**Acknowledgment.** This work was supported, in part, by grants from the National Science Foundation, RIM 7817215, and the National Cancer Institute, CA 16598-06 and CA 28894-03. We thank Dr. Angel A. Román-Franco, Director of the Puerto Rico Cancer Center for his interest and support.

**Registry No.** EDTA, 60-00-4; EDTA·2Na, 139-33-3; $Fe^{2+}$, 15438-31-0; $O_2$, 7782-44-7; $H_2O_2$, 7722-84-1; $Cu^{2+}$, 15158-11-9; $CH_4$, 74-82-8; $HClO_4$, 7601-90-3; $H_2SO_4$, 7664-93-9; $FeSO_4(NH_4)_2SO_4$, 10045-89-3; $CuOCOCH_3$, 598-54-9; $Cu^+$, 17493-86-6; *tert*-butyl alcohol, 75-65-0; ethanol, 64-17-5; ethyl bromide, 74-96-4; 1-chloropropane, 540-54-5; 1-bromopropane, 106-94-5; 2-bromopropane, 75-26-3; ethyl sulfide, 352-93-2; 2-propanol, 67-63-0; ethyl acetate, 141-78-6; *tert*-butyl acetate, 540-88-5; diethyl ether, 60-29-7; *n*-propyl acetate, 109-60-4; ethyl trifluoroacetate, 383-63-1; *N,N*-diethylaniline, 91-66-7; propylene, 115-07-1; ethylene, 74-85-1; isobutylene, 115-11-7; ethane, 74-84-0.

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# A $^{13}C^{13}C$ Spin-Spin Coupling Matrix for Azulene

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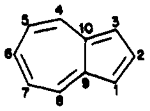
All resolvable $^{13}C^{13}C$ spin-spin coupling constants in 1-methylazulene (**2**) and 5-methylazulene (**3**) have been measured by the 2D-INADEQUATE technique in natural abundance. The data are compared with the results of various $^{13}C$-labeled azulenes and it is shown that the $^{13}C^{13}C$ spin-spin coupling constants are quite different from those in the naphthalene system.

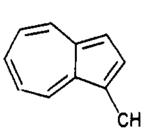
$^{13}C^{13}C$ spin-spin coupling constants can provide a detailed picture of the electronic framework of a molecule.[1] In our earlier work on $^{13}C^{13}C$ spin-spin coupling constants in azulenes,[2,3] we have labeled various substituted and unsubstituted azulenes **1** with one or two $^{13}C$ atoms to enable the determination of $^{13}C^{13}C$ spin-spin coupling constants in these nonalternate aromatic compounds with respect to the labeled center.



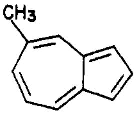
**1**

Although considerable synthetic effort has been spent during this project, a complete description of the spin-spin coupling matrix could not be achieved. Especially the most interesting spin-spin coupling constant of the central bond between C-9 and C-10 is still missing.

With the publication of the INADEQUATE technique[4a] in its two-dimensional version,[4b] it is now possible to measure these values in natural abundance. We have shown that nearly all theoretically possible spin-spin coupling constants in naphthalenes can be obtained by this technique, including the small values over two and three bonds.[5] In this paper, we have extended these studies to 1-methylazulene (**2**) and 5-methylazulene (**3**) in order to compare the values of these molecules with the data of the labeled compounds of our earlier work. Furthermore, a comparison of the magnetic frameworks of the azulene and the naphthalene system is given.



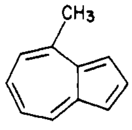
**2**



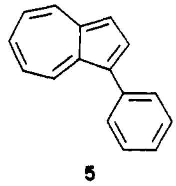
**3**

## Results and Discussion

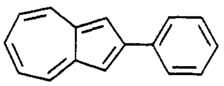
The $^{13}C^{13}C$ spin-spin coupling constants measured in this work are given in Table I; included are the values from partially unpublished labeling studies. For azulene itself the data originate from 4-, 4,7-, and 6-$^{13}C$-labeled azulene **1** as well as from 1D-INADEQUATE measurements. The data for 4-methylazulene (**4**) have been obtained from the 4-$^{13}C$ compound, the data for 1-phenylazulene (**5**) from the 1-, the 3-, and the 4-$^{13}C$-labeled compound and the data for 2-phenylazulene **6** from the 2-$^{13}C$-labeled compound. The 2D-INADEQUATE spectra of **2** and **3** confirm nicely the chemical shift assignment given by Braun.[6]



**4**



**5**



**6**

By comparing the data in the vertical columns of Table I, it becomes evident that the chosen substituents, the phenyl and methyl group, do not have a pronounced effect

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(1) For an authorative recent review, see: Marshall, J. L. In "Methods of Stereochemical Analysis"; Marchand, A. P., Ed.; Verlag Chemie International: Deerfield Beach, FL,; Vol. 2, pp 1-241.

