1971).

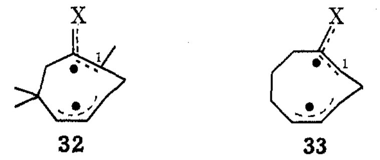
(19) This conclusion is warranted since **4a**, **6**, **4b**, and **16** are produced irreversibly at the temperatures employed.

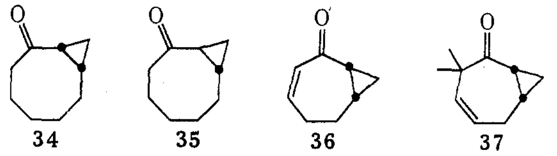
(20) A. C. Cope, S. Moon, C. H. Park, and G. L. Woo, *J. Amer. Chem. Soc.*, **84**, 4865 (1962).

(21) L. A. Paquette, D. E. Kuhla, and J. H. Barrett, *J. Org. Chem.*, **34**, 2879 (1969); W. Hückel and E. Goth, *Chem. Ber.*, **67**, 2104 (1934).



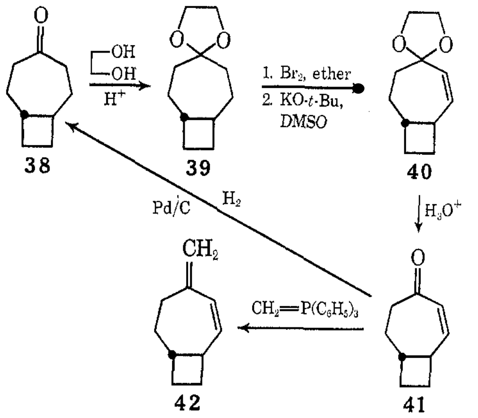
involved.[10,12,14] The apparently lower energies of activation for **1a** and **1b** are therefore presented as evidence for biradical intervention, the additional methyl substitution at C_1 in **32** providing additional transition-state stabilization. The development of allylic radical character in these intermediates is of maximum import as gauged from the complete inertness of ketones **34–37** to thermal activation, even at temperatures as high as 650°.[22]





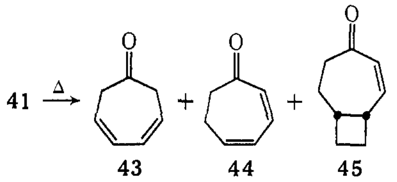
***trans*-Bicyclo[5.2.0]non-2-enes 41 and 42.**—At this point, attention was turned to medium-ring compounds containing a vinylcyclobutane moiety. Despite the failure of *trans*- and *cis*-bicyclo[5.2.0]non-2-ene derivatives to undergo novel excited-state isomerization reactions,[2] the growing number of stereochemically fascinating thermally promoted vinylcyclobutane rearrangements dictated that the response of these molecules to heat be examined.[24]

The synthesis of trans-fused ketone **41** was achieved in four steps by application of the Garbisch procedure[25] to the known saturated ketone **38**.[26] To rule out possible epimerization of the trans-fused ring fusion during this reaction sequence, the α,β-unsaturated ketone so produced (**41**) was catalytically hydrogenated. Starting ketone **38** was produced uncontaminated by the presence of the cis isomer in full support of the indicated structural assignment. For the preparation of **42**, the

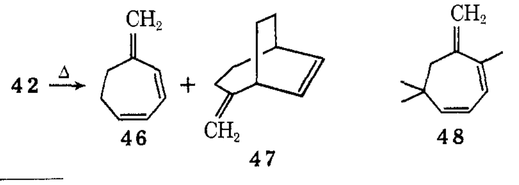


Wittig reaction was again employed. A homogeneous hydrocarbon (**42**) was produced which was distinctly different from the cis isomer (see below). Therefore, although Wittig conditions do frequently serve to induce epimerization, the possibility of trans → cis isomerization in this case may be dismissed.

Upon being heated at 500° in the flow system, ketone **41** underwent 50% conversion to a mixture of 3,5-cycloheptadienone (**43**, 15%), 2,4-cycloheptadienone (**44**, 18%), and the cis isomer **45** (14%). Independent synthesis of **43** was achieved by lithium aluminum hydride reduction of tropone.[27] Thermal activation of **43** results in partial equilibration with **44**[28] from which it is readily separated by vpc techniques. The cis [5.2.0] bicyclic ketone **45** was identified by comparison with authentic material (see below). Pyrolysis at higher temperatures resulted in the formation of more volatile secondary products and heating at lower temperatures resulted simply in lower conversion to the three indicated ketones.



The thermolysis of **42** at 500° (25 mm) led to the formation of two major products amounting to 73 and 18% of the volatile material. A plethora of minor components comprised the remaining 9% and these remain uncharacterized. The possibility that the major substance was triene **46** was suggested by its greatly reduced vpc retention time, ultraviolet spectrum [$\lambda_{max}^{isooctane}$ 283 nm (ε 16,000)] which compares very favorably with that reported for **48** [$\lambda_{max}^{C_2H_5OH}$ 287 nm (log ε 4.04)],[29]



---

[22] Subsequent to completion of this particular phase of our work, Crandall and Watkins[23] have shown that 3- and 4-cyclooctenone do rearrange thermally at 720°.

[23] J. K. Crandall and R. J. Watkins, *J. Org. Chem.*, **36**, 913 (1971).

[24] Consider, for example, the following reports: J. A. Berson and G. L. Nelson, *J. Amer. Chem. Soc.*, **89**, 5303 (1967); W. R. Roth and A. Friedrich, *Tetrahedron Lett.*, 2607 (1969); F. Scheidt and W. Kirmse, *Chem. Commun.*, 716 (1972); E. Vogel, *Justus Liebigs Ann. Chem.*, **615**, 1 (1958).

[25] E. W. Garbisch, Jr., *J. Org. Chem.*, **30**, 2109 (1965).

[26] N. L. Allinger, M. Nakazaki, and V. Zalkow, *J. Amer. Chem. Soc.*, **81**, 4047 (1959).

[27] O. L. Chapman, D. J. Pasto, and A. A. Griswold, *J. Amer. Chem. Soc.*, **84**, 1213 (1962).

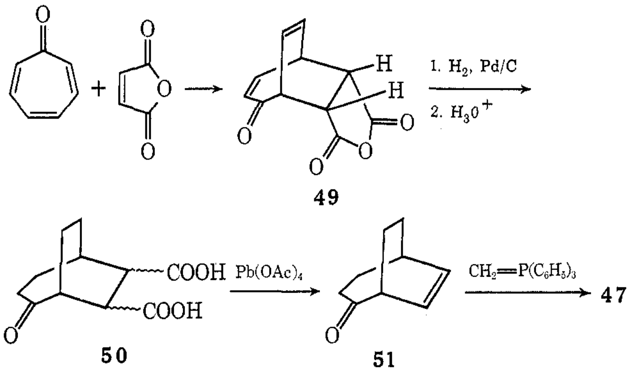
[28] A. P. ter Borg and H. Kloosterziel, *Recl. Trav. Chim. Pays-Bas*, **82**, 1189 (1963).

[29] K. Conrow, *J. Amer. Chem. Soc.*, **83**, 2958 (1961).

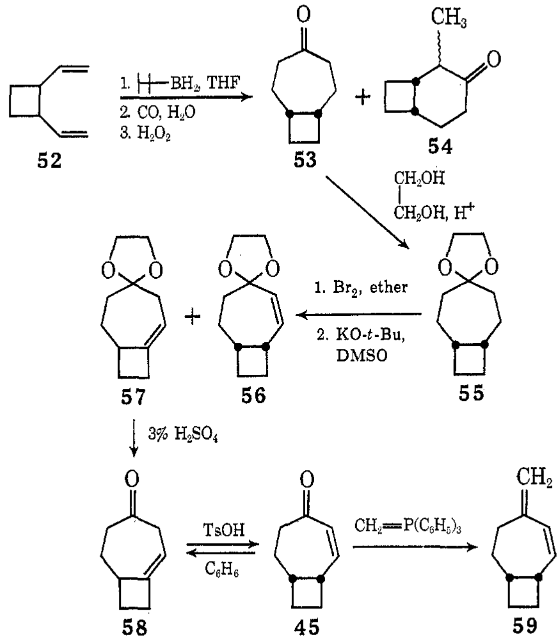
and nmr features. Methylene-2,4-cycloheptadiene (**46**) was then prepared independently by subjecting the thermally equilibrated mixture of **43** and **44** to the Wittig reaction. Somewhat surprisingly, it was found that **43** does not react with methylenetriphenylphosphorane under the usual conditions, whereas **44** is essentially completely converted to **46**. The widely differing reactivity of these ketones permitted facile separation of **46**.

In confirmation of the structural assignment to **47**, a Wittig reaction on **51** was effected. Although this ketone had previously been synthesized by Berson and Jones,[30] it proved more convenient to obtain this substance in quantity from diacid **50** which is readily available from the Diels–Alder reaction of tropone and maleic anhydride.[31] Oxidative bisdecarboxylation of **50** with lead tetraacetate[32] proceeded in acceptable yield (39%).

***cis*-Bicyclo[5.2.0]non-2-enes 45 and 59.**—Synthesis of saturated ketone **53** along the lines previously developed[26] is not only more difficult than that of its trans isomer, but is beset by exceedingly poor yields at one step. Accordingly, a new, rapid, and improved preparation of **53** was developed starting with the readily available *cis*-1,2-divinylcyclobutane (**52**).[33,34] Purified **52** was treated with thexylborane and then carbonylated at approximately 1000 psi of carbon monoxide in the presence of water according to the procedure developed by Brown and Negishi.[35] After oxidative work-up, there was obtained in 27% yield a 75:25 mixture of ketones identified as **53** and **54**. The latter product presumably arises as a result of thexylborane addition to the internal position of one of the vinyl groups *via* a six-center transition state. Although **53** and **54** are separable by efficient distillation, in practice it proved more convenient to ketalize the mixture directly and to isolate **55** at this stage.



