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THE SYNTHESIS OF QUADRICYCLENES

A RETROSPECTIVE LOOK

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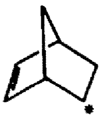
Abstract—Unsuccessful attempts to prepare quadricyclenes are described, as are a number of successful experiments. The initial studies of reactions of quadricyclenes are summarized. The relationships between the preparative methods for and the properties and reactions of quadricyclenes to orbital symmetry theories and to possible methods for solar energy harvesting are briefly discussed.

In the early 1950s the question of the extent of "non-classical" electron delocalization in carbocations, carbanions and radicals had begun to attract the attention of organic chemists.[1] One of the systems which received considerable attention was the homoallyl-cyclopropylcarbinyl system, an example of which is represented by 1 and 2. The questions that were being asked were whether formulas 1 and 2 represented separate species or whether they were to be considered as resonance structures contributing to a hybrid molecule. Members of my research group were among those interested in this question. We were able to show that the rearrangement accompanying addition of a thiyl radical to norbornadiene (3) involved two interceptable species, that is that the radicals analogous to 1· and 2· were separate species and not resonance forms. Put another way, the hybrid of 1· and 2· could be conceived as a transition state between 1· and 2· and not as a stable intermediate.[2] We similarly showed, with experiments using dehydronorcamphor and nortricyclenone, that anions analogous to 1^- and 2^- were separable species and not resonance structures.[3]



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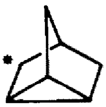

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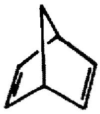

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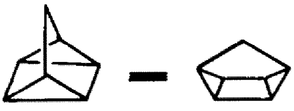

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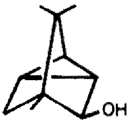
In the 1940s and early 1950s, like that of many other organic chemists, our concept of resonance and mesomerism was dominated by valence-bond descriptions. If the idea was permissible that there is an interaction between the asterisk (+, ·, or −) and the double bond in 1, it seemed reasonable to wonder whether the two double bonds in norbornadiene might similarly interact in a fashion to include 4 as a resonance structure, or whether, on the other hand, 4 might be a stable molecule separable from 3. It also seemed clear that the strain energy in a molecule such as 4 would be very high and the compound might therefore be unstable. On the assumption that 4 would be an isolable species, Snell undertook the problem of preparation of a derivative of 4.

His was not, however, the first attempt to make compounds with what we later dubbed the quadricyclene ring structure. The first publication on this subject was that of Bryusova,[4] who tried to prepare the tetracyclic system from a variety of derivatives of tricyclene. Pyrolysis of the xanthate of the alcohol 5 led to no definite product and oxidation of the hydrazone of 6 with mercuric oxide gave the regenerated ketone rather than the desired diazo compound 7 or the desired hydrocarbon 8. Similar treatment of the *bis*-hydrazone of camphorquinone 9 failed to give 8, upon oxidation with mercuric oxide, as did a variety of seemingly less likely reactions.



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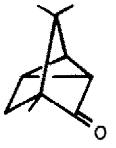

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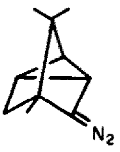

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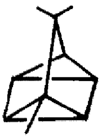

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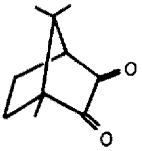

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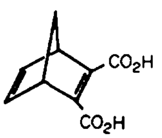
Lipp,[5] in a paper published in 1941, noted reasons for interest in compounds with the tetracyclic ring system 4, and described work done by her and her students, Holz, Sandkuhl and Proth, in Aachen, in the attempts to prepare 8, which she dubbed "tetracyclene". Her synthesis, like that of Bryusova, was planned to involve 3-diazotricyclene (7). However, treatment of the appropriate N-nitroso-carbamate with sodium methoxide led to a mixture of the *exo* and *endo* isomers of 3-tricyclenol 5 and their methyl ethers. Lipp speculated that the diazo hydrocarbon may not have been formed.

In any case, no "tetracyclene" was produced. In her paper, Lipp suggested that the presence of the three-membered ring in the tricyclene compound gave rise to so great a strain that, with ordinary procedures, it would be impossible to close the fourth three-membered ring.

