Fenestranes and the Flattening of Tetrahedral Carbon

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I. Introduction

We have known about strained organic molecules for about 100 years. Systematic investigation of small-ring compounds had a sensational beginning in 1883 with Perkin's synthesis of cyclobutanecarboxylic acid.[1] Rings of fewer than six carbon atoms had not yet been found in nature, and the informed opinion of the day was that they were incapable of existence. Previous reports of both 1,3-cyclobutanedicarboxylic acid[2,3] and cyclopropane[4] had been ignored or discounted, but Perkin's work found immediate acceptance and forced a significant change in structural theory.

Since those early days many types of strained systems have been the subject of discussion, model building, calculation, synthesis, and experimental determination of physical and chemical properties. In recent times strained molecules have multiplied in number and variety as a result of improved synthetic techniques, and more thorough investigations into their properties have been possible by means of increasingly sophisticated physical tools and increasingly powerful theoretical methods. Strained compounds can often be viewed as answering simple "what if?" questions: What if a benzene ring is bent? What if a double bond is twisted? What if a bond angle is severely reduced? Excellent more general treatments of strain are already available,[5,6] and here we will focus attention on a single class of compounds studied in response to one of these "what if?" questions: What if a tetrahedral carbon atom is flattened? Since careful calculations[7] indicate that the energy difference between tetrahedral and square planar methane lies well above typical carbon–hydrogen or carbon–carbon bond strengths, it seems unlikely that simple molecules containing square planar carbon with such ordinary bonds will be experimentally realized. One way to overcome this limitation might be to use other kinds of bonds; calculations suggest, for example, that the unusual and experimentally unknown mole-

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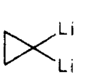
cules **1**–**3** should be planar.[7] Another approach has been to focus attention upon molecules in which a degree of flattening at one carbon atom may be imposed structurally, in some cases with accompanying and compensating delocalization of π electrons. In this review we consider a group of such molecules for which there are both predictions and experimental evidence concerning flattening at a central quaternary carbon atom. These are the fenestranes (**4**), and we will take this class generally to comprise both peripherally unsaturated structures such as **5**, as well as saturated systems such as **6**–**9**. This is an active area of research, where synthesis and physical examination of the most significant compounds are still enticing goals.



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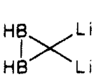

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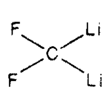

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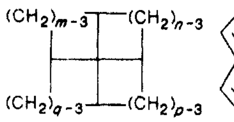

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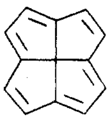

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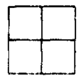

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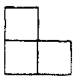

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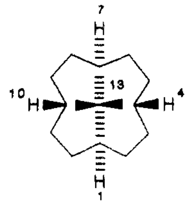

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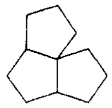

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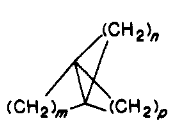
II. Nomenclature and Scope

Georgian and Saltzman introduced the name *fenestrane* [*fenestra* (L.), window] specifically for tetracyclo[3.3.1.0.^{3,9}0^{7,9}]nonane (**6**).[8] This has been conveniently extended[9] to [*m.n.p.q*]*fenestrane* for the class of tetracyclic compounds represented by **4** and [*m.n.p*]-*fenestrane* for the corresponding tricyclic systems. Hydrocarbon **6** then becomes [4.4.4.4]fenestrane, and **7** is [4.4.4]fenestrane. Various other names are also in common use. Related unsaturated systems of five-membered rings are frequently referred to as *polyquinenes* or in tetracyclic cases such as **5**, as *tetraquinenes*, and [5.5.5.5]fenestrane is often called *staurane* [*σταυρος* (Greek), cross].[10] In addition **6** is known as *windowpane*,[11] and tricyclic fenestranes such as **7** are *broken windows*.[5,12] It is also noteworthy that the names employed by *Chemical Abstracts* for these various compounds do not necessarily follow the familiar cycloalkane system of nomenclature. Structures based on [5.5.5.5]fenestrane, for example, are designated by *Chemical Abstracts* as derivatives of a pentalenopentalene.

When specific, written designation of stereochemistry is desired, our preference[13] has been to denote peripheral configurations in the standard α/β system. In compounds of low symmetry, the configuration at the central quaternary carbon atom often can be readily assigned using the Cahn–Ingold–Prelog[14] sequence rule (*R*/*S* convention). Unfortunately, this system is either difficult to apply or ambiguous for some highly symmetrical parent hydrocarbons such as **8**. Even when it can be applied unambiguously, the stereochemistry of the central asymmetric or pseudoasymmetric quaternary atom can be deduced from the designator only with considerable effort. These difficulties can be avoided by indicating stereochemistry at this central atom using syn/anti periplanar designators, and this is the method recommended by *Chemical Abstracts*. These designators describe the relationship of the two end atoms of one of the dihedral angles involving the quaternary carbon in its central bond. Using cycloalkane nomenclature, the isomer of [5.5.5.5]fenestrane depicted in **8** then is (1,13-*syn*,1α,4β,7α,10β)tetracyclo[5.5.1.0.^{4,13}0^{10,13}]tridecane, where *1,13-syn* indicates that the preferred[14] atoms bonded to C(1) [C(1)H] and to C(13) [C(7)] have a syn periplanar relationship in the dihedral angle C(1)H–C(1)–C(13)–C(7). It is also possible to dispense with the α/β assignments for the bridgehead centers and to indicate instead all the syn/anti periplanar relationships; the designation for **8** then becomes (1,13-*syn*,4,13-*syn*,7,13-*syn*,10,13-*syn*) or (*all-syn*). We prefer, however, to retain the α/β designators because they are so immediately understandable. We also find the cycloalkane names too cumbersome for frequent use, but combination of the stereochemical prefix with the fenestrane name yields a convenient designation, provided that the numbering of the ring system is understood. No specific convention for numbering has been employed with the fenestrane system of names; our own use is to retain the numbers assigned with the cycloalkane name, which are the numbers shown with **8**. This gives finally for **8** the name (1,13-*syn*,1α,4β,7α,10β)[5.5.5.5]fenestrane. In some compounds of interest the central quaternary atom is neither asymmetric nor pseudoasymmetric; in other cases designation of its configuration is often unnecessary, since for fenestranes with relatively small rings only one configuration of the central atom leads to a physically likely compound. Assignment at this center may be necessary, however, in providing systematic names and in specifying hypothetical structures.

Keese has introduced a nomenclature for stereochemistry whereby **8** is *all-cis*-[5.5.5.5]fenestrane, reflecting the fact that it may be constructed entirely from subunits of *cis*-bicyclo[3.3.0]octane.[15,16] This is effectively the same feature indicated above by (*all-syn*). The reader unfamiliar with Keese's usage should note that the prefix does not designate the relative stereochemistry of the bridgehead hydrogen atoms; in fact, in Keese's terminology the hydrocarbon isomeric with **8** having these four hydrogens mutually cis (1α,4α,7α,10α) is *cis,trans,cis,trans*-[5.5.5.5]fenestrane. Simply for uniformity and convenience, we shall employ the fenestrane nomenclature; the usual suffixes are adopted, so that, for example, a singly unsaturated derivative is a *fenestrene*; and when necessary, stereochemistry will be denoted using the syn/anti, α/β system.