Some difficulties were encountered in introducing the requisite unsaturation. When **55** was brominated and subsequently treated with potassium *tert*-butoxide in dimethyl sulfoxide solution, incomplete dehydrobromination took place. When somewhat more forcing conditions were employed, some isomerization to **57** was noted. Also, when unreacted bromo ketal was recycled, only **57** was obtained. These results suggest that two different monobromides are produced, one of which dehydrobrominates with sufficient reluctance that base-catalyzed double bond isomerization accompanies the process.



Upon hydrolysis of **57**, only β,γ-unsaturated ketone **58** was isolated. When heated at reflux in benzene solution containing *p*-toluenesulfonic acid for several hours,[36] an equilibrium distribution consisting of 43% of **58** and 57% of **45** was attained. Clearly, the cis-fused bicyclo[5.2.0]nonen-4-one system finds little stabilization to be gained by conjugation perhaps as a consequence of adverse conformational and steric factors. The difference in chemical shifts of the α and β protons in **45** (28 Hz) indicates the absence of significant conjugative overlap with the carbonyl group compared to a highly conjugated ketone like 2-cyclopentenone ($\nu_a - \nu_b = 101.5$ Hz).[36] These same factors are less evident in trans isomer **41** for which $\nu_a - \nu_b = 54$ Hz.

Submission of **45** to thermolysis at various temperatures afforded varying quantities of bicyclo[3.2.2]non-6-en-2-one (**51**) and cycloheptadienones **43** and **44** (Table VI). Since it was of paramount interest to determine whether *cis*-3a,4,5,7a-tetrahydro-1-indanone (**60**) was produced in this reaction, this previously unknown ketone was synthesized. To this end, the photoisomerization of **51** was studied in the expectancy that

TABLE VI

PYROLYSIS OF 45 AT VARIOUS TEMPERATURES

Temp, °C	Pyrolysate composition, % **45**	**51**	**43**	**44**	Unknowns
385	96	2			2[a]
430	78	6	6	5	5
490	18	22	21	24	15[b]
555	5	42	11	5	37[b]

[a] Present in starting material. [b] A considerable amount of this material consists of low-boiling products.

---

(30) J. A. Berson and M. Jones, Jr., *J. Amer. Chem. Soc.*, **86**, 5017, 5019 (1964).

(31) T. Nozoe, T. Mukai, T. Nagese, and Y. Toyooka, *Bull. Chem. Soc. Jap.*, **33**, 1247 (1960).

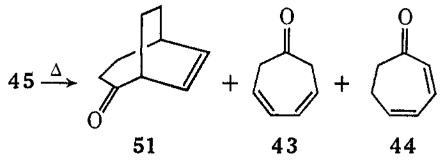
(32) C. M. Cimarusti and J. Wolinsky, *J. Amer. Chem. Soc.*, **90**, 113 (1968).

(33) P. Heimbach and W. Brenner, *Angew. Chem., Int. Ed. Engl.*, **6**, 800 (1967); *Angew. Chem.*, **79**, 813 (1967); W. Brenner, P. Heimbach, H. Hey, E. W. Müller, and G. Wilke, *Justus Liebigs Ann. Chem.*, **727**, 161 (1969); G. S. Hammond, N. J. Turro, and R. S. H. Liu, *J. Org. Chem.*, **28**, 3297 (1963).

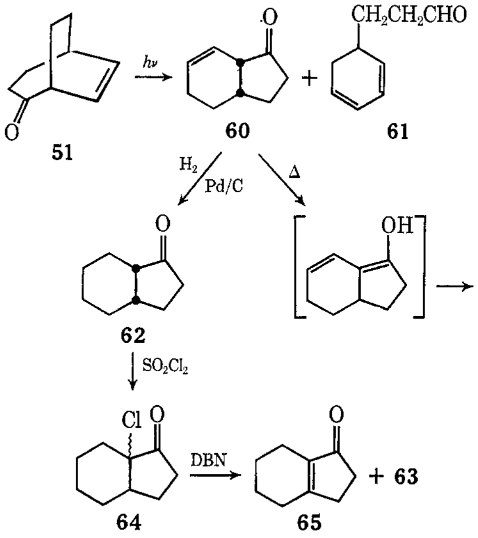
(34) We thank Dr. Paul Heimbach and the Max Planck Institut für Kohlenforschung for providing us with a generous supply of **52**.

(35) H. C. Brown and E. Negishi, *J. Amer. Chem. Soc.*, **89**, 5477 (1967); H. C. Brown and E. Nigishi, *Chem. Commun.*, 594 (1968).

(36) N. Heap and G. H. Whitham, *J. Chem. Soc. B*, 164 (1966).



its excited-state behavior would parallel that of norbornenone, which readily gives bicyclo[4.2.0]oct-2-en-8-one upon photolysis.[37] In point of fact, direct irradiation of **51** did result in facile 1,3-sigmatropic acyl shift with formation of **60** (85% yield). Less efficient conversion to aldehyde **61** (13%) was also operative. Any question that the ring system in **60** be of some other type was removed by its catalytic hydrogenation to *cis*-perhydroindanone (**62**). The location of the double bond was confirmed when it was discovered that passage of **60** through a gas chromatographic column at temperatures in excess of 165° resulted in partial conversion to the conjugated isomer **63**. The hypothetical dienol is seemingly the significant intermediate in this interconversion. Authentic **63** was obtained as the minor product from the chlorination–dehydrochlorination of **62**.[38]



The ultraviolet spectrum of **61** is that of a simple 1,3-cyclohexadiene chromophore [$\lambda_{\max}^{\text{cyclohexane}}$ 260 nm (ϵ 5000)].[39] In addition, its nmr spectrum features four olefinic protons (δ 5.5–6.1) and a low-field triplet centered at δ 9.84 (J = 1.5 Hz) characteristic of a $-CH_2CHO$ functional group. The presence in **61** of these structural parameters typifies the substance as the result of well-precedented[40] Norrish type I cleavage of **51** followed by intramolecular hydrogen abstraction.[41]

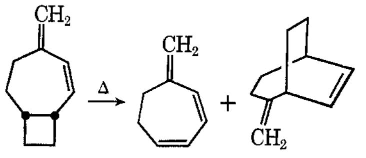
The results obtained from gas-phase pyrolysis of **59** at 390–555° (Table VII) are seen to be very similar to those realized from heating of the trans isomer **42** with **46** and **47** arising as the major products.

TABLE VII

PYROLYSIS OF 59 AT VARIOUS TEMPERATURES

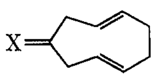
Temp, °C	Pyrolysate composition, %			
	59	46	47	Unknowns
390	99	0.5		0.5
430	88	7	3	2
465	53	31	13	2
505	15	59	21	5[a]
555	3	68	20	9[a]

[a] The major constituents are low-boiling substances.

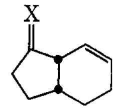


59 46 47

These experimental data can now be contrasted with those from the rearrangement of the [5.1.0] bicyclics **3a** and **3b**. Whereas a 1,5-homodienyl shift is easily effected in the low-temperature pyrolysis of the cyclopropyl compounds, none of the corresponding products **66** (no stereochemical implication intended) is observed from either stereoisomeric cyclobutane series. Furthermore, whereas significant amounts of material arising from 1,3 migration of the internal cyclopropyl bond in **3a** and **3b** are formed at the higher temperatures studied, no evidence was gained for the production of either **60** or **67** upon thermal activation of the [5.2.0] bicyclics. Rather, the experimental observations realized from heating of the various vinylcyclobutanes can be most economically explained in terms of rupture of the external C_1–C_9 bond of the four-membered ring with formation of stabilized biradicals of type **68**. Continuation of the bond-breaking process leads to the loss of ethylene, while radical recombination either returns the original carbon framework (with or without loss of stereochemistry) or leads to [3.2.2] bicyclic product (see scheme). There exists no need to postulate the intervention of biradicals such as **69**. Should central bond homolysis occur in these systems, however, it is clear that rebonding to produce less strained [4.3.0] bicyclics does not operate.



66



60, X = O
67, X = CH_2

Control experiments conducted on **60** have shown that at 490° the material is recovered 90% unchanged. At 555°, 62% of the unreacted ketone was returned. In both instances, isomerization to **63** was the only process in evidence. Consequently, if **60** had been formed during the pyrolysis of **41** and **45**, major amounts of this substance would have been easily detected.

In contrast to the proclivity of cis ketone **45** for isomerization to bicyclo[3.2.2]non-6-en-2-one (**51**), trans isomer **41** gives no comparable vinylcyclobutane rearrangement product. It is easily seen from Dreiding molecular models that the rigid and highly puckered framework of the trans-fused system precludes facile

---

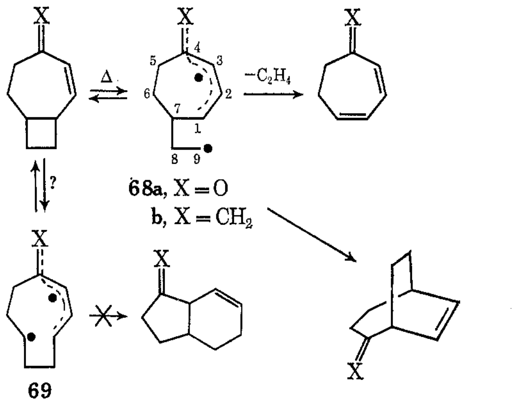
[37] R. S. Givens, W. F. Oettle, R. L. Coffin, and R. G. Carlson, *J. Amer. Chem. Soc.*, **93**, 3957 (1971); R. S. Givens and W. F. Oettle, *ibid.*, **93**, 3963 (1971).