(2) Berger, S.; Zeller, K. P. *Tetrahedron* **1980**, *36*, 1891-1893.

(3) Zeller, K. P.; Berger, S. *Z. Naturforsch. B: Anorg. Chem., Org. Chem.* **1981**, *36B*, 858-864.

(4) (a) Bax, A.; Freeman, R.; Kempsell, S. P. *J. Am. Chem. Soc.* **1980**, *102*, 4849-4851. (b) Mareci, T. H.; Freeman, R. *J. Magn. Reson.* **1982**, *48*, 158-163.

(5) Berger, S. *Org. Magn. Reson.* **1984**, *22*, 47-51.

(6) Braun, S.; Kinkeldei, J. *Tetrahedron* **1977**, *33*, 1827-1832.

**Table I. $^{13}C^{13}C$ Spin-Spin Coupling Constants (Hertz) in Azulenes 1-6**

| no. | $^1J_{12}$ | $^2J_{13}$ | $^3J_{14}$ | $^4J_{15}$ | $^4J_{16}$ | $^3J_{17}$ | $^2J_{18}$ | $^1J_{19}$ | $^2J_{110}$ | $^1J_{23}$ | $^3J_{24}$ | $^4J_{25}$ | $^5J_{26}$ | $^4J_{27}$ | $^3J_{28}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1[a] | 56.0 | | 2.0 | | 2.1 | 8.5 | | 58.5 | | 56.0 | | | 2.6 | 1.2 | |
| 2[b] | 56.9 | | 1.9 | | | 9.2 | | | | 56.9 | 8.0 | | 3.2 | | 7.0 |
| 3[b] | 56.0 | | 1.9 | | | 9.7 | | | 9.8 | 56.0 | 8.1 | | | | 8.0 |
| 4[c] | | | 2.0 | | | | | | | | 7.5 | | | | |
| 5[d] | 56.9 | 1.4 | 1.8 | 2.2 | | 8.2 | | 60.5 | 10.4 | 57.1 | | | | | |
| 6[e] | 57.2 | | | | 2.1 | | | | | 57.2 | 8.1 | 1.4 | 2.7 | 1.4 | 8.1 |

| no. | $^2J_{29}$ | $^2J_{210}$ | $^2J_{34}$ | $^3J_{35}$ | $^4J_{36}$ | $^4J_{37}$ | $^3J_{38}$ | $^2J_{39}$ | $^1J_{310}$ | $^1J_{45}$ | $^2J_{46}$ | $^3J_{47}$ | $^3J_{48}$ | $^2J_{49}$ | $^1J_{410}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | | | 1.2 | | 2.1 | 3.2 | | | 58.5 | 58.8 | 1.6 | 3.7 | | 5.5 | 61.0 |
| 2 | | | | | | | | | 58.7 | 59.0 | | 3.7 | | | 61.5 |
| 3 | 3.2 | 4.4 | | 8.4 | | | | 9.8 | | 60.1 | 3.2 | | | 5.7 | |
| 4 | | | 0.95 | | | | | | | 60.5 | 0.8 | 3.4 | 2.0 | 6.0 | 61.0 |
| 5 | | | 1.8 | 8.6 | 2.0 | 2.0 | 2.1 | 9.1 | 57.3 | 58.9 | | | | 5.5 | 61.4 |
| 6 | 4.3 | 4.3 | | | | | | | | | | | | | |

| no. | $^1J_{56}$ | $^2J_{57}$ | $^3J_{58}$ | $^3J_{59}$ | $^2J_{510}$ | $^1J_{67}$ | $^2J_{68}$ | $^3J_{69}$ | $^3J_{610}$ | $^1J_{78}$ | $^2J_{79}$ | $^3J_{710}$ | $^1J_{89}$ | $^2J_{810}$ | $^1J_{910}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 58.4 | | | | | 58.4 | 1.7 | 3.2 | 3.2 | 58.8 | 1.7 | 0.6 | 61.0 | | |
| 2 | 58.9 | 1.9 | 3.4 | | | 58.7 | | | | 59.6 | | | 61.7 | | 45.5 |
| 3 | | 1.9 | 3.8 | | | 59.8 | | 5.1 | 5.1 | 59.8 | | | | 5.6 | |