Our interest here is in fenestrane derivatives relevant to the flattening of a tetrahedral carbon atom. As we shall see, this broadly means saturated tetracyclic systems containing five-membered and smaller rings, unsaturated systems with five- and six-membered rings, and a few other systems that are closely related for one reason or another. We shall exclude derivatives of [5.5.5]fenestrane (**9**) since, as *triquinanes*, they have a well-developed and well-reviewed chemistry of their own in connection with polycyclopentanoid natural products,[17] and they have little pertinence to our present topic. Also excluded are propellanes (10) and paddlanes (11),[18] which are two other systems with flattened carbon that have been studied for almost 20 years;[19] structures, such as 12[20] and the vespirenes (13),[21] that contain fenestranes embedded in more complex ring systems; and heterocyclic compounds such as 14.[22]



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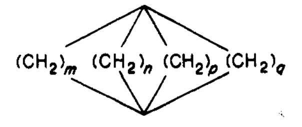

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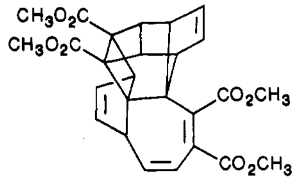

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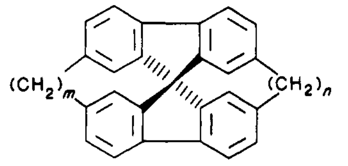

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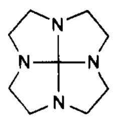

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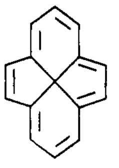
III. Theoretical Considerations

There has been disagreement concerning both the electronic structure and the energy of planar methane, as well as a lack of unanimity on just which fenestranes, from a theoretical point of view, should be the most rewarding synthetic goals. While the disagreements are not yet resolved, these theoretical discussions have served as a frutiful source of ideas about possible targets for synthesis and physical study. In 1970 Hoffmann proposed[23] a structure for planar methane that is summarized in the following description. It should have a normal set of sp^2 bonds at carbon. Two of these would form normal two-electron bonds with two hydrogen atoms, using two of the valence electrons. The third sp^2 hybrid would participate in a two-electron, three-center bond with the two remaining hydrogen atoms, utilizing only hydrogen electrons. The two additional carbon valence electrons would be placed in the remaining 2p orbital perpendicular to the molecular plane, and resonance among equivalent structures would render all four carbon–hydrogen bonds equivalent. It was suggested[24] not long afterward that a triplet state version of this model should be energetically competitive with the closed-shell singlet description, and in 1980 Snyder reported[25] calculations indicating that the most stable structure for planar methane, by some 25–30 kcal/mol, was an open-shell singlet. This biradical differed from Hoffmann's structure in transfer of one of the unused carbon valence electrons from the 2p orbital into an antisymmetric hydrogen d-type orbital. Over the years there have been calculations of the total energy of planar methane by a variety of techniques, and these have yielded estimates from 95 to 250 kcal/mol as the energy required to flatten the tetrahedral molecule.[5,7,11,23–27] Perhaps the most rigorous of these estimations is that of Schleyer, Pople, and their co-workers. This employed restricted Møller–Plesset second-order perturbation theory as applied to calculations at the 6-31G** level; it gave an energy difference between planar and tetrahedral singlet methane of 157 kcal/mol.[7]

Hoffmann suggested that it might be possible to stabilize a planar carbon atom by placing it at the center of an annulene that would be aromatic if planar. In particular, he proposed the [5.6.5.6]- (15) and [5.5.6.6]fenestraheptaenes (16), along with the more complex hydrocarbon 17, as promising stabilized systems, and he also stated that the corresponding [4.4.4.4], [4.5.4.5], and [5.5.5.5] unsaturated systems 18, 19, and 5 were expected not to be stable.[23] Keese disagreed with this prediction for 5, arguing that this derivative of [12]annulene should be stabilized and flattened owing to interaction between the energetically unfavorable HOMO at the central atom and the LUMO of the peripheral 12 π-electron system. His calculations also indicated that the delocalization energy in homoconjugated 20 was nearly as great as that in 5, and he suggested that both 5 and 20 should be attractive goals for synthesis.[28] Gleiter reported MINDO/3[29] calculations indicating that 5, 15, and 16 all would be unstable and nonplanar.[30] Schleyer presented a MNDO[31] study that agreed with Hoffmann's prediction of instability for 5, 18, and 19 and supported Gleiter's conclusion that 15 would be olefinic rather than aromatic.[32]



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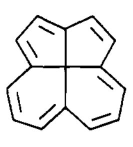

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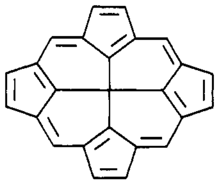

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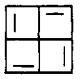

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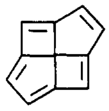

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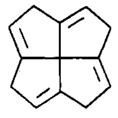

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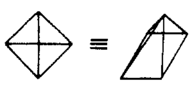
Saturated fenestranes have also been the subject of several theoretical studies. Here there has been less controversy, and ab initio molecular orbital calculations give acceptable estimates of energies and structures.[33] Semiempirical methods have also proved quite useful, but molecular mechanics calculations for fenestranes are less accurate, though of course much easier to carry out. Experience indicates that with the usual force constants molecular mechanics tends to overestimate the energy required for large deformation of bond angles, introducing the possibility of sizable errors both in absolute strain energy and in molecular geometry.[34,35] These empirical calculations are very convenient, however, for estimating energy differences between homologous or isomeric systems.

The smallest member of the saturated series, [3.3.3.3]fenestrane (21), is usually referred to as *pyramidane*, and in fact MINDO/3 calculations by Minkin, Minyaev, and their co-workers on this system show that the square pyramidal structure is a minimum on the potential energy surface and suggest that 21 should possess some kinetic stability.[36] They have also provided semiempirical calculations concerning the energetics along reaction paths that might lead to this experimentally unknown hydrocarbon.[37] Wiberg has reported[38a] extensive ab initio calculations on three of the



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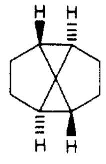

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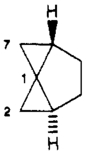

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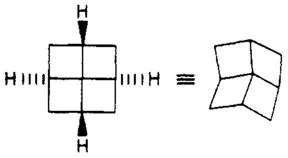

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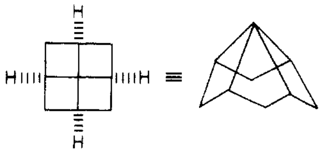

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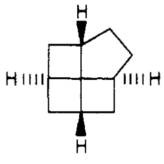
unknown [3.5.3.5]fenestranes, the 1α,2β,5α,6β isomer depicted in **22**, as well as its 1α,2β,5β,6β and 1α,2α,5α,6α diastereomers; estimated strain energies are in the range of 148–157 kcal/mol. It proved impossible to construct stable structures for the remaining two isomers, 1α,2α,5β,6β and 1α,2β,5β,6α. This study included similar calculations on the two diastereomeric [3.5.3]fenestranes. The structure calculated for the known[38a,39] 3α,6β isomer (**23**), preparation of which is mentioned below, agrees well with the values obtained experimentally by electron diffraction.[40] The calculated strain energy of **23** is 80 kcal/mol, and the unknown 3α,6α isomer is predicted to have an energy 46 kcal/mol greater.