[38] The procedure employed was patterned after that employed in the 1-decalone series: H. O. House and H. W. Thompson, *J. Org. Chem.*, **26**, 3729 (1961).

[39] R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," Wiley, New York, N. Y., 1967, pp 157–158.

[40] For a recent discussion of the mechanism of this type of photochemical reaction, see H. Sato, N. Furutachi, and K. Nakanishi, *J. Amer. Chem. Soc.*, **94**, 2150 (1972).

[41] For another recent example, note J. Meinwald and R. A. Chapman, *J. Amer. Chem. Soc.*, **90**, 3218 (1968).

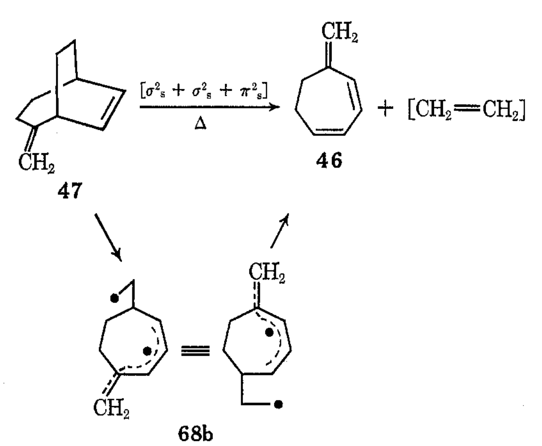


approach of C$_9$ to C$_3$ (see **68**) in a suprafacial shift unless simultaneous pivoting about the C$_1$–C$_7$, C$_6$–C$_7$, and C$_7$–C$_8$ σ bonds also obtains. Without the benefit of these ancillary motions, the hydrogen at C$_7$ would be prohibitively forced into the interior of the molecule. In this context, it is not surprising that C$_1$–C$_9$ recombination of the 1,4-butanediyl (with or without inversion of configuration) proceeds faster than more deep-seated skeletal changes. Since the reluctance toward 1,3 shift is an apparent consequence of the trans-fused cyclobutane ring in **41**, elimination of this barrier as in cis isomer **45** removes the obstacle for rearrangement. That the **45** produced *in situ* during the pyrolysis of **41** undergoes no further isomerization is a reflection of the quite short contact time.

The similarity of results for **42** and **59** may reflect a greater lifetime for biradical **68b** relative to **68a** as they originate from trans-fused precursors. A longer lifetime for the hydrocarbon species would allow for conformational readjustments necessary for ultimate isomerization to **47**. The possibility also remains that **42** suffers initial rearrangement to **59** which in turn experiences yet more rapid conversion to **47**.

Lastly, we call attention to the fact that concerted thermal extrusion of ethylene from the four [5.2.0] bicyclics could proceed in the [$_\sigma 2_a + {}_\sigma 2_s$] mode. Disregarding for the moment the attractiveness of the diradical mechanism, we point out that postulation of such concerted cleavage reactions actually leads to inaccurate predictions. Since simultaneous rupture of two diametrically opposed cyclobutane bonds in a + s fashion requires extensive twisting of the four-membered ring in the transition state, then loss of ethylene should be more facile than isomerization in the trans series where the cyclobutane is already markedly contorted. However, the combined experimental data are in contradiction with this proposal. In addition, whereas postulation of orbital symmetry control would necessitate the competitive operation of a second mechanism to explain the formation of isomerized compounds, a single biradical intermediate is able to account for all products.

Some measure of further support for the biradical process was derived from pyrolysis studies of **47**. When heated to 555° in the flow system, 10% conversion to **46** resulted. One reasonable explanation of this observation is that **47** is also a source of biradical **68b**, which again is partitioned in the direction of ethylene loss and formation of **47**. This interpretation does not uniquely accommodate the facts, however, since a retro Diels–Alder pathway also serves to explain this observation. In this connection, the related ketone **51** was found not to fragment ethylene at 555°.



68b

Summary.—In conclusion, it is to be noted that cis-[5.1.0] bicyclics exhibit thermal rearrangement chiefly by two pathways. The first of these is the vinylcyclopropane–cyclopentene bond reorganization and, indeed, ring contraction by 1,3 shift of the *internal* cyclopropane bond is followed exclusively by **1**. Isomerization to a less strained bicyclic system by vinylcyclopropane rearrangement involving an *external* cyclopropyl bond is of significance in the case of **3**. However, the 1,5-homodienyl hydrogen shift process which gives rise to a 1,4-cyclooctadiene derivative is now seen to be a competitive reaction. No 1,3 shift of the *internal* cyclobutane bond was evidenced in the thermal behavior of the several cis and trans [5.2.0] bicyclics studied. Allylic rearrangement of an *external* cyclobutane bond to afford [3.2.2]bicyclic products does operate in certain examples, but the major pathway is fragmentation with loss of ethylene and formation of cycloheptadiene systems.

Experimental Section

General.—Melting points are corrected. Proton magnetic resonance spectra were obtained with a Varian A-60A spectrometer and apparent coupling constants are cited. Elemental analyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark.

Compounds were pyrolyzed in a flow system consisting of a 28 cm × 16 mm quartz tube packed with quartz chips heated in a 12-in. furnace. Samples were introduced by volatilization (usually at 20–30 mm) into a slow stream of nitrogen (flow *ca.* 1 ml/min) and products were collected in a U tube cooled in a Dry Ice–isopropyl alcohol bath. For analytical runs, 2–3-mg samples were pyrolyzed, collected, diluted with an inert solvent such as ether or pentane, and analyzed by vpc methods. The percentage composition of mixtures was determined by manual integration of vpc traces. Final purification of samples was accomplished by preparative vpc unless otherwise noted. All vpc columns employed were constructed of 0.25-in. Al tubing and, except where noted, liquid phases were coated on 60–80 mesh Chromosorb G: A, 12 ft, 5% XF-1150; B, 6 ft, 5% QF-1; C, 12 ft, 5% SF-96; D, 12 ft, 5% SE-30; E, 6 ft, 20% AF-1 packed on 60–80 mesh Chromosorb W; F, 6 ft, 5% SE-30; G, 6 ft, 5% SF-96; H, 7 ft, 6% AF-1; I, 6 ft, 5% XF-1150; J, 6 ft, 5% Carbowax 2000M.

Thermal Isomerization of *cis*-Bicyclo[5.1.0]oct-2-en-4-one (3a).—Pyrolysis of **3a**[2] at various temperatures gave the result summarized in Table I. Analyses were performed with column A at 150°. The first compound to elute was identified as *cis*-bicyclo[3.3.0]oct-7-en-2-one (**4a**) by comparison of spectra with those of an authentic sample.[2,42] Bicyclo[3.2.1]oct-6-en-2-one

---

(42) L. A. Paquette, G. V. Meehan, and R. F. Eizember, *Tetrahedron Lett.*, 995 (1969).

(**6**) was the second compound eluted; this ketone was identical with a sample prepared in unambiguous fashion (see below). 3,6-Cyclooctadienone (**5**), the third component collected, had the following spectral properties: ν_{max}^{neat} 1720 cm^{-1}; $\lambda^{isooctane}$ end absorption; $\delta_{TMS}^{CDCl_3}$ 5.78 (m, 4, olefinic), 3.18 (d, J = 4.0 Hz, 4, -CH$_2$CO-), and 2.78 (m, 2, doubly allylic protons); calcd *m/e* 122.0732, found 122.0729.

Anal. Calcd for $C_8H_{10}O$: C, 78.65; H, 8.25. Found: 78.25; H, 8.19.

Recovered **3a** was the last material to elute from the column.

Hydrogenation of 5.—A 23.6-mg sample of **5** dissolved in 3.5 ml of anhydrous ether was hydrogenated over 10 mg of 5% Pd/C for 3 hr at atmospheric pressure. The catalyst was separated by filtration, the solution was concentrated in a stream of nitrogen, and the lone product was isolated by preparative vpc on column B at 120°. There was obtained 15.5 mg of cyclooctanone.

3,6-Cyclooctadienol (7).—To a solution of 30 mg of **5** in 2 ml of absolute methanol cooled to 5° was added 95 mg (tenfold excess) of sodium borohydride. The solution was stirred for 2 hr while gradually warming to room temperature. Pentane and saturated sodium chloride solution were added and the layers were separated. The aqueous phase was extracted several times with additional pentane and the combined organic layers were dried and evaporated to give 20 mg of crude **7**. Molecular distillation at 60° (15 mm) afforded pure **7**, identical in all respects with an authentic sample.[3]

Alternate Synthesis of Bicyclo[3.2.1]oct-6-en-2-one (6). A. 2-(2-Hydroxybicyclo[2.2.1]hept-5-enyl)methylamine (12).—To a refluxing stirred slurry of 3.80 g (0.10 mol) of lithium aluminum hydride in 100 ml of anhydrous ether was added over a period of several hours a solution of 8.85 g of **11**[6] in 35 ml of dry ether. The mixture was heated at reflux overnight and treated sequentially with 4 ml of water, 4 ml of 30% potassium hydroxide solution, and 10 ml of water with efficient ice-bath cooling. Usual processing was followed by distillation *in vacuo*, bp 81–83° (1.3 mm).