Another unsuccessful attempt of a chemical synthesis was reported in 1954.[6] Based upon earlier experiments in which reduction with sodium of bornylidene dichloride led, in part, to tricyclenes, the authors converted tricyclenone to its dichloride, but treatment of this compound gave no "tetracyclene".

Snell, in our laboratory, decided to try the irradiation of norbornadienedicarboxylic acid (**10**), reasoning that irradiation should lead to a biradical at C-2 and C-3 and that this might close to the tetracyclic compound **11**. There was obvious excitement when irradiation of a solution of **10** in absolute ether resulted in the precipitation of a white solid, isomeric with **10**, whose IR spectrum showed the absence of C=C bonds and whose properties were consistent with the dicarboxylic acid **11**. This work was communicated in 1954,[7] and a full paper was published in 1958.[8] We first dubbed the 4 system, "nortetracyclene", based upon Lipp's suggestion for the unknown dehydroterpene **8**, but certain objections were raised to this name, based upon the similarities to tetracycline and tetracyclone. Accordingly, we coined[8] the name "quadricyclene" for the ring.†



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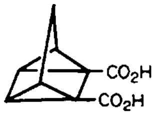

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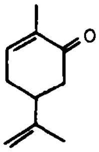

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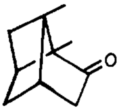

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At the time **11** was prepared, we had only IR and UV spectroscopy available, but such data plus chemical evidence were adduced to support the proposed structure. It thus joined a very small number of compounds known at the time in a class called "valence tautomers".[12] It should be mentioned that there was some skepticism expressed privately to us by colleagues who proposed alternative (and presumably more palatable) structures for our product. Nonetheless, the structure was correct; the photochemical transformation of a norbornadiene to a quadricyclene was of interest to many others, and it became a model[13] for a host of intramolecular [2+2]photocycloadditions.‡ The parent quadricyclene was reported in 1961 from Dauben's[9] and Hammond's[10] laboratories and many quadricyclenes have since been prepared.[13]

Compound **11** was surprisingly stable, decomposing at temperatures above 225° with evolution of gas, rather than isomerizing to **10**. One should note, of course, that the ideas of Woodward and Hoffmann for the theoretical treatment of concerted reactions[16] and the corresponding ideas of "forbidden" and "allowed" reactions were still ten years away when our work was done, so the "forbiddenness" of the $[2_s+2_s]$cycloreversion in this system was anything but obvious.

As our interests were focused on the reactions of **11** and on the result of bringing two cyclopropane rings into juxtaposition and possible conjugation, we studied a number of addition reactions of **11**. To our great disappointment, the addition of bromine, under both ionic and radical conditions, gave no evidence for conjugative addition to the bicyclopropyl system, but gave simply the product of addition to one of the cyclopropane rings[17] to form a substituted nortricyclene. Addition of hydrogen over palladium gave Δ^2-norbornenedicarboxylic acid, but our hope that we were observing a *bis*-homoconjugative addition was tempered by the observation that **11** was isomerized to **10** over palladium on charcoal.[8]

Just as we were unaware of the theoretical significance of our excited-state $[2_s+2_s]$cycloaddition, we were similarly unaware of the significance of the transition-metal-catalyzed $[2_s+2_s]$cycloreversion, although the transformation of **11** to **10** is, to the best of our knowledge, the first observation of such a phenomenon.

The combination of photochemical isomerizations of norbornadienes to quadricyclenes as energy-storing reactions and the catalyzed cycloreversions from the highly strained tetracyclic system as energy-releasing reactions has received considerable attention as a solar-energy harvesting system.[18] Whether any useful system will be developed remains to be seen, however.

While most quadricyclenes have been prepared by photoisomerization of norbornadienes, Moriarty[11] showed that quadricyclene could be prepared by photoextrusion of nitrogen from the azo compound **14**. We were somewhat disconcerted by this report, as we had had the precursor molecules in hand,[19] and had irradiated **14** (unpublished work), but recovered norbornadiene rather than quadricyclene. After Moriarty's publication, we looked into our experiment and noted that we had distilled the product through a platinum-wire fractionating column, thereby causing the cycloreversion.