Both MINDO/3 and MNDO semiempirical calculations suggest that (1α,3β,5α,7β)[4.4.4.4]fenestrane (**24**) should be more stable than its 1α,3α,5α,7α isomer **25** and that neither species would be planar; the favored geometries at the quaternary carbon atom are a somewhat flattened tetrahedron in **24** and a pyramid in **25**.[41,42] These conclusions found strong support in later ab initio calculations.[43,44] Several interesting features emerge from these studies. For **24** the carbon–carbon bond to the central atom is unusually short, 1.480 Å; the external carbon–carbon bond is rather long, 1.600 Å; and the bond angle across the central atom is 130.4°. The very short bond seems to be the result of poor directionality, leading to markedly bent bonds. The strain energy of **24** is predicted to be 160 kcal/mol, and the pyramidal isomer **25** should be less stable by 48 kcal/mol. The calculated energy necessary to distort **24** to a square planar conformation is some 130 kcal/mol. While the strain energy of cubane (155 kcal/mol)[45] is about 6 times that of cyclobutane (27 kcal/mol), the calculated strain of **24** (160 kcal/mol) is much more than 4 times that of cyclobutane. Per ring then, fenestrane **24** is much more strained than cubane. It is interesting to note how little of this strain seems attributable to bond-angle distortion at the central atom. A symmetrically distorted methane with the bond angles calculated for **24** has a predicted energy only 20 kcal/mol greater than that of tetrahedral methane.[46] Similar calculations for **25** are also quite instructive. Methane with this pyramidal geometry has a distortion energy of 139 kcal/mol. This means that methanes with the geometries calculated for **24** and **25** differ by 119 kcal/mol, but the two fenestranes themselves differ by only 48 kcal/mol. The pyramidal fenestrane **25** apparently enjoys 71 kcal/mol of extra stabilization, and this is attributed[44] to an electronic structure reminiscent of that described earlier for planar methane, with only three electron pairs forming the four bonds to the pyramidal atom, and the other pair in a nonbonding orbital pointing away from the molecule. This leads to a remarkably large dipole moment of 3.2 D calculated for **25**. Some years earlier Greenberg and Liebman had suggested that the unusual stabilization available in a pyramidal structure would actually make **25** more stable than **24**,[47] and Snyder had found that for methane the pyramidal structure was energetically slightly preferable to the square planar.[25]

Fenestranes larger than the [4.4.4.4] system have not been the subject of published ab initio calculations, but Keese has made MNDO studies of several of these hydrocarbons.[48] For [4.4.4.5]fenestrane (**26**) and its [4.4.5.5] homologue **27**, the calculated angles across the quaternary atom agree within 1° or better with experimental results to be mentioned later. For some of these systems Wiberg has carried out molecular mechanics calculations that permit estimations of the difference in strain between homologous systems.[34] The increase in strain energy on contraction of **27** to **26** was found to be 38 kcal/mol, while that between **26** and **24** was 73 kcal/mol. The former value may be compared with a calculated difference of 28 kcal/mol between [4.4.5]- and [4.4.4]fenestrane. The absolute strain energies given by these calculations are considered upper limits, and it is not yet clear how reliable the estimated differences are.



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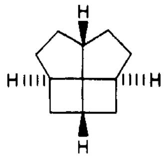

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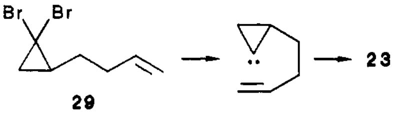

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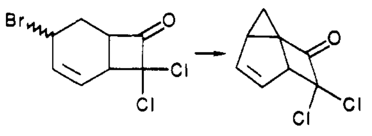

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Two other sorts of studies deserve mention here. Gund and Gund have enumerated the ways that rings can share a common carbon atom in polycyclic hydrocarbons, providing a novel scheme for categorizing such ring systems, as well as one means of fitting the fenestranes into a larger conceptual framework of molecular structure.[35] Finally, there has been extensive examination of distortion at a spiro carbon atom. Wiberg has presented ab initio calculations on bending (cf. **28a**) and twisting (cf. **28b**) of spiropentane, demonstrating bending to be energetically more economical than twisting.[38a] While these results were applied specifically to the distortions in [3.5.3]- and [3.5.3.5]fenestranes, they are of general significance in the detailed and quantitative evaluation of flattening at a carbon atom. Keese has collected data both from crystal structures and from MNDO calculations for a wide variety of spiro systems, including the embedded spiro systems of several fenestranes, and has used this information to classify these systems according to the amounts of compression and twisting contributing to bond defor-

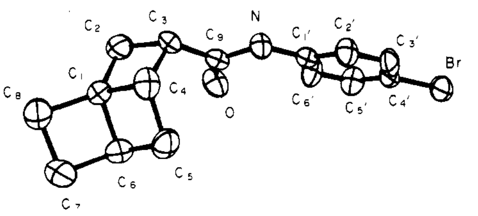


Figure 1. ORTEP drawing of [4.4.4]fenestrane derivative **40** showing 50% probability ellipsoids. Reprinted with permission from *J. Am. Chem. Soc.* 1980, *102*, 7467. Copyright 1980 American Chemical Society.

mation at the spiro atom.[49,50] Plots of these data show that among the systems examined fenestranes are unique in that flattening at the central carbon atom occurs almost solely through compression with little or no twisting.

IV. Synthesis and Properties

The material in this section is organized by increasing ring size of the fenestranes. In synthetic work employing ring closures and contractions more than one fenestrane ring system is often encountered in a particular sequence of transformations.