In a second identical run but without distillation, the ethereal solution of **12** was treated with 9.50 g (0.05 mol) of *p*-toluenesulfonic acid monohydrate dissolved in 100 ml of ether with ice cooling. After overnight storage at 0°, the precipitated solid was filtered. There was obtained 11.3 g (72% overall) of tosylate salt **13**. Recrystallization from methanol–chloroform and ethyl acetate–methanol (3:1) gave crystals: mp 172–172.5° dec; $\delta_{DSS}^{D_2O}$ 7.54 (AA'BB' q, 4, aromatic), 6.47 (m, 1, olefinic), 6.18 (m, 1, olefinic), 3.26 (br s, 2, –CH$_2$N<), 2.88 (br m, 2, bridgehead protons), 2.38 (s, 3, methyl), and 1.0–2.1 (br m, 4).

Anal. Calcd for $C_{15}H_{21}NO_4S$: C, 57.85; H, 6.80; N, 4.50. Found: C, 58.01; H, 6.75; N, 4.41.

B. Deamination of 13.—Tosylate **13** (11.2 g, 0.036 mol) was dissolved in 200 ml of cold water and 2.5 ml of acetic acid was added. A solution of 2.75 g (0.04 mol) of sodium nitrite in 25 ml of water was added, but no gas evolution was observed until the solution was warmed to 20–30°. After *ca.* 1 hr, 450 ml of nitrogen had been evolved and the solution became light yellow. An additional 3 ml of acetic acid and 2.50 g of sodium nitrate was added and the solution was stirred for several hours at room temperature. The product was extracted with ether (4 × 200 ml) and the combined organic layers were washed with saturated sodium bicarbonate and sodium chloride solutions. The majority of the solvent was distilled from the dried solution at atmospheric pressure and the residue was sublimed at 30 mm and 40–80° (bath temperature). The yield of white volatile solid was 1.10 g. Vpc analysis (column A at 150°) indicated a 55:45 ratio of **6** to **14**. Isolated **14** melted at 97.5–100° (lit.[7] mp 99–100.5°) and its ir and nmr spectra conformed to those in the literature report. Isolated **6** melted at 76.5–79° and was identical with the ketone isolated from the pyrolysis of **3a**: $\nu_{max}^{CHCl_3}$ 1717 cm^{-1}; $\delta_{TMS}^{CHCl_3}$ 6.15 (symmetrical eight-line pattern, 2, olefinic), and 1.6–3.1 (br m, 8).

Anal. Calcd for $C_8H_{10}O$: C, 78.65; H, 8.25. Found: C, 78.29; H, 8.21.

Thermal Rearrangement of 4-Methylene-*cis*-bicyclo[5.1.0]oct-2-ene (3b).—Pyrolyses were conducted as previously described giving the results summarized in Table III. The products were analyzed and separated with the aid of column C at 110°. 2-Methylenebicyclo[3.2.1]oct-6-ene (**16**) was eluted first and showed ir and nmr spectra identical with those of the authentic sample prepared below. The second component proved to be 8-methylene-*cis*-bicyclo[3.3.0]oct-2-ene (**4b**).[42] The third compound was 7-methylene-1,4-cyclooctadiene (**15**): $\delta_{TMS}^{CDCl_3}$ 5.60 (symmetrical ten-line multiplet, 4, ring vinyls), 4.79 (m, 2, terminal methylene), 2.95 (m, 6, bisallylic protons).

Anal. Calcd for C_9H_{12}: C, 89.94; H, 10.06. Found: C, 89.82; H, 9.98.

Unchanged **3b** emanated last from this column.

Hydrogenation of 15.—Triene **15** (21.9 mg) dissolved in 5 ml of ether was hydrogenated over 20 mg of 10% Pd on carbon until hydrogen uptake was complete. The mixture was filtered through a short column of Celite and the filtrate was carefully concentrated. The hydrocarbon isolated upon vpc purification (column C, 110°) exhibited ir and nmr features identical with those of methylcyclooctane.

2-Methylenebicyclo[3.2.1]oct-6-ene (16).—An impure sample of **6** dissolved in dry ether was heated at reflux overnight under nitrogen in the presence of excess methylenetriphenylphosphorane. After cooling, water was added and the mixture was extracted with pentane. The solvent was carefully removed and the resulting diene **16** was isolated from column C at 110°: $\delta_{TMS}^{CDCl_3}$ 5.93 (m, 2, ring vinyls), 3.03 (dd, 2, terminal methylene), 2.6 (m, 1), 1.7–2.4 (m, 3), and 1.3–1.7 (m, 3).

Anal. Calcd for C_9H_{12}: C, 89.94; H, 10.06. Found: C, 90.20; H, 10.02.

This hydrocarbon was identical with that isolated above from the pyrolysis of **3b**.

Pyrolysis of 1,4,4-Trimethyl-*cis*-bicyclo[5.1.0]oct-5-en-2-one (1a).—An 82-mg sample of **1a**[43] was pyrolyzed at 550° (10 mm) as before. Molecular distillation [50° (10 mm)] afforded 65 mg (81%) of a colorless liquid, vpc analysis of which on column G at 115° showed the material to contain less than 1% of **1a** and to be otherwise homogeneous. The isolated product was identical with **2a** in all respects.

Pyrolysis of 2-Methylene-1,4,4-trimethyl-*cis*-bicyclo[5.1.0]oct-5-ene (1b).—An 81-mg sample of **1b**[2] was pyrolyzed in the usual manner at 550° (10 mm). Molecular distillation at 50° (10 mm) of the collected product gave 61 mg (70%) of a colorless liquid homogeneous of vpc (column G, 115°). This hydrocarbon was identical with authentic **2b**.[2]

***cis*-Bicyclo[6.1.0]non-6-en-2-one (25).**—A mixture of 0.03 mol of oil-free sodium hydride and 7.0 g (0.03 mol) of trimethyloxosulfonium iodide in 50 ml of dry dimethyl sulfoxide was stirred under nitrogen at room temperature for 30 min. A solution of 3.6 g (0.03 mol) of freshly distilled 2,4-cyclooctadienone (**24**)[20] in 20 ml of dimethyl sulfoxide was added and stirring was maintained for 2 hr. The solution was poured into 100 ml of water and extracted with ether. The combined organic layers were dried, filtered, and evaporated. Fractionation of the residual oil afforded 3.4 g (80%) of **25**: bp 85–86° (2 mm); ν_{max}^{neat} broad carbonyl absorption at 1750–1700 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 5.6 (m, 2, olefinic) and 1.0–2.7 (m, 10).

The semicarbazone melted at 165–166°.

Anal. Calcd for $C_{10}H_{15}N_3O$: C, 62.15; H, 7.82; N, 21.75. Found: C, 62.20; H, 7.91; N, 21.43.

2-Methylene-*cis*-bicyclo[6.1.0]non-6-ene (26).—To a suspension of 3.6 g (0.01 mol) of methyltriphenylphosphonium bromide in 50 ml of anhydrous ether under nitrogen was added dropwise 4.3 ml (0.011 mol, 1.6 *M*) of *n*-butyllithium in hexane and stirring was maintained for 3 hr. A solution of 1.34 g (0.01 mol) of **25** in 10 ml of ether was added dropwise and the resulting suspension was refluxed for 12 hr. Water (50 ml) was added, the ether layer was separated, and the aqueous layer was reextracted with ether. The ethereal layers were combined, washed with brine, dried, and carefully evaporated *in vacuo*. Pentane (50 ml) was added and the suspension was filtered. Concentration of the filtrate and distillation furnished 1.1 g (82%) of **26** as a colorless liquid: bp 76–78° (10 mm); $\delta_{TMS}^{CDCl_3}$ 5.5 (br s, 2, olefinic), 4.8 (s, 2, methylene protons), and 0.2–2.7 (br m, 10).

Anal. Calcd for $C_{10}H_{14}$: C, 89.49; H, 10.51. Found: C, 89.28; H, 10.49.

Thermal Rearrangement of 25.—A 100-mg (0.7 mmol) sample of **25** was pyrolyzed in the flow system at 650° (10 mm) (contact time ≤3 sec). The collected product was molecularly distilled at 50° (10 mm) to give 84 mg (84%) of a clear liquid. Vpc analysis on column G showed the ratio of **25** to a single product to be 2:1. The new substance was isolated and was assigned structure **27**: ν_{max}^{neat} 1710 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 5.7 (m, 2, olefinic) and 1.2–3.4 (br m, 10). This ketone was not identical with either **60** or **63**.

---

[43] E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1353 (1965).

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 78.99; H, 9.03.

Hydrogenation of *cis*-Bicyclo[4.3.0]non-7-en-2-one (27).—To a solution of 25 mg (0.2 mmol) of **27** in 25 ml of hexane was added 4 mg of 10% palladium on carbon and hydrogenation was effected at atmospheric pressure for 2 hr (uptake of 4 ml of H_2). The mixture was filtered through Celite to remove the catalyst, concentrated, and subjected to vpc isolation (column G). There was obtained 16 mg (60%) of **29**, identical in all respects with an authentic sample.[21]

Thermal Rearrangement of 26.—A 100-mg sample (0.2 mmol) of **26** was pyrolyzed at 600° (10 mm) as previously described. Molecular distillation of the collected product at 50° (10 mm) yielded 92 mg (92%) of a colorless liquid, vpc analysis of which revealed the presence of >98% of a single product (**28**). Purification was effected by preparative isolation from column G: ν_{max}^{neat} 1645, 1440, 893, 884, and 705 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 5.8 (m, 2, olefinic), 4.17 (br s, 2, methylene protons), and 1.0–3.1 (br, 10).

Anal. Calcd for $C_{10}H_{14}$: C, 89.49; H, 10.51. Found: C, 89.66; H, 10.45.

Hydrogenation of 2-Methylene-*cis*-bicyclo[4.3.0]non-7-ene (28).—A solution of 67 mg (0.5 mmol) of **28** in 25 ml of hexane containing 5 mg of 5% palladium on carbon was hydrogenated at atmospheric pressure as before. Isolation of the product by preparative-scale vpc techniques yielded 57 mg (80%) of **31**, indicated in all respects with the authentic sample prepared below.