The production of a quadricyclene by a ground-state chemical, rather than a photochemical, process remained an interesting pursuit. The reactions of 3,5-dibromonortricyclene (**15**) and its diiodo analogue with

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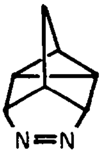
† This name has been used by a variety of investigators, as has the name "quadricyclane". The latter name is preferred by some, as it reflects the fact that the compound has no carbon–carbon double bonds, but is deficient in its historical aspect, and in the use of quadricyclene by other early investigators.[9–11]

‡ It shoud be noted that the first report[14] of intramolecular cyclobutane formation preceded our experiment by almost half a century in the conversion of carvone (**12**) to carvonecamphor (**13**) by one-year's irradiation in Italian sunlight, but this was not brought to light until its confirmation by Büchi and Goldman,[15] who carried out the same reaction in half the time in California. (I recommend Colorado sun over either of the other sources.)



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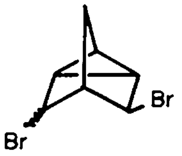

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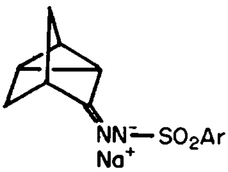

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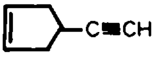

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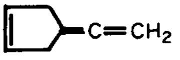

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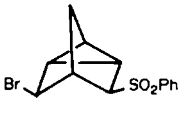
magnesium, with lithium and with phenyllithium, all reactions which generally lead to 1,3-elimination, were attempted.[20] Only homoconjugate elimination to norbornadiene was observed, however. In our laboratory, Cristol and Harrington[21] decomposed the sodium salt of the *p*-toluenesulfonylhydrazone of nortricyclenone (**16**), using carbenoid conditions, and, like the tetracyclene experiments described above, failed to get quadricyclene. Instead the ring-opened compounds **17** and **18** were produced.

A successful chemical synthesis of a quadricyclene was finally accomplished in our laboratory by Singer.[22] We had previously learned[23] that the free-radical addition of benzenenesulfonyl bromide to norbornadiene gave, in addition to the 1,2-addition product, the homoconjugate addition products **19** and **20**, whose structures were assigned by Singer. It was then shown that treatment of **19** with potassium t-butoxide in dimethyl sulfoxide gave quadricyclyl phenyl sulfone **21** in a few minutes, while the isomeric **20** was unreactive in a 7-h treatment under similar conditions, although it suffered deuterium exchange of the hydrogen atom geminal to the sulfonyl group under much milder conditions. This was, to the best of our knowledge, the first published example of the requirement for inversion of configuration at the γ carbon atom in a 1,3-elimination reaction to form a cyclopropane, although it was obviously much earlier anticipated in reactions involving epoxide formation,[24] and inversion had been demonstrated earlier in an acyclic system.[25]



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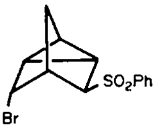

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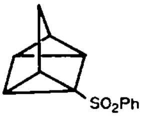

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SUMMARY AND APOLOGY

While our work on the formation and reactions of quadricyclenes is now several decades old, its significance perhaps justifies its inclusion in this symposium and I therefore summarize its influences. At the time of its first preparation, the quadricyclene ring system held the record for the number of rings per carbon atom. The photochemical reaction became a model for intramolecular [2+2]cycloadditions to form cyclobutanes. The transition-metal [2+2]cycloreversion was the first reported, although it was generally overlooked. The chemical synthesis was the first example of the requirement of inversion in γ-eliminations to give cyclopropanes. The stabilities of these "valence tautomers" were important experimental precursors to orbital symmetry theories. Finally, the strain inherent in the quadricyclene ring system, the barrier to cycloreversion and its catalysis by certain transition metals have been utilized by chemists interested in the storage of light energy as chemical energy.

Acknowledgements—The author is obviously indebted to those students whose work is referred to in the body of this paper. That work was supported by the Office of Naval Research, the Office of Ordnance Research, U.S. Army, the Petroleum Research Fund of the American Chemical Society and the National Science Foundation.

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