[a] Data from 4-, 6-, and 4,7-$^{13}$C-labeled azulene 1 and from 1D INADEQUATE measurements. [b] Data from 2D-INADEQUATE measurements. [c] Data from 4-$^{13}$C-labeled-4. [d] Data from 1-, 3-, and 4-$^{13}$C-labeled 5. [e] Data from 2-$^{13}$C-labeled 6.

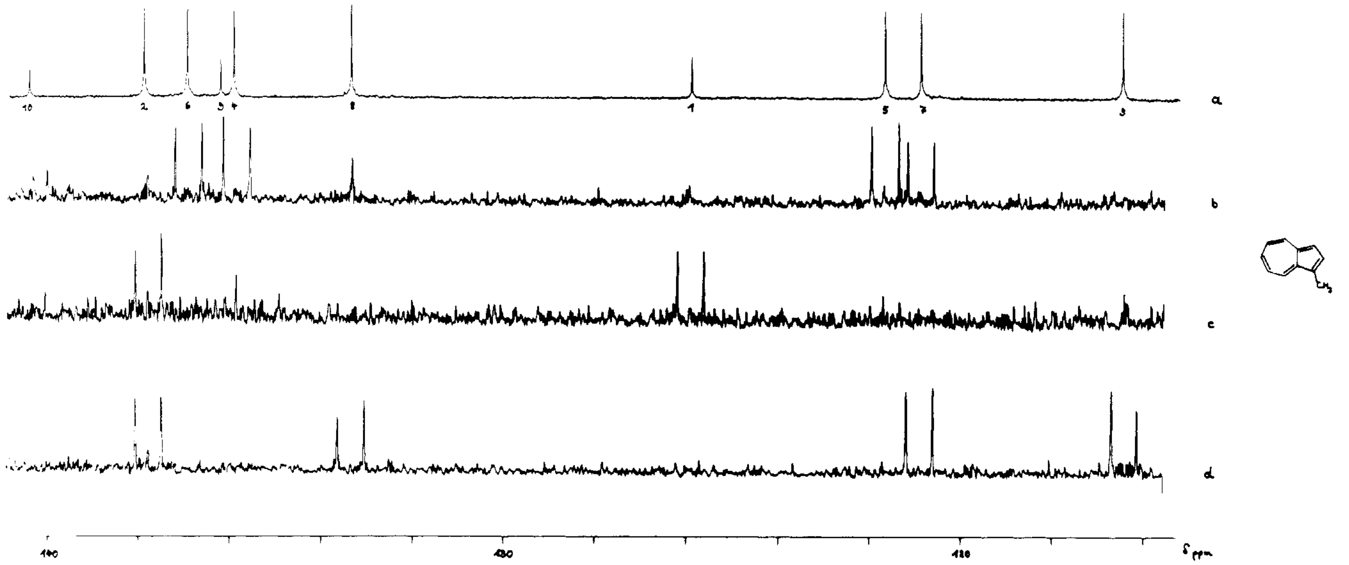
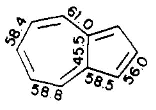


**Figure 1.** Examples of cross sections from the two-dimensional data matrix of **2** showing $^1J_{CC}$ spin–spin coupling constants. (a) Normal $^{13}$C NMR spectrum (aromatic region only). (b) Trace with $^4J_{C\text{-}6\text{–}C\text{-}7}$ and $^1J_{C\text{-}4\text{–}C\text{-}5}$. (c) Trace with $^1J_{C\text{-}1\text{–}C\text{-}2}$. (d) Trace with $^1J_{C\text{-}2\text{–}C\text{-}3}$ and $^1J_{C\text{-}7\text{–}C\text{-}8}$.

on the spin–spin coupling constants. Only the carbon atoms directly attached to the substituent show slightly larger spin–spin coupling values over one bond. Therefore, from Table I values can be estimated for the parent system 1 in cases where they cannot be measured directly for symmetry reasons. Further discussion is therefore restricted to azulene 1 itself.