2-Methylene-*cis*-bicyclo[4.3.0]nonane (30).—Reaction of 3.5 g (0.001 mol) of methyltriphenylphosphonium bromide, 12 ml (0.001 mol) of 1.2 *M* *n*-butyllithium in hexane, and 91 mg of **29** in the predescribed fashion led to the isolation of 64 mg (80%) of **30**: ν_{max}^{neat} 1635, 1440, 1025, and 890 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 4.7 (br s, 2, methylene protons) and 0.9–2.7 (br, 14 H).

Anal. Calcd for $C_{10}H_{16}$: C, 88.16; H, 11.84. Found: C, 87.91; H, 11.97.

2-Methyl-*cis*-bicyclo[4.3.0]nonane (31).—A solution of 41 mg (0.3 mmol) of **30** dissolved in 25 ml of hexane containing 5 mg of 5% palladium on carbon was hydrogenated as before at atmospheric pressure to give 32 mg (75%) of **31** after vpc isolation (column J): ν_{max}^{neat} 1450, 1375, and 1300 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 1.0–2.8 (br envelope).

Anal. Calcd for $C_{10}H_{18}$: C, 86.88; H, 13.12. Found: C, 87.09; H, 13.05.

***trans*-Bicyclo[5.2.0]nonan-4-one Ethylene Ketal (39).**—To 5.48 g (0.0398 mol) of **38**[26] dissolved in 50 ml of benzene was added 100 mg of *p*-toluenesulfonic acid and 3.71 g (0.0597 mol) of ethylene glycol. The flask was fitted with a Dean–Stark trap and heated under reflux for 8 hr. At the end of this time, most of the benzene was removed at reduced pressure and 50 ml of ether was added. The mixture was washed with saturated sodium carbonate solution, and the aqueous layer was extracted with 25 ml of ether. The combined ether extracts were dried and distilled to give 6.23 g (86%) of ketal **39**: bp 79–82° (0.9 mm); $\delta_{TMS}^{CCl_4}$ 3.82 (s, 4, $-OCH_2-$) and 1.7 (m, 14).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.59; H, 9.89.

***trans*-Bicyclo[5.2.0]non-2-en-4-one Ethylene Ketal (40).**—To a solution of 9.73 g (0.0535 mol) of **39** in 45 ml of anhydrous ether at room temperature was slowly added 8.85 g (0.055 mol) of bromine. After addition was complete, a previously prepared solution of monosodium ethyleneglycolate in ethylene glycol (30 ml, 0.075 mol of base) was added with vigorous stirring. The resulting heterogeneous mixture was poured into water and extracted with additional portions of ether. The combined organic layers were dried and evaporated. The residue was dissolved in 80 ml of dry dimethyl sulfoxide at room temperature and 13.5 g (0.12 mol) of potassium *tert*-butoxide was added in small portions. The mixture was stirred for 2 hr at room temperature, poured into saturated sodium chloride solution, and extracted with ether. The organic phase was dried and the solvent was removed. Vacuum distillation of the residue gave 7.70 g (80%) of **40**, bp 58–68° (0.35 mm). Vpc analysis indicated that this material was greater than 98% pure: $\delta_{TMS}^{CCl_4}$ 5.63 (center of ABX, 2, J_{AB} = 2.2, J_{BX} = 2.8 Hz, olefinic), 3.88 (s, 4, $-OCH_2-$), 2.7 (m, 1, H_1), and 1.8 (br m, 9).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.47; H, 9.19.

***trans*-Bicyclo[5.2.0]-*cis*-non-2-en-4-one (41).**—A mixture of 7.70 g of **40** and 50 ml of 3% sulfuric acid was stirred at room temperature for 1 hr. The mixture was extracted with ether and the combined extracts were washed with sodium bicarbonate and sodium chloride solutions. The dried solution was distilled at atmospheric pressure to remove solvent, and then under reduced pressure to give 5.34 g (91%) of **41**: bp 77–79° (2.7 mm); $\delta_{TMS}^{CCl_4}$ 6.85 (center of A portion of ABX pattern, 1, J_{AB} = 11, J_{AX} = 2 Hz, H_2), 5.79 (d of q, B portion of ABX with further coupling, probably across the carbonyl, 1, H_3), 1.4–3.4 (br m, 12). The semicarbazone derivative melted at 187.5–191.0° (from ethanol).

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.29; H, 8.91.

Hydrogenation of 41.—A 73-mg sample of **41** dissolved in 5 ml of ethyl acetate was hydrogenated at atmospheric pressure over 20 mg of 10% palladium on carbon. The mixture was filtered through Celite and concentrated under a stream of nitrogen. Saturated ketone **28** was isolated by preparative vpc (column D, 110°) and had ir and nmr spectra identical with those of a sample previously prepared.

4-Methylene-*trans*-bicyclo[5.2.0]non-2-ene (42).—To 5.90 g (16.5 mmol) of methyltriphenylphosphonium bromide in 60 ml of anhydrous ether was added under nitrogen 10.3 ml of 1.6 *N* *n*-butyllithium in hexane. After this solution was stirred for 45 min, 1.10 g (8.1 mmol) of **41** dissolved in 5 ml of ether was added. The mixture was refluxed for 12 hr, quenched with water, and extracted with additional ether. The dried ether extracts were evaporated and the residue was triturated with pentane. The filtered solution was distilled at atmospheric pressure and then under vacuum to give 638 mg of **42**, bp 72–80° (15 mm). Vpc analysis indicated that this material was 98–99% pure: $\lambda_{max}^{isooctane}$ 235 nm (ϵ 14,900), and 275 (1030); $\delta_{TMS}^{CCl_4}$ 5.77 (AB with further splitting, 2, H_2 and H_3), 4.70 (br s, 2, methylene protons), and 1.0–3.1 (br m, 10).

Anal. Calcd for $C_{10}H_{14}$: C, 89.49; H, 10.51. Found: C, 89.57; H, 10.58.

Pyrolysis of 41.—Ketone **41** (344 mg) was pyrolyzed in the apparatus already described at 500° (10–15 mm). A total of 306 mg of condensate was collected in the cold trap. By vpc analysis (column F at 118°), this material was found to consist of a mixture of **43** (15)%, **44** (18%), starting ketone **41** (50%), and **45** (14%), with several additional minor products totaling 3%. Isolated 3,5-cycloheptadienone (**43**) (29 mg), 2,4-cycloheptadienone (**44**) (33 mg), and **45** (38 mg) were identified by their nmr spectra and by comparison with the authentic samples prepared below.

Unambiguous Synthesis of 43 and 44.—3,5-Cycloheptadienone (**43**) was obtained by lithium aluminum hydride reduction of tropone according to the literature procedure.[27] Purified **43** (53.5 mg) was pyrolyzed in the flow system at 390° (10 mm).[28] A quantitative mass balance was realized. Vpc analysis column F, 80°) indicated the presence of only two components in a ratio of *ca.* 50:50. The first component to be eluted from the column was **43**, while the second was the fully conjugated isomer **44**, identical with the sample obtained from pyrolysis of **41**.

Pyrolysis of 42.—Pyrolysis of 97.6 mg of **42** was carried out as before at 500° (25 mm). There was collected 73.2 mg of liquid that was analyzed by vpc and found to consist of **46** (73)%, **47** (18%), and 9% of several minor components. The mixture was separated by preparative vpc (column E, 65°). Triene **46** proved to be unstable and polymerized on standing: $\lambda_{max}^{isooctane}$ 283 nm (ϵ 16,000), 275 (sh, 15,000), and 299 (11,000); $\delta_{TMS}^{CCl_4}$ 5.5–6.3 (m, 4, olefinic), 4.7–5.0 (br d with further splitting, 2, methylene protons), and 2.1–2.7 (m, 4, allylics); calcd *m/e* 106.0782, observed 106.0783. Compound **47** was identified by synthesis as described below.

Alternate Preparation of 46. Wittig Reaction of 43 and 44.—To 4.63 g of methyltriphenylphosphonium bromide in 50 ml of anhydrous ether was added under a nitrogen atmosphere 8.1 ml of 1.6 *N* *n*-butyllithium in hexane. After this solution was stirred for 30 min, 700 mg of a 50:50 mixture of **43** and **44** dissolved in 5 ml of dry ether was added, and the mixture was refluxed overnight. At the conclusion of the reflux period, the mixture was quenched with water and extracted with ether. The ether solution was dried and carefully evaporated at atmospheric pressure. The residue was triturated with pentane to precipitate residual phosphorous compounds, and after filtration the pentane solution was evaporated and the residue was analyzed by vpc (column B, 65°). The major component (102 mg, 66% of the volatile material) was identical with **46** isolated from the pyrolysis. Also obtained was unreacted 3,5-cycloheptadienone (20%). In a control experiment carried out as above on 502 mg of pure **43**, there was isolated a mixture consisting of 78% unreacted **43** and six minor products.