A. [3.5.3]Fenestrane

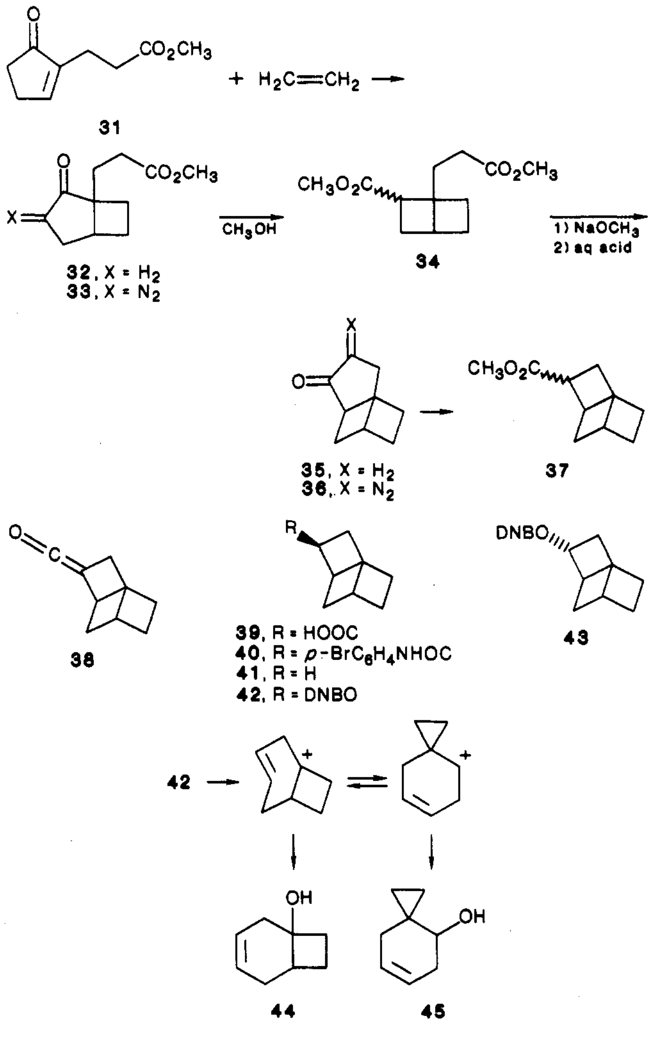
The $3\alpha,6\beta$ isomer **23** of this bridged spiropentane was prepared some years ago from **29** by treatment with an alkyllithium to form a carbene or carbenoid that inserts in the double bond.[39] Structure and stereochemistry of **23** rest of electron diffraction studies[40] and nuclear magnetic resonance (NMR) measurements.[38a] A remarkable feature is the C(2)–C(1)–C(7) bond angle of 162°. The considerable strain in this [3.5.3]fenestrane is responsible for an unusual reaction; on exposure to a platinum complex its carbon skeleton undergoes rearrangement to that of 5-methylenebicyclo[2.1.1]hexane.[38b]

B. [3.5.4]Fenestrane

In a surprising transformation, dehydrobromination of 4-bromo-8,8-dichlorobicyclo[4.2.0]oct-2-en-7-one leads to **30**, a derivative of [3.5.4]fenestrane whose structure was proved by crystallographic methods.[51] No information has been published about this unique compound other than its anomalous ultraviolet absorption maxima: 242.5 nm ($\epsilon = 1240$) and 302 (88) in octane.

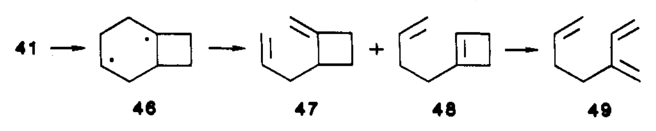
C. [4.4.4]Fenestrane

Synthesis and careful investigation of this tricyclic fenestrane in 1980 by Wiberg and his collaborators provided an important impetus to experimental investigations in the general area.[34] Cyclopentenone **31** added ethylene photochemically to give **32** in good yield. Diazo ketone **33** was obtained by conversion of **32** first to the α-hydroxymethylene ketone with ethyl formate and then reaction with *p*-toluenesulfonyl (tosyl) azide. Ring contraction by way of photochemical Wolff rearrangement in methanol then led to **34**, a mixture of bicyclo[2.2.0]hexane diesters. This sequence of diazotization and Wolff rearrangement has proved to be the most useful and reliable method of contraction for formation of strained four-membered rings, and it will reoccur several times in our discussion. Dieckmann cyclization of **34** and decarboxylation gave the [4.4.5]fenestrane ketone **35**, and a second ring contraction via **36** furnished esters **37**. Mixtures such as **34** and **37** arise by way of an intermediate ketene (**38** in the latter case) that is the proximate product of Wolff rearrangement. This ketene can be captured by solvent methanol from either side, and predominant attack from the less hindered rear side is anticipated. Hydrolysis of **37** afforded the major acid **39** in crystalline form, and this was derivatized to anilide **40** for X-ray analysis and also converted to the parent hydrocarbon, [4.4.4]fenestrane (**41**).



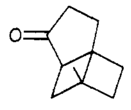
DNB = 3,5-dinitrobenzoyl

The solvolytic behavior of the endo (β) and exo (α) 3,5-dinitrobenzoates **42** and **43**, which were available in several steps from **39**, was parallel to that of the analogous 2-bicyclo[2.2.0]hexyl esters.[52] Exo isomer **43** was stable, but the endo ester **42** underwent reaction in 80% acetone at 70 °C to form **44** and **45**. Thermolysis of **41** at ~180 °C led to a mixture of **47** and **49**, both of which may be explained by initial cleavage to biradical **46**. Opening of **46** in the two possible senses leads to **47** and **48**, and under these conditions cyclobutene **48** would be expected to give **49**. Activation energy for this thermolysis is 36.5 kcal/mol, essentially the same as for thermolysis of bicyclo[2.2.0]hexane.[53]



The X-ray structure of **40** (Figure 1) shows that the internal cyclobutane ring is essentially planar with no atom deviating from the least-squares plane by more than 0.003 Å. The two external rings are slightly puckered, with dihedral angles of 10.8° [C(1)–C(2)–C(3)–C(4)] and 12.6° [C(1)–C(6)–C(7)–C(8)]. The two shortest carbon–carbon bonds are associated with C(1); C(1)–C(2) is 1.515 Å, and C(1)–C(8) is 1.524 Å. C(1)–C(4) and C(1)–C(6) are 1.552 and 1.571 Å, respectively, slightly shorter than the long (1.577 Å) internal carbon–carbon bond of bicyclo[2.2.0]hexane.[54]

A shorter synthesis of **35** and its methyl derivative **50** was devised by Wolff and Agosta through intramolecular photocyclization of cyclopentenones **51** and **52**, respectively.[12,55] This closure is regiospecific in the case of **52**, where the methyl substituent effectively controls the regiochemistry of cyclization;[56] from **51** a mixture of **35** and the crossed [2 + 2] product **53** was obtained. Through transformations similar to those already discussed for **35**, ketone **50** was contracted to esters **54** and **55**. Thermolysis of these [4.4.4]fenestranes yielded olefinic esters analogous to **47** and **49**.



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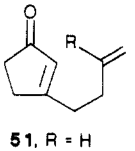
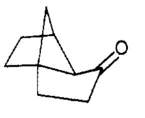


51, R = H
52, $R = CH_3$



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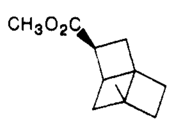

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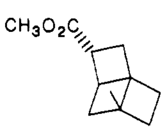
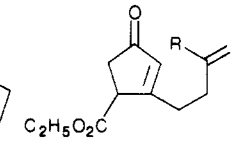
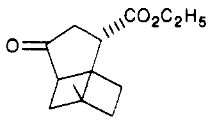