To demonstrate the resolving power and the quality of the 2D-INADEQUATE spectra obtained by us, some typical traces of the two-dimensional matrix for compounds **2** and **3** displaying spin–spin coupling constants over different bonds are reproduced in Figures 1 and 2. For comparison purposes the spin–spin coupling values of 1- and 2-methylnaphthalene are reproduced in Table II.[5]

**Spin–Spin Coupling Constants over One Bond.** The $^1J_{CC}$ values for azulene (**1**) are given in the formula below.



1

The comparison of these with the corresponding values in naphthalene reveals as most significant difference a remarkably lower spin–spin coupling constant for the central C-9–C-10 bond in azulene (ca. 15%). It has been argued in theoretical papers[7] that the central bond in azulene is rather weak and for HMO calculations a overlap integral of 0.8 was proposed.[8]

We feel that the $^{13}C^{13}C$ spin–spin coupling constant is—apart from the longer bond distance—the first experimental evidence for this theoretical prediction. However, the attempt to relate the $^1J_{CC}$ values in azulene to HMO $\pi$ bond orders—as has been done with fair success for naphthalene—completely fails. The question is, whether the $\pi$ bond orders are not very descriptive for the system or whether the different bond angles of the azulene ring compared with naphthalene perturb the spin–spin coupling values. Since a correlation cannot be found with quantum mechanical data of much higher sophistication, such as the calculation of the Fermi contact contribution to the spin–spin coupling constant according to Blizzard

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[7] Heilbronner, E. In "Nonbenzenoid Aromatic Compounds"; Ginsburg, D., Ed.; Interscience: New York, 1959; Chapter 5.

[8] Kirby, E. C. *J. Chem. Res., Synop.* **1982**, 303.

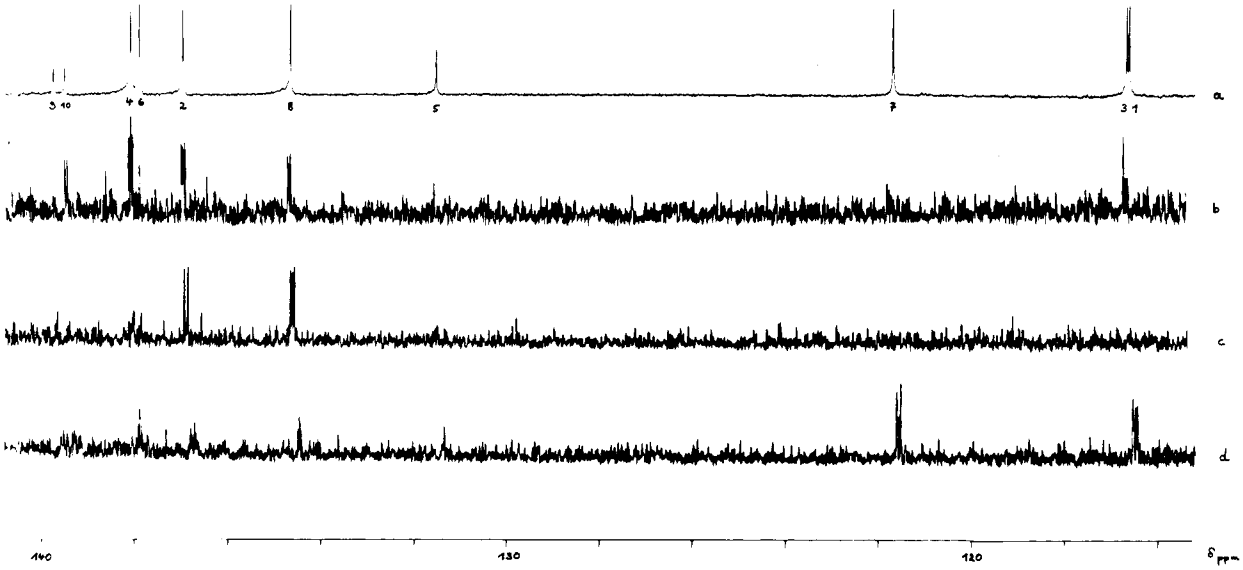
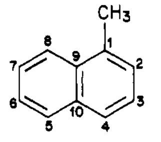
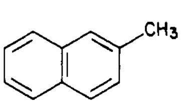