Synthesis of Authentic 47. A. Diels–Alder Reaction of Tropone and Maleic Anhydride.—This reaction was carried out as described[31] with the modification that unreacted maleic anhydride in the product was removed by sublimation at 80–90° (12–15 mm) until the nmr spectrum no longer showed the maleic anhydride singlet (88.5% yield). Hydrogenation and hydrolysis to **93** were carried out as previously outlined.[31]

B. Bicyclo[3.2.2]non-6-en-2-one (**51**).—To 55 ml of pyridine through which oxygen had been bubbled for 15 min was added 5.0 g (0.0221 mol) of diacid **50** and 14.7 g (0.0332 mol) of lead tetraacetate. The flask was immersed in a preheated oil bath at 68–73° for a period of 10 min. Gas evolution began shortly after immersion. At the conclusion of this time, the mixture was cooled in ice water, poured into cold, dilute (3 *M*) nitric acid, and extracted with ether. The combined organic extracts were washed with sodium bicarbonate solution, dried, and concentrated under reduced pressure to leave 1.72 g of crude yellow-brown semisolid. This material was sublimed at 60° (25 mm) to give 1.18 g (39%) of **51**, mp 87.5–88.5° (lit.[30] mp 89–90.8°). This compound is very volatile and will sublime at atmospheric pressure and room temperature: $\delta_{\mathrm{TMS}}^{\mathrm{CDCl_3}}$ 5.95–6.6 (m, 2), 3.06 (br m, 1), 2.6–2.9 (m, 3), 1.6–2.1 (br m, 6).

C. 2-Methylenebicyclo[3.2.2]non-6-ene (**47**).—To 3.17 g (8.8 mmol) of methyltriphenylphosphonium bromide in 50 ml of dry ether was added under a nitrogen atmosphere 7 ml (9.1 mmol) of 1.3 *N* *n*-butyllithium in hexane. After this solution was stirred for 15 min at room temperature, 0.600 g (4.4 mmol) of **51** dissolved in 3 ml of dry ether was added *via* a syringe. After refluxing for 13 hr the mixture was quenched with water and extracted with pentane. The combined pentane extracts were washed, dried, and filtered, and the solvent was evaporated at atmospheric pressure. The residue was vacuum transferred and the volatile material was found to contain greater than 95% of **47** by vpc analysis (column G at 118°): $\delta_{\mathrm{TMS}}^{\mathrm{CDCl_3}}$ 5.9–6.3 (m, 2, H_6, H_7), 4.57 (m, 2, methylene protons), 2.97 (br m, 1, H_1), 2.2–2.7 (m, 3), and 1.3–1.7 (m, 6, protons on C_4, C_8, C_9); calcd *m/e* for $C_{10}H_{14}$ 134.1095, observed 134.1092.

Anal. Calcd for $C_{10}H_{14}$. C, 89.49; H, 10.51. Found: C, 89.65; H, 10.57.

***cis*-Bicyclo[5.2.0]nonan-4-one** (**53**) **and 2-Methyl-*cis*-bicyclo[4.2.0]octan-3-one** (**54**).—To 0.452 mol of diborane (calcd as BH_2) (418 ml, 1.08 *M* in tetrahydrofuran) was added at 0° under a nitrogen atmosphere 39.1 g (0.465 mol) of 2,3-dimethyl-2-butene.[35] After stirring for 1.5 hr, the solution was transferred *via* syringe to one of two 500-ml addition funnels attached to a 2-l. three-necked flask also fitted with a magnetic stirrer and nitrogen inlet. The other addition funnel was charged with 48.5 g (0.45 mol) of *cis*-1,2-divinylcyclobutane[33] (90% pure, containing 4% butadiene, 4% 4-vinylcyclohexene). Sufficient dry tetrahydrofuran was added to the hydrocarbon to bring the two addition funnels to the same volume, and the two solutions were added simultaneously over a 5-hr period at 20–25° to 50 ml of dry tetrahydrofuran. The solution was cooled briefly to 0° and transferred rapidly under nitrogen pressure to a metal autoclave liver containing 16.5 g (0.92 mol) of distilled water. After the autoclave was sealed and flushed with carbon monoxide, the bomb was charged with *ca.* 900 psi of carbon monoxide and heated slowly over a period of 2 hr to 65°. Heating was discontinued and the mixture was allowed to cool slowly to room temperature overnight. The contents of the bomb were transferred to a flask, concentrated to about 100 ml under reduced pressure, and treated with 150 ml of 3 *N* sodium acetate solution. Hydrogen peroxide (150 ml, 30%) was added at such a rate to maintain the temperature at 30–45°. After addition was complete, the temperature was maintained for 1 hr at 50–60°. This cooled mixture was diluted with water and extracted with ether. After a crude distillation, the material boiling between 40° (3.0 mm) and 105° (0.3 mm) was combined with another run (0.124-mol scale) and redistilled. There was obtained 23.54 g (22%) of a 75:25 mixture of **53** and **54**, greater than 95% pure by vpc (column G at 140°), bp 65–80° (3.0 mm). Isolated **53** was identical with a sample prepared by the literature method.[26] **54** had $\delta_{\mathrm{TMS}}^{\mathrm{CDCl_3}}$ 3.0–1.3 (m, 11) and 2.1–1.8 (two overlapping d, $J = 6.5$ Hz, 3, methyls).

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 77.98; H, 10.22.

***cis*-Bicyclo[5.2.0]nonan-4-one Ethylene Ketal** (**55**).—A mixture of 7.32 g (0.053 mol) of ketones **53** and **54** (*ca.* 65% of **53**), 6.58 g (0.016 mol) of ethylene glycol, and 100 mg of *p*-toluenesulfonic acid monohydrate was refluxed with stirring for 2 hr in 70 ml of benzene under a Dean–Stark trap. The mixture was cooled, diluted with water, and extracted with ether. The combined organic extracts were washed with saturated sodium bicarbonate and sodium chloride solutions and dried. The solvent was removed *in vacuo* and the residue was distilled, bp 69–80° (1.3 mm), yield 8.71 g (90%). Even on simple distillation with a short-path apparatus the latter fractions were enriched in **55**. **55** had $\delta_{\mathrm{TMS}}^{\mathrm{CCl_4}}$ 3.86 (s, 4, $-OCH_2-$) and 1.1–2.8 (br m, 14).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.44; H, 9.86.

***cis*-Bicyclo[5.2.0]non-2-en-4-one Ethylene Ketal** (**56**).—To 5.0 g (0.0274 mol) of somewhat impure **55** in 50 ml of dry ether was added dropwise at room temperature 4.65 g (0.0290 mol) of bromine. When all of the bromine had been consumed, a previously prepared solution of monosodium ethyleneglycolate (prepared from 1.27 g of sodium and 25 ml of ethylene glycol) was added with stirring. Water was added, the ether layer was separated, the aqueous phase was extracted several times with ether, and the combined organic extracts were dried and concentrated under reduced pressure. The last traces of solvent were removed *in vacuo* and the residue, without purification, was dissolved in 80 ml of dry dimethyl sulfoxide. To this solution was added 6.45 g (0.0575 mol) of potassium *tert*-butoxide with slight cooling. After stirring for 2 hr at room temperature, the dark mixture was poured into cold water and extracted four times with pentane. The combined pentane layers were washed with water and saturated sodium chloride solution, dried, and concentrated under reduced pressure. The residue was separated by distillation into two fractions. The first, bp 87–105° (1.3 mm), consisted of 3.05 g (62%) of unsaturated ketals (mostly **56**) and the second, boiling above 111° (1.3 mm), contained 1.21 g of unreacted bromo ketal. An analytical sample of **56** was prepared by preparative vpc (column F, 143°): $\delta_{\mathrm{TMS}}^{\mathrm{CCl_4}}$ 5.40 (br s, 2, olefinic), 3.84 (s, 4, $-OCH_2-$), and 1.0–3.0 (br, 10).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.19; H, 9.07.

***cis*-Bicyclo[5.2.0]non-2-en-4-one** (**45**).—A mixture of 3.05 g (0.017 mol) of unsaturated ketals in 1 ml of ether was stirred with 20 ml of 3% sulfuric acid for 3.5 hr at room temperature. At the conclusion of this time, the mixture was extracted four times with ether and the combined extracts were washed with water, sodium bicarbonate solution, and saturated salt solution. The dried solution was concentrated under reduced pressure to give 2.30 g of crude ketones. This material was distilled to remove a small amount of material with a very long vpc retention time, bp 62–75° (1.2 mm). The distillate was found by vpc analysis to be a mixture of about 50% of **45** and 50% of three other compounds which were not characterized. Pure **45** was obtained by preparative vpc on column H at 150°: $\delta_{\mathrm{TMS}}^{\mathrm{CDCl_3}}$ d of d (A portion of ABX, peak centers at 6.31 and 6.11, $J_{1,2} = 3.5$, $J_{2,3} = 12.5$ Hz, 1, H_2), d of t centered at 5.82 and 5.62 (1, H_3), 3.3 (br m, 1, H_1), and 1.4–3.0 (m, 9).

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 78.98; H, 8.89.

Recycling of Unreacted Bromoketal. Bicyclo[5.2.0]non-1-en-4-one Ethylene Ketal (**57**).—To 0.75 g (2.9 mmol) of the recovered bromo ketal in 15 ml of dry dimethyl sulfoxide was added 0.64 g (5.8 mmol) of potassium *tert*-butoxide. After stirring for 17 hr at room temperature, the mixture was poured into water and extracted with pentane. The combined pentane extracts were washed with sodium chloride solution, dried, and evaporated to give 0.46 g (88%) of pale yellow oil identified by nmr analysis as **57**. The sample was purified by molecular distillation (0.36 g recovered), and vpc analysis (column F at 150°) indicated that this material was greater than 85% of a single component. An analytical sample was obtained by preparative vpc on the same column: $\delta_{\mathrm{TMS}}^{\mathrm{CDCl_3}}$ 5.2 (m, 1, olefinic), 3.92 (s, 4, $-OCH_2-$), and 1.0–3.3 (br m, 11).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.44; H, 8.99.

Hydrogenation of Bicyclo[5.2.0]non-1-en-4-one Ethylene Ketal (**57**).—Using the procedure previously employed, 30 mg of **57** was hydrogenated in 4 ml of ethyl acetate over 12 mg of 10% palladium on carbon. There was obtained 19 mg of saturated cis ketal **55** that was identical with material previously synthesized.