55



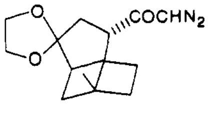
56, $R = CH_3$
57, R = Cl



58

D. [4.4.4.5]Fenestrane

An approach modelled on that just described for preparation of **54** and **55** led to the synthesis of [4.4.4.5]fenestranes.[13] Upon irradiation keto ester **56** underwent regiospecific cyclization to **58** and a smaller amount of the less stable epimeric ester. The ketone carbonyl of **58** was protected as its ethylene ketal, and diazo ketone **59** was prepared by way of the free acid and acyl chloride. The keto carbene formed on exposure of **59** to rhodium acetate cleanly inserted into the only readily accessible carbon–hydrogen bond, yielding the [4.4.5.5]fenestrane **60**. Success in this insertion reaction was acutely dependent upon the pattern of substitution in the tricyclic skeleton of the diazo ketone. The insertion failed completely, for example, if the ketal ring of **59** was replaced by a methylene group. Reductive removal of both ketone and ketal from **60** afforded 1-methyl[4.4.5.5]fenestrane (**61**), whose simple eight-line ^{13}C NMR spectrum attested to its symmetry and supported the structural assignments. Similar removal of only the carbonyl group of **60**, followed by hydrolysis of the ketal, gave **62**. This was elaborated to diazo ketone **63**, and photochemical Wolff rearrangement in methanol then yielded the [4.4.4.5]fenestrane methyl ester **64**, along with a lesser amount of the epimeric ester and also α-methoxy ketone **66**. Unrearranged ether **66** results from competitive insertion of the keto carbene into solvent, and its formation suggests that ring contraction here is relatively slow.[57] Ester **64** and its epimer showed no unusual thermal instability, surviving gas chromatography at 130 °C for a half hour with only slight decomposition. Treatment[58] of **64** with the complex formed from trimethylaluminum and *p*-bromoaniline yielded *p*-bromoanilide **65** for X-ray analysis.



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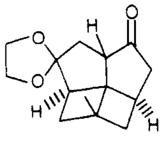

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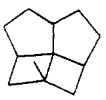
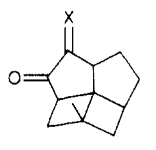
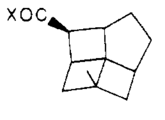


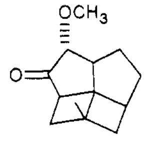
61



62, $X = H_2$
63, $X = N_2$



64, $X = CH_3O$
65, $X = p\text{-}BrC_6H_4NH$



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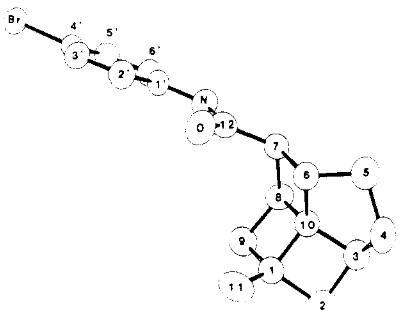
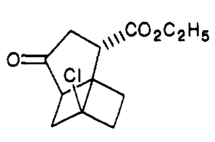


Figure 2. ORTEP drawing of [4.4.4.5]fenestrane derivative **65** showing 50% probability ellipsoids. Reprinted with permission from *J. Am. Chem. Soc.* **1985**, *107*, 5732. Copyright 1985 American Chemical Society.

There are several noteworthy features in the crystallographic studies on **65** (Figure 2). The angles C(1)–C(10)–C(6) and C(3)–C(10)–C(8), which reflect the enforced flattening at C(10) are 128.3° and 129.2°, respectively. Two of the bond distances involving C(10) are quite short, with both C(3)–C(10) and C(6)–C(10) only 1.49 Å. The perimeter bonds for the cyclobutane rings are correspondingly lengthened to an average value of 1.574 Å. These values are in quite good agreement with those given by MNDO calculations.[48] The shortened bonds to C(10) are also in line with the ab initio calculations for [4.4.4.4]fenestrane (**24**) discussed above, although in **65** the two shortest bonds to C(10) are associated with the five-membered ring. These representatives of the [4.4.4.5] series are currently the tetracyclic fenestranes of smallest ring size and most flattened central carbon atom that have been synthesized and studied experimentally.

E. [4.4.5.5]- and [4.5.5.5]Fenestranes

In a investigation[59] closely related to the synthesis of **64** and **65**, irradiation of the chlorodienone **57** yielded **67** regio- and stereospecifically. Ketalization and reduction with lithium in liquid ammonia gave the chlo-



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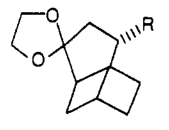
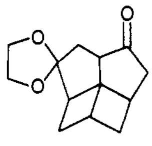


68, R = CH_2OH
69, R = COOH
70, R = $COCHN_2$



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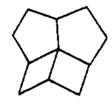
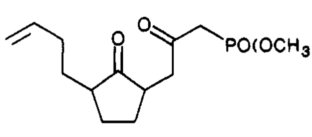


72

rine-free hydroxy ketal **68**, and reoxidation then furnished ketal acid **69**. This was converted to diazoketone **70** which was cyclized to afford **71**. Reduction in several steps then provided the parent hydrocarbon, [4.4.5.5]fenestrane (**72**). This sequence demonstrated that a chlorine atom does control regiochemistry in the initial photochemical cyclization critical to this synthetic approach and that the chlorine can subsequently be removed; the general route then is applicable to fenestranes without alkyl substitution.

A few years earlier Dauben and Walker had first prepared derivatives of [4.4.5.5]fenestrane using a different sort of intramolecular [2 + 2] photocycloaddition.[60] Diketo phosphonate **73**, available in several steps from dimethyl adipate by way of 2-carbomethoxycyclopentanone, underwent intramolecular Wadsworth–Emmons cyclization[61] to afford enone **74**, where the butenyl side chain has been equilibrated through enolization to the more stable exo configuration. Irradiation of **74** yielded the [4.5.5.5]fenestranone **75**, and Wolff rearrangement of the derived diazo ketone then gave [4.4.5.5]fenestrane esters **77**. Wolff–Kishner reduction of **75** also furnished the parent [4.5.5.5]fenestrane (**76**). This series of transformations was remarkably efficient; the overall yield of **77** from dimethyl adipate was 29%.



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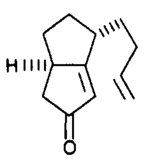

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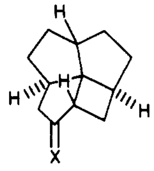
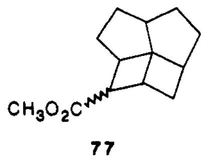


75, X = O
76, X = H_2



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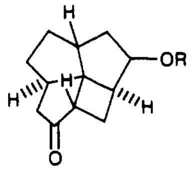

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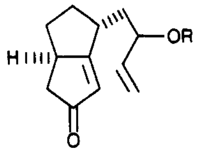

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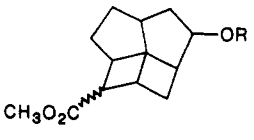

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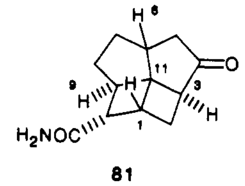


81

R = $Si(CH_3)_2C(CH_3)_3$

In a subsequent study[62] the oxygenated [4.5.5.5]fenestranone **78** was prepared from **79** following a similar route. Ring contraction as before gave **80**, and removal of the silyl protecting group and oxidation afforded two keto esters. These were separated, and the major isomer was converted to [4.4.5.5]fenestrane keto amide **81** for X-ray analysis. The resulting structure (Figure 3) reveals considerable flattening at C(11); angle C(1)–C(11)–C(6) is 128.2°, and C(3)–C(11)–C(9) is 123.0°. Once again these observed values are in excellent agreement with MNDO calculations performed by Keese.[48]

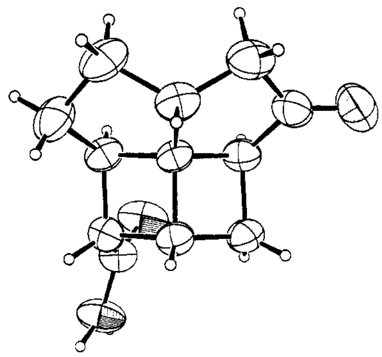
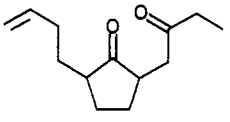


Figure 3. ORTEP drawing of [4.4.5.5]fenestrane derivative 81 showing 50% probability ellipsoids.