**Figure 2.** Examples of cross sections from the two-dimensional data matrix of **3** showing $^2J_{CC}$ and $^34_{CC}$ spin–spin coupling constants. (a) Normal $^{13}C$ NMR spectrum (aromatic region only). (b) Trace with $^2J_{C\text{-}8\text{-}C\text{-}10}$ and $^3H_{C\text{-}2\text{-}C\text{-}4}$. (c) Trace with $^3J_{C\text{-}2\text{-}C\text{-}8}$. (d) Trace with $^3J_{C\text{-}1\text{-}C\text{-}7}$.

**Table II.** $^{13}C^{13}C$ Spin–Spin Coupling Constants (Hertz) in 1- and 2-Methylnaphthalene[5] (**7** and **8**)



**7**



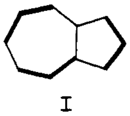
**8**

| no. | $^1J_{12}$ | $^2J_{13}$ | $^3J_{14}$ | $^3J_{15}$ | $^4J_{16}$ | $^3J_{17}$ | $^2J_{18}$ | $^1J_{19}$ | $^2J_{110}$ | $^1J_{23}$ | $^2J_{24}$ | $^4J_{25}$ | $^5J_{26}$ | $^4J_{27}$ | $^3J_{28}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 7 | 62.0 | 1.3 | 7.8 | 2.8 | | 5.0 | | 55.2 | | 54.0 | 2.4 | | | | 4.2 |
| 8 | 62.0 | | 7.0 | 2.9 | | 5.5 | 2.3 | 56.3 | | 53.6 | 1.7 | | | | 5.5 |
| **no.** | $^2J_{29}$ | $^3J_{210}$ | $^1J_{34}$ | $^3J_{35}$ | $^4J_{36}$ | $^5J_{37}$ | $^4J_{38}$ | $^3J_{39}$ | $^2J_{310}$ | $^2J_{45}$ | $^3J_{46}$ | $^4J_{47}$ | $^3J_{48}$ | $^2J_{49}$ | $^1J_{410}$ |
| 7 | | 7.5 | 59.8 | 5.7 | | | | 7.0 | | 2.1 | 5.4 | | 2.7 | | 55.5 |
| 8 | 1.1 | 7.4 | *a* | 5.5 | | | | 7.0 | 1.5 | 2.4 | 5.4 | | 2.7 | | 55.7 |
| **no.** | $^1J_{56}$ | $^2J_{57}$ | $^3J_{58}$ | $^2J_{59}$ | $^1J_{510}$ | $^1J_{67}$ | $^2J_{68}$ | $^3J_{69}$ | $^2J_{610}$ | $^1J_{78}$ | $^2J_{79}$ | $^3J_{710}$ | $^1J_{89}$ | $^2J_{810}$ | $^1J_{910}$ |
| 7 | 59.7 | 2.4 | 8.2 | | 55.3 | *a* | 2.4 | 7.3 | 1.6 | 59.9 | 1.5 | 8.0 | 56.3 | | 53.5 |
| 8 | 60.0 | 2.1 | 7.9 | | 55.8 | 53.2 | 2.2 | 7.9 | 1.5 | 60.1 | 1.4 | 7.9 | 55.6 | | 52.3 |

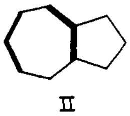
[a] Not observed.[5]

and Santry[9] or with ab initio calculations with expanded basis set,[10] where the geometry of azulene is the basis of the calculations, the demand for a satisfactory theory of spin–spin coupling constant transmission is quite obvious.

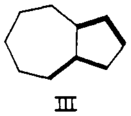
**Spin–Spin Coupling Constants over Two Bonds.** The possible geminal spin–spin coupling constants in the azulene ring are drawn in the formula I–IV and can be



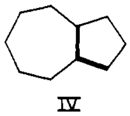
I



II



III

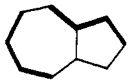


IV

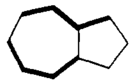
divided into those belonging to the seven-membered ring and those belonging to the five-membered ring. One coupling constant (formula III) connects both ring systems.