Hydrolysis of Ketal 57. Bicyclo[5.2.0]non-1-en-4-one (**58**).—A mixture of 0.30 g of **57** dissolved in ether (1 ml) and 15 ml of 3% sulfuric acid was stirred at room temperature for 4 hr. After an ether extraction followed by washes of water and saturated sodium bicarbonate solution, the organic layer was dried and the solvent was removed under reduced pressure to give 0.18 g (80%) of **58**, $\delta_{\mathrm{TMS}}^{\mathrm{CDCl_3}}$ 5.2 (m, 1, olefinic) and 1.1–3.5 (br m, 11).

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.07; H, 8.81.

Hydrogenation of Bicyclo[5.2.0]non-1-en-4-one (58).—Ketone **58** (8 mg) was hydrogenated in 3 ml of ethyl acetate over 12 mg of 10% palladium on carbon. After filtration of the catalyst and concentration of the solution, preparative vpc (column E at 150°) yielded 6 mg of **53**, whose identity was confirmed by an infrared spectrum. There was a minor impurity (*ca.* 5%) that was too limited in quantity for identification.

Acid Equilibration of 45 and 58.—Ketone **58** (25 mg) and 1 mg of *p*-toluenesulfonic acid monohydrate were dissolved in 3 ml of benzene. This solution was heated to reflux and progress of the reaction was followed by periodic examination of aliquots by gas chromatography (column F). After 1 hr, the peaks due to **45** and **58** were of approximately equal size. After several hours the relative areas did not change and integration of the peak areas indicated a 43:57 mixture of **58** and **45**.

4-Methylene-*cis*-bicyclo[5.2.0]non-2-ene (59).—To 6.30 g (17.6 mmol) of methyltriphenylphosphonium bromide in about 60 ml of anhydrous ether was added under nitrogen 13.5 ml of 1.3 *N* *n*-butyllithium in pentane (0.018 mol). After this solution was stirred for 15 min at room temperature, ketone **45** (1.20 g of a mixture 50% in **45**, 8.8 mmol) dissolved in 5 ml of dry ether was added *via* syringe. After being refluxed overnight, the reaction mixture was quenched with water and extracted with pentane. The combined pentane extracts were dried and the solvent was removed by distillation at atmospheric pressure. The residue was vacuum transferred from nonvolatile phosphorous compounds and shown by vpc (column F at 115°) to consist of two major and two minor components; the first component eluted (possibly still a mixture) was not identified but was clearly not the desired compound by nmr analysis; the second component was the desired **59**, and the third and fourth components were small amounts of unreacted ketones **58** and **45**. **59** had $\delta_{\mathrm{TMS}}^{\mathrm{CDCl_3}}$ 5.91 (d with further coupling, 1, H_3, A portion of ABX, $J_{2,3} = 12.5$ Hz), 5.35 (d of d, B portion of ABX, $J_{2,3} - 12.5$, $J_{1,2} = 4.3$ Hz, H_2), 4.82 (br s, 2, methylene protons), 3.2 (br m, 1, H_1), and 1.2–2.9 (m, 9) (double irradiation of H_1 (341 Hz) on a Jeolco 100-MHz nmr instrument collapsed H_2 and H_3 to a clean AB quartet); calcd *m/e* 134.1095, observed *m/e* 134.1096.

Anal. Calcd for $C_{10}H_{14}$: C, 89.49; H, 10.51. Found: C, 89.14; H, 10.53

Pyrolysis of *cis*-Bicyclo[5.2.0]non-2-en-4-one (45).—Pyrolysis was carried out as before, giving the results summarized in Table VI. 2,4- and 3,5-Cycloheptadienones (**44** and **43**) were identified by their infrared spectra. The order of elution from column F (140°) was **43**, **44**, **51**, and **45**. Bicyclo[3.2.2]non-6-en-2-one (**51**) displayed ir and nmr spectra identical with those of the authentic material prepared above.

Photoisomerization of 51. *cis*-3a,4,5,7a-Tetrahydro-1-indanone (60).—An analytical run was performed by photolyzing a 1% ether solution of **60** and cyclododecane in a Pyrex test tube attached to a Pyrex immersion well which housed a 200-W Hanovia lamp. Aliquots were removed at various intervals and analyzed by vpc. Starting material slowly disappeared and was replaced by one major component (84%), a second less predominant product (13%), and two very minor substances which remain unidentified. The major product was characterized as ketone **60** and the minor as aldehyde **61**.

A preparative run was carried out by photolyzing 480 mg of **51** in 25 ml of dry ether (purged with nitrogen) for 43 hr. At the end of this time, the mixture was concentrated under reduced pressure and the products were isolated by preparative vpc isolation from column H at 150°. **60** had $\delta_{\mathrm{TMS}}^{\mathrm{CDCl_3}}$ 5.65–5.90 (m, 2, olefinic) and 1.2–2.9 (10 H).

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 78.98; H, 8.88.

61 had $\delta_{\mathrm{TMS}}^{\mathrm{CDCl_3}}$ 9.84 (t, J = 1.5 Hz, 1, -CHO), 5.5–6.1 (m, 4, olefinic), 1.4–2.7 (br m, 7); $\lambda_{\max}^{\mathrm{cyclohexane}}$ 260 mm (ϵ 5000); calcd *m/e* 136.0888, observed 136.0889. The 2,4-dinitrophenylhydrazone melted at 84–86.5° (from ethanol). The lack of sufficient material precluded elemental analysis.

Hydrogenation of 60 to *cis*-Perhydroindanone (62).—A sample of **60** (21 mg) in 5 ml of dry ether was hydrogenated over 25 mg of 10% palladium on carbon for 2 hr. The catalyst was filtered through Celite and the filtrate was concentrated in a stream of dry nitrogen. Vpc analysis on column H at 150° indicated that the product was greater than 95% pure. A sample collected from the vpc had an infrared spectrum identical with that of authentic *cis*-perhydroindanone (**62**).[44]

Isomerization of 60.—A pure sample of **60** was injected into a 12 ft × 0.25 in. vpc column packed with 10% QF-1 on 60/80 mesh Chromosorb G at 165–170° and was collected. The infrared spectrum of the material which was eluted last was identical with that of authentic **63**. On the second pass through the vpc column, approximately 50% conversion to **63** was achieved. When the temperature of the column was lowered to 145°, no isomerization of **60** was noted.

Chlorination–Dehydrochlorination of *cis*-Perhydro-1-indanone (62).—To 2.00 g (0.0145 mol) of **62**[44] in 10 ml of carbon tetrachloride at 0–15° was added dropwise 2.35 g (0.0174 mol) of sulfuryl chloride dissolved in 5 ml of CCl_4 over a period of 30–45 min. The mixture was stirred for an additional 1.5 hr, at which time water was added and the layers were separated. The organic layer was washed with saturated sodium bicarbonate and saturated sodium chloride solutions, and dried, and the solvent was distilled through a short column at reduced pressure. The residue (2.18 g) was dissolved in 30 ml of dry tetrahydrofuran and 1.87 g (0.0151 mol) of 1,5-diazabicyclo[4.3.0]non-5-ene was added. The mixture was refluxed for 5 hr, cooled, and diluted with pentane and water. The aqueous phase was extracted with pentane, and the combined organic extracts were dried and concentrated. The residue weighed 610 mg and it consisted of 2% minor components, 21% of the desired 3a,4,5,6-tetrahydro-1-indanone (**63**), and 77% of 4,5,6,7-tetrahydro-1-indanone (**65**). The mixture was separated by preparative vpc (column B at 142°) and furnished 62 mg of **63** and 243 mg of **65**. **63** had $\nu_{\max}^{\mathrm{neat}}$ 1720 and 1650 cm^{-1}; $\delta_{\mathrm{TMS}}^{\mathrm{CCl_4}}$ 6.49 (m, 1, olefinic), 1.7–2.9 br m, 11); calcd *m/e* 136.0888, observed *m/e* 136.0889. **65** had $\nu_{\max}^{\mathrm{neat}}$ 1690 and 1640 cm^{-1}; $\delta_{\mathrm{TMS}}^{\mathrm{CCl_4}}$ 1.4–2.6 (br m); calcd *m/e* 136.0888, observed *m/e* 136.0889.

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.19; H, 9.12.

Pyrolysis of 59.—A 36.1-mg sample of pure **59** was pyrolyzed at 540° as before and 33.9 mg of a mixture was collected. After preparative vpc separation on column F at 95°, the three individual components, **59** (4%), **46** (68%), and **47** (21%), were identified by their infrared spectra.

Control Pyrolysis of 60.—Ketone **60** (44.3 mg) was pyrolyzed at 490° (30 mm), and the resulting mixture was analyzed by vpc (column I at 140°). Starting material represented 90% of the mixture (20.8 mg was isolated and identified by its infrared spectrum), and **63** was the largest other component (5%, 1.1 mg isolated), identified by its infrared spectrum. A similar control pyrolysis at 555° (25 mm) of 21.9 mg of **60** gave a mixture consisting of **62** starting material (3.6 mg isolated) and 11% of **63** (0.9 mg isolated). In both cases, the remainder of the material was distributed among no less than light minor components.

Preparative Scale Pyrolysis of 47.—Pure **47** (71.5 mg) was pyrolyzed in the flow apparatus at 555° (30 mm) under a slow stream of nitrogen carrier gas. Vpc analysis of the condensate indicated that 10% of the mixture was **46** and 85% consisted of unreacted **47**; there was also produced in a combined yield of 5% a mixture of five minor components. After preparative vpc (column G at 115°), 4.3 mg of **46** was collected and identified by its nmr spectrum; 47.9 mg of unreacted **47** was also collected for an overall mass balance of 75%.