In a prior brief report without details Saltzman recorded the closely related preparation of a methyl homologue of **75**.[63] On exposure to base cyclopentanone **82** cyclized to **83**, and this closed on irradiation to the methyl[4.5.5.5]fenestranone **84**. The authors noted that the methyl group facilitated the base-catalyzed cyclization but led to a sluggish [2 + 2] reaction.



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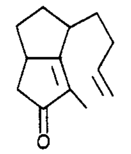

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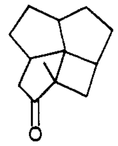

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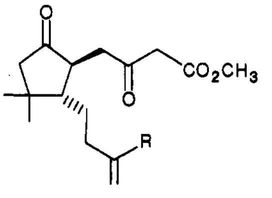

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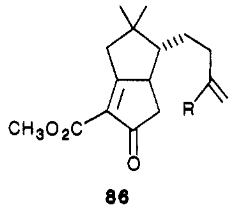

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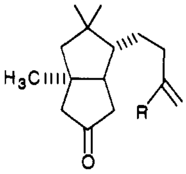

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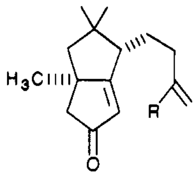

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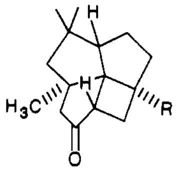


89

a, R = H; b, R = CH_3

Two final examples of preparation of [4.5.5.5]fenestranes by way of bicyclo[3.3.0]octenones come from Crimmins,[64,65] who prepared the dienone substrate required for cycloaddition somewhat differently. Keto esters **85a,b**, available from 4,4-dimethylcyclopentenone in straightforward fashion, underwent methoxide-catalyzed ring closure to **86a,b**. Decarboxylation and conjugate addition of lithium dimethylcopper furnished **87a,b** which were oxidized by way of the silyl enol ether to the desired substrates **88a,b**. Irradiation of **88a** at room temperature gave the [4.5.5.5]fenestrane **89a** in

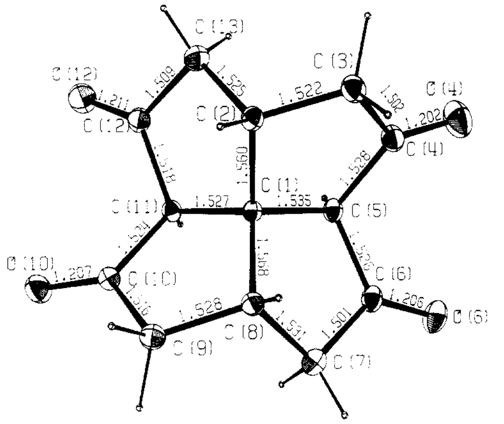
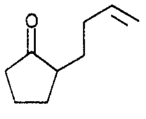


Figure 4. ORTEP drawing of [5.5.5.5]fenestrane derivative **95** showing 50% probability ellipsoids. Reprinted with permission from *Tetrahedron* 1981, *37*, 4521. Copyright 1981 Pergamon Press, Ltd.

high yield, but photocyclization of **88b** required an elevated temperature. This difference in reactivity was attributed to steric crowding between the methyl group on the side chain and the methyl at the ring junction in the conformation of **88b** required for cycloaddition; there are other examples of such a temperature effect on the rates of related reactions.[55,56] Subsequent cleavage of the four-membered ring of **89a** with trimethylsilyl iodide was a key step in the total synthesis of the sesquiterpene silphinene, which is a tetramethyl[5.5.5]fenestrene.[65] These [4.5.5.5]fenestranes were also of particular interest as models for a projected synthesis of laurenene, a naturally occurring [5.5.5.7]-fenestrane that is mentioned below.

F. [4.5.5.6]- and [4.5.6.6]Fenestranes

Georgian and Saltzman deserve credit not only for coining the name *fenestrane* but also for first drawing attention to [4.4.4.4]fenestrane as a worthwhile synthetic target and for carrying out the initial syntheses of model saturated fenestranes.[8] Condensation of 3-buten-2-one with the pyrrolidine enamine derived from 2-(3-butenyl)cyclopentanone (**90**) afforded **91**, and irradiation of this dienone gave **92**. A parallel series starting with 2-(3-butenyl)cyclohexanone furnished **93**. The structures of these photoproducts were deduced from spectroscopic properties and from the conversion of **93** to **94** through Baeyer–Villiger oxidation, hydrolysis, and treatment with chromic acid. Infrared absorption typical of a cyclobutanone in **94** provided evidence that a [2 + 2] cycloaddition had occurred. No stereochemical assignments have been made for any of these compounds.



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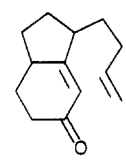

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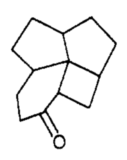

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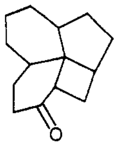

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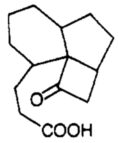
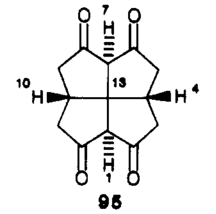


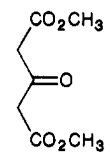
94

G. [5.5.5.5]Fenestrane

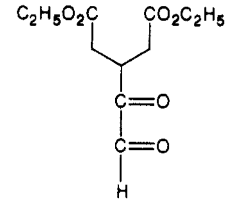
There has been greater synthetic activity in this series of fenestranes than any other, owing partly to theoretical predictions concerning the possible aromaticity of unsaturated [5.5.5.5]fenestranes such as **5** and **20** and partly to widespread enthusiasm in recent years for polycyclopentanoid chemistry. The first simple member of the series to be prepared was tetraketone **95**.[10,67]