The geminal coupling constants within the five-membered ring can also be understood as vicinal coupling constants. Therefore, it seems possible to observe unusual values for these $^{13}C^{13}C$ spin–spin coupling constants. In fact, a rather large geminal coupling value of 10 Hz is measured for $^2J_{C\text{-}1\text{-}C\text{-}10}$ involving the central bond. However, the other spin–spin coupling constants of the five-membered ring range in the usual order of 1–3 Hz. In line with these findings all geminal spin–spin coupling constants of the seven-membered ring are again very small except $^2J_{C\text{-}4\text{-}C\text{-}9}$ which also involves the central bond. Thus, the geminal coupling constants including the central bond in azulene are quite unusual and have no equivalent in the naphthalene series.

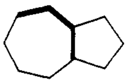
**Spin–Spin Coupling Constants over Three Bonds.** The vicinal spin–spin coupling constants of the azulene ring can be divided in three topologically different groups and are drawn in the formulas V–IX. The different



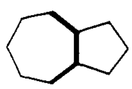
V



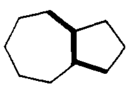
VI



VII



VIII



IX

characters are associated with cisoid linkages, e.g., $^3J_{C\text{-}10\text{-}C\text{-}6}$, transoid linkages along the outer perimeter, e.g., $^3J_{C\text{-}2\text{-}C\text{-}4}$,

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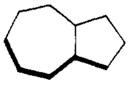
[9] Blizzard, C.; Santry, D. P. *J. Chem. Soc., D* **1970**, 87–88. We used the SCF-FERMI program written by I. Brown, Quantum Chemistry Program Exchange, Indiana University, No. 457.

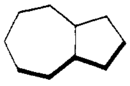
[10] Buenker, R. J., Peyerimhoff, *Chem. Phys. Lett.* **1969**, *3*, 37–42.

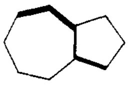
and a transoid linkage through the central bond, ${}^3J_{C\text{-}1\text{-}C\text{-}4}$.

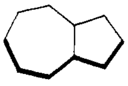
Compared to the naphthalene system where the cisoid vicinal coupling constants, e.g., ${}^3J_{C\text{-}1\text{-}C\text{-}4}$ or ${}^3J_{C\text{-}7\text{-}C\text{-}10}$ are large (ca. 8 Hz) and the transoid vicinal coupling constants, e.g., ${}^3J_{C\text{-}2\text{-}C\text{-}8}$ or ${}^3J_{C\text{-}1\text{-}C\text{-}7}$ are smaller (ca. 4–5 Hz), the reversed situation holds for azulene. In this case, the transoid linkages like ${}^3J_{C\text{-}1\text{-}C\text{-}7}$ or ${}^3J_{C\text{-}2\text{-}C\text{-}4}$ show values of about 8 Hz and the cisoid linkages like ${}^3J_{C\text{-}4\text{-}C\text{-}7}$ and ${}^3H_{C\text{-}6\text{-}C\text{-}10}$ values of 3–4 Hz. For the cisoid linkages again a double pathway is possible and these values can be understood as a sum of ${}^3J$ and ${}^4J$ spin–spin coupling constants. Thus the low values for the cisoid linkages suggest that the ${}^4J$ spin–spin coupling constants are negative. Only the small transoid spin–spin coupling constant through the central bond is in accordance with the similar coupling in naphthalene. Again, a correlation with quantum mechanical data like $\pi$ bond orders fails for the azulene system.

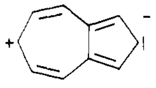
**Spin–Spin Coupling Constants over Four and Five Bonds.** In azulene three different ${}^4J_{CC}$ connections are possible. Furthermore, a ${}^5J_{CC}$ spin–spin coupling constant relates C-2 with C-6. In the formulas X–XIII these linkages are shown. Contrary to the naphthalene system these spin–spin coupling constants can easily be observed with 1 to 2 Hz. The rather large ${}^5J_{C\text{-}2\text{-}C\text{-}6}$ value of 2.6 Hz is especially remarkable. If long-range ${}^{13}C{}^{13}C$ spin–spin coupling constants are related to $\pi$-electron polarizability, this value would suggest that polar forms like XIV are of some significance.