Acknowledgment.—Partial financial support of this research has been provided by the Army Research Office (Durham).

Registry No.—**1a**, 24217-77-4; **1b**, 24217-81-0; **3a**, 24217-80-9; **3b**, 24217-82-1; **5**, 40954-22-1; **6**, 34956-68-8; **11**, 40954-24-3; **12**, 40954-25-4; **13**, 40954-26-5; **14**, 3721-60-6; **15**, 41021-31-2; **16**, 40954-28-7; **24**, 10095-80-4; **25**, 40954-30-1; **25** semicarbazone, 40954-31-2; **26**, 40954-32-3; **27**, 40954-33-4; **28**, 40954-34-5; **29**, 3513-11-9; **30**, 40954-37-8; **31**, 19744-63-9; **38**, 40954-

---

[44] H. O. House and G. H. Rasmusson, *J. Org. Chem.*, **28**, 31 (1963). We thank Professor House for making the spectra of *cis*- and *trans*-perhydroindanone available to us.

38-9; **39,** 40954-39-0; **40,** 40954-40-3; **41,** 40954-41-4; **41** semicarbazone, 40954-42-5; **42,** 40954-43-6; **43,** 1121-65-9; **44,** 1901-34-4; **45,** 40954-46-9; **46,** 40954-47-0; **47,** 40954-48-1; **50,** 40954-49-2; **51,** 934-62-3; **52,** 16177-46-1; **53,** 40954-52-7; **54,** 40954-53-8; **55,** 40954-54-9; **56,** 40954-55-0; **57,** 40954-56-1; **58,** 40954-57-2; **59,** 40954-58-3; **60,** 40954-59-4; **61,** 40954-60-7; **61** 2,4-DNPH, 40954-61-8; **62,** 2826-65-5; **63,** 40954-63-0; **65,** 22118-00-9.

The Synthesis of an Analog of Camptothecin by a General Method

ROBERT E. LYLE,* JAMES A. BRISTOL,[1a,b] MICHAEL J. KANE,[1a] AND DAVID E. PORTLOCK

Department of Chemistry, Parsons Hall, University of New Hampshire, Durham, New Hampshire 03824

Received May 1, 1973

The introduction of the α-hydroxybutyrate chain on the 4 position of β-picoline *via* the 4-lithio derivative gave **7**. The oxidation of the 3-methyl substituent required for lactone formation between the substituents on the 3 and 4 positions of **7** to give **14** could only be accomplished after introducing a chloro group adjacent to the ring nitrogen. The quaternization of **2** and the hydrolysis of the aryl-α-chloro substituent completed the synthesis of the camptothecin analog **16**.

The discovery was made that the alkaloid camptothecin (**1**) possessed a high activity against several mouse lymphocytic leukemias[2] and inhibited the growth of solid tumors as well. The isolation of the 10-hydroxy- and 10-methoxycamptothecin as minor alkaloids from *Camptotheca acuminata* provided compounds with activity against leukemia, L1210.[3] The limited availability of the natural material provided an impetus for the synthesis of camptothecin and led to several successful preparations during a 1-year period.[4] The toxicity observed on continued administration of camptothecin led to an increased interest in the synthesis of close structural analogs as a possible means of obtaining compounds which retained the desirable anticancer effects but with reduced chronic toxicity. This article reports a general method for the synthesis of such compounds using an analog with the A and B rings carbocyclic and a seco ring C to illustrate the method.

The antineoplastic activity of camptothecin has been shown to be associated with the pyridone and lactone systems of the D and E rings.[2] Simple D and E ring analogs having methyl substituents on the pyridone ring at the 6 position[4c] or 1 position[4f,g] have been reported and the former was reported to have 0.01 times the activity of camptothecin as a cytotoxic agent. The synthetic methods used for these analogs were not readily applicable for the preparation of a variety of N-substituted derivatives which might be converted to pentacyclic analogs. The synthetic scheme utilized in this study provided a logical approach to any aromatic pentacyclic analog as well as natural camptothecin.

The crucial intermediate in this synthesis was the pyrido-δ-lactone **2**. β-Picoline *N*-oxide[5] was nitrated following the procedure of Taylor and Crovetti to give the 4-nitro derivative **3**, which was converted by acetyl bromide[6] or hydrobromic acid[7] to 84 or 81% of 4-bromo-β-picoline 1-oxide (**4**), respectively. Attempts to cause the displacement of the nitro group by bromine and reduction of the *N*-oxide in the same reaction with phosphorus tribromide[7] gave a mixture of **5** and 4-nitro-β-picoline (**6**). A more satisfactory route to **5** was by the two-step conversion from **3** using Raney nickel catalyst to remove the *N*-oxide function from **4** following a procedure described for a related reaction.[8] This reaction gave 83% yields of **5**, isolated as the hydrobromide, with no complication of nucleophilic displacement of the 4-bromo group as was observed when phosphorus trichloride was used for the reduction.

Alkylation of 4-nitro-β-picoline 1-oxide (**3**) or 4-bromo-β-picoline 1-oxide (**4**) by nucleophilic displacement of the 4 substituent by a carbanion proved unsuccessful. Thus the sodium salts of ethyl cyanoacetate and diethyl ethylmalonate in several solvents failed to give reaction. Spectroscopic evidence for a very small yield from the reaction of the sodium salt of diethyl malonate and 4-bromo-β-picoline 1-oxide (**4**) was obtained. The yield could not be improved by the application of more vigorous reaction conditions, so the introduction of the 4 side chain by this approach was abandoned.

---

(1) (a) This research was abstracted from the theses of J. A. B. and M. J. K. presented to the Graduate School of the University of New Hampshire in partial fulfillment of the requirements for the Ph.D. degree. (b) NDEA Fellow, 1969–1971; UNH Dissertation Year Fellow, 1971–1972.

(2) (a) M. E. Wall, Abstracts, 4th International Symposium on the Biochemistry and Physiology of Alkaloids, Halle, East Germany, Academic Press, Berlin, 1969, pp 77–87; (b) R. C. Gallo, J. Whang-Peng, and R. H. Adamson, *J. Nat. Cancer Inst.*, **46,** 789 (1971); (c) H. B. Bosmann, *Biochem. Biophys. Res. Commun.*, **41,** 1412 (1970); (d) R. S. Wu, A. Kuman, and J. R. Warner, *Proc. Nat. Acad. Sci. U. S.*, **68,** 3009 (1971); (e) D. Kessel, *Cancer Res.*, **31,** 1883 (1971); (f) J. A. Gottlieb, A. M. Guarino, J. B. Call, V. T. Oliverio, and J. B. Block, *Cancer Chemother. Rep. Part 1*, **54,** 461 (1970); (g) J. L. Hartwell and B. J. Abbott, *Advan. Pharmacol. Chemother.*, **7,** 137 (1969); (h) L. G. Hart, J. B. Call, and V. T. Oliverio, *Cancer Chemother. Rep.*, **53,** 211 (1969); (i) S. Danishefsky and J. Quick, *Tetrahedron Lett.*, (1973).

(3) (a) M. C. Wani and M. E. Wall, *J. Org. Chem.*, **34,** 1364 (1969); (b) M. Shamma, *Experientia*, **24,** 107 (1968).

(4) (a) G. Stork and A. Schultz, *J. Amer. Chem. Soc.*, **93,** 4074 (1971); (b) R. Volkmann, S. Danishefsky, J. Eggler, and D. M. Solomon, *J. Amer. Chem. Soc.*, **93,** 5576 (1971); (c) M. C. Wani, H. F. Campbell, G. A. Brine, J. A. Kepler, M. E. Wall, and S. G. Levine, *ibid.*, **94,** 3631 (1972); M. E. Wall, H. F. Campbell, M. C. Wani and S. G. Levine, *ibid.*, **94,** 3632 (1972); (d) E. Winterfeldt, T. Korth, D. Pike, and M. Boch, *Angew. Chem., Int. Ed. Engl.*, **11,** 289 (1972); (e) M. Boch, T. Korth, J. M. Nelke, D. Pike, and E. Winterfeldt, *Chem. Ber.*, **105,** 2126 (1972); (f) C. Tang and H. Rapoport, *J. Amer. Chem. Soc.*, **94,** 8615 (1972); J. J. Plattner, R. D. Gless and H. Rapoport, *ibid.*, **94,** 8613 (1972); (g) T. Sugasawa, T. Toyoda, and K. Sasakura, *Tetrahedron Lett.*, 5109 (1972); (h) A. S. Kende, T. J. Bentley, R. W. Draper, J. K. Jenkins, M. Joyeux, and I. Kubo, *ibid.*, 1307 (1973); (i) A. I. Meyers, R. L. Nolen, E. W. Collington, T. A. Narwid, and R. Strickland, *J. Org. Chem.*, **38,** 1974 (1973); J. F. Hansen, K. Kamata, and A. I. Meyers, *J. Heterocycl. Chem.*, **10,** in press; (j) a summary of the research on camptothecin will appear by A. G. Schultz, *Chem. Rev.*, in press; (k) M. Shamma, D. S. Smithers, and V. St. Georgiev, *Tetrahedron*, **29,** 1949 (1973).

(5) E. C. Taylor and H. J. Crovetti, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 654.

(6) S. Kajuhara, *Nippon Kagaku Zasshi*, **86,** 1060 (1965); *Chem. Abstr.*, **65,** 16936 (1966).

(7) R. A. Abramovitch and M. Saha, *Can. J. Chem.*, **44,** 1765 (1966).

(8) E. Hayashi, H. Yamanaka, and K. Shimigu, *Chem. Pharm. Bull.*, **7,** 141 (1959).