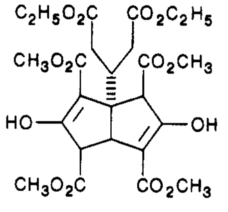
95



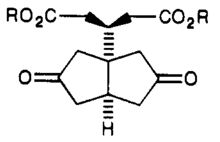
96



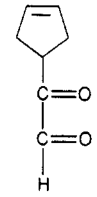
97



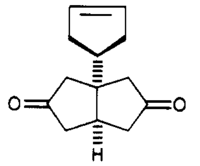
98



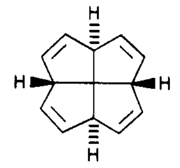
99, R = H
100, R = CH3



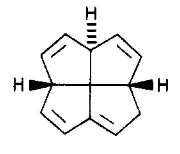
101



102



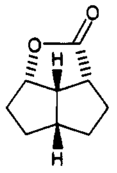
103



104

This synthesis by Cook, Weiss, and their co-workers is the prototype of several studies of polyquinanes by these investigators, and it originated in the earlier discovery by Weiss[68] of a very general condensation reaction between an α-dicarbonyl compound and 2 equiv of β-ketoglutaric ester (**96**) that leads to a derivative of bicyclo[3.3.0]octane. In the case at hand, α-ketoaldehyde **97** condensed with **96** to afford the enolized diketone **98**. Hydrolysis and decarboxylation in acetic acid containing hydrochloric acid gave the diketo diacid **99**, and this could be cyclized to **95** in good yield in hot cumene–diglyme containing a large quantity of 1-naphthalenesulfonic acid. An X-ray study confirmed the structure of **95** (Figure 4) and showed that in the crystal the molecule exists in a chiral conformation with each crystal composed of a single enantiomer. As one would expect, in this [5.5.5.5] system there is less flattening at the central atom [C(13)] than in the fenestranes with four-membered rings. Angle C(1)–C(13)–C(7) is 117.5°, and C(4)–C(13)–C(10) is 115.1°; bond lengths at C(13) range from 1.527 Å [C(7)–C(13)] to 1.568 Å [C(10)–C(13)]. The stereochemistry of **95** ($1\alpha,4\beta,7\alpha,10\beta$) is such that the approach of a nucleophile from either side of the molecule to one of the carbonyl groups is sterically equivalent to the hindered endo approach in a *cis*-bicyclo[3.3.0]octanone. This unavoidable steric interaction nicely rationalizes the relative stability of **95** to base-catalyzed ring opening of its two β-dicarbonyl groupings.[69] Treatment with methoxide leads to slow, regiospecific cleavage, forming only **100** and none of its spiro-fused isomer.

Refinement of this initial synthesis of **95** was possible through use of keto aldehyde **101**, where the ester groupings of **97** are masked as a cyclopentene.[70] This change led to reduced steric interactions in the reaction with **96** and significantly improved this condensation. Acid-catalyzed decarboxylation of the initial product furnished **102**, and scission of the cyclopentene double bond, using osmium tetroxide followed by Jones's reagent, then afforded **99** in a much higher overall yield. Finally, reduction of **95** with diborane in tetrahydrofuran gave a diastereomeric mixture of tetrahydroxy compounds that was dehydrated by hot hexamethylphosphoramide to provide ($1\alpha,4\beta,7\alpha,10\beta$)-2,5,8,11-[5.5.5.5]fenestratetraene (**103**) along with a smaller amount of the isomeric bridgehead alkene **104**.[70] Proton and carbon nuclear magnetic resonance spectra of **103** are consistent with its expected D_{2d} symmetry. These two hydrocarbons are the most highly unsaturated fenestranes presently known.



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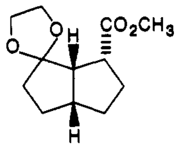

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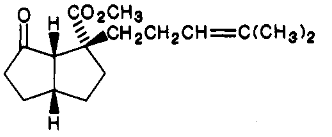
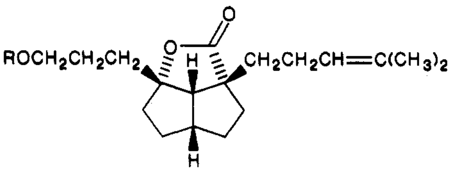
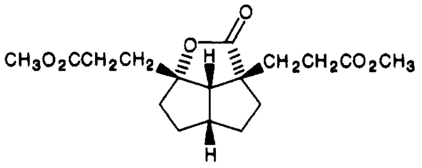


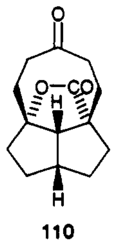
107



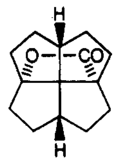
108
R = 1-ethoxyethyl



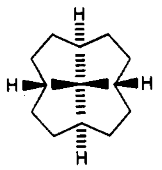
109



110



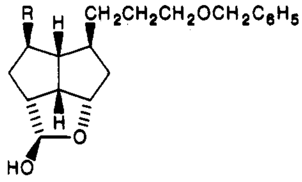
111



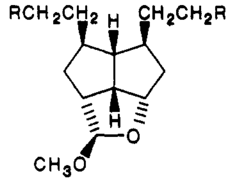
112

The other research group active in synthesis of [5.5.5.5]fenestranes has been Keese's. Starting at about the same time as Cook and Weiss, this group has explored totally different routes to these systems. The first of these proceeds from lactone **105**, available in several steps from 1,5-cyclooctadiene.[28,71] Oxidation under basic conditions, followed by esterification and treatment with ethylene glycol, yielded the ketal ester **106**. Alkylation with 5-bromo-2-methyl-2-pentene and hydrolysis of the ketal then gave **107** stereospecifically. Hydroxypropylation of the ketone with subsequent lactonization afforded **108**, where the stereochemistry is assured by formation of the lactone. The two side chains were oxidized simultaneously with ruthenium tetroxide, and the carboxylic acid groups formed were esterified with diazomethane. The resulting diester **109** underwent Dieckmann cyclization, and decarboxylation furnished cyclooctanone **110**. Photolysis of the potassium salt of the derived tosylhydrazone then gave a carbene that inserted in the nearer tertiary carbon–hydrogen bond. This furnished the pentacyclic fenestrane lactone **111**, the structure of which could be assigned from its spectroscopic properties. In an unusual transformation **111** was converted to (1,13-*syn*,$1\alpha,4\beta,7\alpha,10\beta$)[5.5.5.5]fenestrane (**112** ≡ **8**) on heating in an ampoule at 310 °C for 4.5 h in the presence of palladium-on-carbon and hydrogen.[15] Without added hydrogen, **111** is essentially stable under these conditions; with hydrogen present, the product is a single hydrocarbon accompanied by ~10% starting material. This hydrocarbon had spectroscopic properties appropriate for a [5.5.5.5]fenestrane, and its stereochemistry was assigned as depicted in **112** on the basis of the following considerations. The ^{13}C NMR spectrum consisted of a three-line pattern compatible only with the symmetry of one of the two $1\alpha,4\beta,7\alpha,10\beta$ isomers, **112** (1,13-*syn*) or the contorted compound with inverted stereochemistry (1,13-*anti*) at the central carbon atom. Since the calculated strain energy of the latter species is ~182 kcal/mol, Keese concluded that the reaction conditions leading to this product assured that it was the relatively strain-free **112** rather than its highly unstable isomer.