X


XI


XII


XIII


XIV

## Conclusion

We have shown in this work that a complete ${}^{13}C{}^{13}C$ spin–spin coupling matrix can be obtained by the 2D-INADEQUATE technique. Data from earlier labeling studies were helpful in cases where the limited digital resolution of the data system used was not sufficient. Although the sign of the spin–spin coupling constants cannot be extracted from these measurements at present the qualitative interpretion of these values raises interesting questions on the electronic system of the azulene moiety. Unfortunately, a quantitative agreement between MO theory and these experimental results is not in sight.

## Experimental Section

The 2D-INADEQUATE spectra of **2** and **3** have been measured on a Bruker WH-400 NMR spectrometer with a 80 k Aspect 2000 computer and a Diablo Series 30 disk drive; ca. 0.5 g of freshly chromatographed ($Al_2O_3$/petroleum ether) **2** or **3** was dissolved in 2 mL of $CDCl_3$ and transferred to 8-mm sample tubes. The temperature of the NMR probe was maintained at 32 °C and the solutions were not degassed. The spectral width was 2604.2 Hz, 32 FIDs on 8192 data points were taken for each 2D experiment, resulting in 256K data. The 90° pulse width was 18 $\mu$s, for each FID 256 scans were accumulated and a relaxation delay of 12 s was used which gave a total experiment time of about 35 h for one $\tau$ value. A squared sine bell was used as a weighting function in $f_1$ dimension; Gaussian multiplication was applied in the $f_2$-dimension. 2D-Fourier transformation yielded a 2D datafile of 512K computer words giving a digital resolution of 46.7 Hz in the $f_1$ and 0.32 Hz in the $f_2$ dimension after zero-filling. The pulse sequence of the 135° pulse angle method as published by Freeman was used.[4] To detect all possible spin–spin coupling constants the measurements have been performed with refocusing delays ($\tau$ values) adjusted to 3, 5, 7, and 57 Hz. Quadrature detection was used in both dimensions, with a phase cycling procedure described in ref 11 using 32 steps, thus the spectral width in $f_1$ dimension was the same as in $f_2$. The measurements were repeated with the standard 1D-INADEQUATE technique in high resolution using 64K data points which led partly to a confirmation of the 2D results.

The 1D-INADEQUATE measurements of **1** have been performed on 0.8 g of freshly chromatographed ($Al_2O_3$/petroleum ether) **1** dissolved in 4 mL $CDCl_3$ using a 10-mm o.d. NMR tube at 32 °C. The labeled material was measured on the same instrument with standard high-resolution techniques. The preparation of the ${}^{13}C$-labeled azulenes is described elsewhere: 4-${}^{13}C$-**1**,[1,12] 4,7-${}^{13}C$-**1**,[2] 6-${}^{13}C$-**1**,[13] 1-${}^{13}C$-**5**,[14] 3- and 4-${}^{13}C$-**5**,[15] and 2-${}^{13}C$-**6**.[15] The chemical shifts of **5** and **6** will be reported in ref 15.

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**Registry No.** **1**, 275-51-4; 1-*4*-${}^{13}C$, 74626-95-2; 1-*6*-${}^{13}C$, 87295-52-1; 1-*4,7*-${}^{13}C_2$, 78950-01-3; **2**, 769-31-3; **3**, 1654-55-3; **4**, 17647-77-7; **5**, 7206-60-2; **6**, 19227-07-7; **7**, 90-12-0; **8**, 91-57-6.

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# Total Synthesis of Curzerenone, Epicurzerenone, and Pyrocurzerenone

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Curzerenone (**1**) and epicurzerenone (**2**), representative furanoelemanoids, and pyrocurzerenone (**3**) were synthesized via the 3-methylfuran annulation reaction using 1-nitro-1-(phenylthio)propene (**4**) as the crucial step. The cyclic 1,3-dione **6**, derived from $\gamma$-keto ester **7**, reacted with the nitro olefin **4** with KF catalysis to yield dihydrofuran **14** as a diastereomeric mixture, which was converted to 3-methylfuran **5** on $NaIO_4$ oxidation followed by elimination of benzenesulfenic acid from the resulting sulfoxides in good overall yield. Curzerenone (**1**) and epicurzerenone (**2**) were synthesized from **5** in three steps.

Although the elemane skeleton is quite common, only five furanoelemanoids, curzerenone (**1**),[1] epicurzerenone (**2**),[1] sericenine,[2] isofuranogermacrene,[1a] and isolinderalactone,[3] have so far been found in nature. In addition,

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