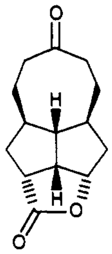
A related second route to **112** begins with aldehyde **113**, which is available in a few steps from dicyclopentadiene.[72,73] Chain extension in **113** with ethyl (diethoxyphosphinyl)acetate gave the intermediate **114**, which was transformed into diester **115** by hydrogenation, followed by formation of the acetal, oxidation, and esterification. Unlike **109** above, **115** did not cyclize in the Dieckmann reaction, so it was converted to the corresponding dinitrile **116** for Ziegler–Thorpe ring closure. This cyclization was successful, and exposure of the resulting enamino nitrile to acid hydrolysis and then Jones oxidation yielded keto lactone **117**. In this case the carbene insertion failed, although **110** might appear to be an apt model for **117**. This behavior is reminiscent of that of **59** and related diazo ketones mentioned above, and there are many prior examples of the effects of structural and conformational change



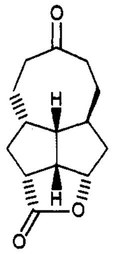
113, R = CHO
114, R = CH═CHCO2C2H5



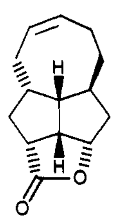
115, R = CO2CH3
116, R = CN



117



118

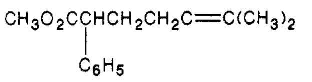


119

on the success of such intramolecular insertions.[74] These differences in the fates of closely related carbenes presumably reflect changes in dynamic conformation as a function of specific structure. In contrast to the carbene insertion, the thermal reaction in the presence of palladium-on-carbon used previously on **111** did succeed with **117**, giving directly a modest yield of **112**.

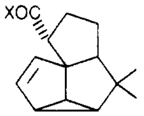
In an attempt to reach an isomeric [5.5.5.5]fenestrane, Keese also prepared the epimeric keto lactone **118** from dicyclopentadiene. Here decomposition of the tosylhydrazone salt led only to the corresponding olefin **119**. Once again the high temperature palladium and hydrogen process was effective, but the product was **112** rather than the desired (1α,4α,7α,10β)[5.5.5.5]fenestrane.[50] According to calculations, this latter unknown isomer is more strained than **112**; molecular mechanics gives a difference in strain energy of 13 kcal/mol, and MNDO gives 21 kcal/mol.[75]

Keese has also made use of the intramolecular arene–alkene photocycloaddition reaction to develop another route to [5.5.5.5]fenestranes.[76] Irradiation of **120** gave a mixture of products from which the desired adduct **121** could be obtained. Structure and stereochemistry of this tricyclic ester are supported both by earlier experience with the photochemistry of 5-phenyl-1-pentenes[77] and by NMR spectra. The corresponding diazo ketone **122** was prepared by way of the mixed anhydride with isovaleric acid, and on treatment with trifluoroacetic acid **122** lost nitrogen and closed to a mixture (2.2:1) of fenestradienone **123** and trifluoroacetoxyfenestrenone **124**. The structures of these products were established by proton and ^{13}C NMR spectra. Hydrogenation of **123** over palladium-on-carbon in methanol selectively reduced only the less substituted double bond and furnished **125**.

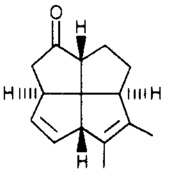


$CH_3O_2C\underset{C_6H_5}{\underset{|}{C}}HCH_2CH_2C{=}C(CH_3)_2$

120



121, X = CH_3O
122, X = N_2CH



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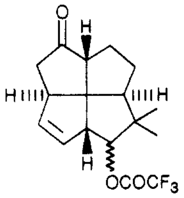
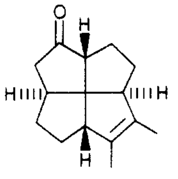
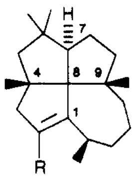


124



125



126, R = H
127, R = Br

H. [5.5.5.7]Fenestrane

The only reported tetracyclic fenestrane from natural sources is the diterpene laurenene (**126**, assigned numbering shown).[78] Its structure rests on an X-ray study of the derived bromide **127**, so that bond lengths and angles are known. The structural points of greatest interest are that bonds to C(8) are normal-to-long, 1.527 to 1.609 Å, and that the angles across this atom are 117.9° [C(1)–C(8)–C(7)] and 118.9° [C(4)–C(8)–C(9)], indicative of a small measure of flattening in this [5.5.5.7]fenestrane. Studies on synthetic approaches to laurenene have led to the preparation of [4.5.5.5]fenestranones that were mentioned above.[64,65]

V. Closing

There has been creditable progress since 1970 in the theoretical description, synthesis, and determination of properties of both saturated and unsaturated fenestranes. It is apparent, however, that significant problems remain for the future. We noted earlier that the fenestranes of greatest interest are still experimentally unknown, and indeed at present the clearest need in this area is the synthesis of these compounds. Among unsaturated systems these include **5**, **15**, **16**, **19**, and **20**. Whether planar or not, they are esthetically pleasing structures, and an added inducement for their preparation is the testing of theoretical predictions of their properties. No compounds similar to **15**, **16**, or **19** have been reported, but now that [5.5.5.5]fenestrane derivatives such as **95**, **103**, **104**, and **123** are available, preparation of **5**, **20**, and related substances may be forthcoming. In this regard it is worth noting that molecular mechanics calculations suggest that there is an increase in strain energy of ~48 kcal/mol on shifting the four double bonds in the known hydrocarbon **103** to their positions in its unknown isomer **20**, if **20** is treated as an ordinary alkene with no special stabilization.[75] In the saturated fenestranes two outstanding problems are synthesis of [4.4.4.4]- and [3.5.3.5]fenestranes. There is no assurance that these strained carbon skeletons are capable of existence under ordinary conditions, and, in fact, there is a specific prediction that [4.4.4.4]fenestranes **24** and **25** are not.[42] Nonetheless, the availability of differentially substituted keto ketals **60** and **71** encourages synthetic attempts toward the [4.4.4.4] series. Similarly, the existence of a simple route to (3α,6β)[3.5.3]fenestrane (**23**) stimulates efforts toward the [3.5.3.5] series. Another potentially significant factor in such undertakings is the increasing usefulness of calculations to assist in the planning of synthetic routes. The interplay between calculation and transformation could be particularly important in designing and executing syntheses of such fragile systems. With preparation of these various unsaturated and saturated fenestranes their physical properties could be determined, theoretical models could be evaluated, and our knowledge of bonding and structure would be materially enhanced. Good low-temperature X-ray data for such compounds would contribute to the determination of force constants for the severely distorted bonds to their central atoms, and measurement of heats of combustion of the parent hydrocarbons would lead to bond energies for these peculiar bonds.

Finally there is the virtually unexplored question of the chemical reactivity of these strained systems; investigations here should provide novel chemistry and instructive lessons. This applies equally well to systems already known, such as the [3.5.3]-, [3.5.4]-, and [4.4.4.5]fenestranes. The strained bonds to the central atom in the [4.4.4.5]fenestranes, for example, should influence the chemistry of this ring system just as the bent and shortened carbon–carbon bonds of cyclopropane[79] dominate its behavior. All in all there is a wealth of problems to pursue, and their solution will surely go some way toward answering the question: What if a tetrahedral carbon atom is flattened?

Acknowledgments. For correspondence and information we are indebted to Drs. James M. Cook, William

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