

The Structures of *E* and *Z* Methyl Octa-6-ene-2,4-Diynoate by Total Synthesis and NMR

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Os ácidos *E* e *Z*-octa-6-eno-2,4-diínicos e seus respectivos ésteres metílicos foram sintetizados e determinaram-se suas estruturas por métodos espectroscópicos. Os acoplamentos CH a longa distância, observados nos espectros totalmente acoplados de RMN de ^{13}C foram particularmente elucidativos. Foram obtidos cálculos semi-empíricos e *ab initio*, na tentativa de avaliar as correlações entre cargas atômicas e os deslocamentos químicos observados.

The *E* and *Z* isomers of octa-6-ene-2,4-diynoic acid, were synthesized. Their respective methyl esters were prepared and the structures were determined by spectral data. Long-range CH coupling observed in ^{13}C -NMR fully coupled spectra was particularly elucidating. Semiempirical and *ab initio* calculations were also carried out in an attempt to evaluate the correlation between atomic charges and the observed chemical shifts.

Keywords: *E* and *Z* Methyl octa-6-ene-2,4-diynoate, ^{13}C -NMR and semi-empirical and *ab initio* calculations

Introduction

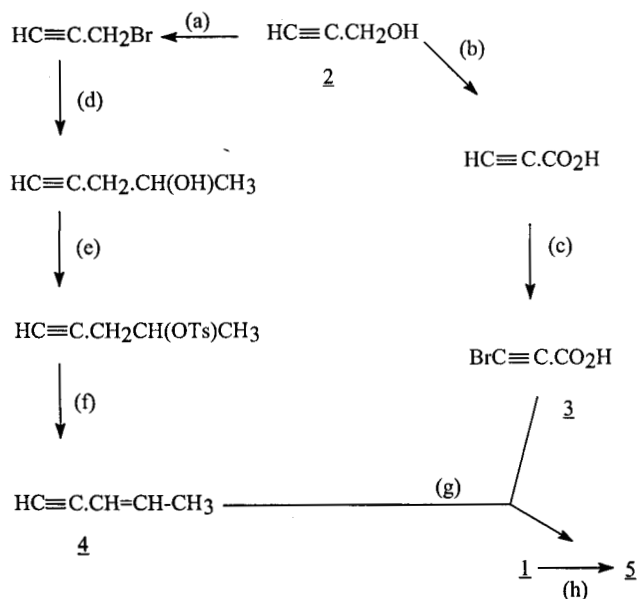
We have previously reported the occurrence of (*E*) octa-6-ene-2,4-diynoic acid (*I*) in the roots of *Siphocampylus sulfureus* (*Campanulaceae*), the molecular structure of which was proposed by means of ^1H -NMR (100 MHz) and mass spectra data¹. At that time we could not register the infrared spectrum, while the ultraviolet data were not consistent with those of the synthetic product prepared by Jones².

At present, considering that acetylenic acids are usually fungi metabolites, and noting the rare occurrence of natural C-8 polyacetylenes, we decided to resynthesize *I* in order to unambiguously elucidate its molecular structure.

Results and Discussion

Starting from propargyl alcohol (*2*) we obtained bromopropargylic acid (*3*), which was then condensed with a

mixture of *E/Z*-penta-3-ene-1-yne (*4*) [from propargyl bromide and acetaldehyde, via a Reformatsky reaction, followed by tosylation and elimination³] through a Cadiot-Chodkiewicz reaction⁴ (Scheme 1). After methylation with methanol acid, followed by chromatography, we were able to isolate each of the corresponding methyl esters (*5E* and *5Z*), which were submitted to several NMR experiments (Table 1), including the application of bi-dimensional techniques. We want to emphasize the usefulness of totally coupled ^{13}C -NMR spectra for the assignment of C-5 and C-4 chemical shifts in both isomers, taking into account the characteristic values of the respective long-range coupling constants ($^2J_{\text{CH}}$ and $^3J_{\text{CH}}$)⁵. As such, for the *E* isomer (*5E*) the chemical shifts of C-5 at δ 82.8 ($^2J_{\text{CH}} = 2.1$ and $^3J_{\text{CH}} = 7.0$ Hz) and C-4 at δ 70.4 ($^3J = 4.6$ Hz) were found. The broad bands at δ 70.7 and 71.7 correspond to the chemical shifts of C-2 and C-3, respectively.



Scheme 1. Reagents: (a) PBr_3 , pyridine; (b) CrO_3 , $\text{H}_2\text{SO}_4\text{-H}_2\text{O}$, $(\text{Et})_2\text{CO}$; (c) NaOBr , H_2O ; (d) Zn , $(\text{Et})_2\text{O}$, CH_3CHO ; (e) TsCl , pyridine; (f) reflux, H_2O ; (g) Cu_2Cl_2 , $\text{NH}_2\text{OH}\cdot\text{HCl}$, $\text{EtNH}_2(\text{aq})$; (h) CH_3OH , H_2SO_4 (4%).

These data are also in agreement with a *cis* relation of C-5 and H-7 and reinforces the *E* configuration already shown by the coupling constants of H-6 and H-7 protons ($J = 16.0$ Hz) in the $^1\text{H-NMR}$ spectrum (300 MHz), and by the strong absorption band at 950 cm^{-1} in the infrared spectrum.

For the *Z* isomer (*5Z*), chemical shifts of C-5 at δ 81.0 ($^2J_{\text{CH}} = 2.3$ and $^3J_{\text{CH}} = 14.3$ Hz) and C-4 at δ 76.2 ($^3J_{\text{CH}} = 4.9$ Hz) were found. The singlets at δ 71.4 and 71.8 correspond to the chemical shifts of C-2 and C-3, respectively. These data are also in agreement with a *trans* relation of C-5 and H-7 and reinforces the *Z* configuration already shown by the coupling constants of H-6 and H-7 protons ($J = 11.0$ Hz) in the $^1\text{H-NMR}$ spectrum, and by an absorption band at 722 cm^{-1} in the infrared spectrum.

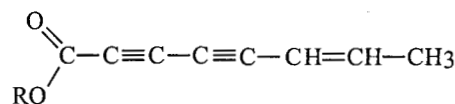
Although the chemical shifts of C-2 and C-3 are very near in both isomers, we believe that C-2 is more shielded than C-3, based on valence bond theory, considering the resonance hybrids.

Semi-empirical and *ab initio* calculations were carried out in an attempt to evaluate the agreement between atomic charges and the observed $^{13}\text{C-NMR}$ shifts. All calculations were made using the GAUSSIAN 92 program⁶. The *ab initio* results were obtained at the Hartree-Fock level of theory with the 6-31G** basis set. The semiempirical calculations were made using the AM1 method⁷ from the GAUSSIAN program. Figure 1 shows the fully optimized geometry of the *E* isomer from both levels of calculation. The results show that no significant discrepancies were observed in the optimized structures, either at the *ab initio* or semi-empirical (values in parentheses) levels. The larger

Table 1. ^1H - and $^{13}\text{C-NMR}$ data of *5E* and *5Z*

Position	Chemical shifts (δ)			
	$^1\text{H}(5E)$	$^1\text{H}(5Z)$	$^{13}\text{C}(5E)$	$^{13}\text{C}(5Z)$
1			153.4	153.6
2			70.7	71.4
3			71.7	71.8
4			70.4	76.2
5			82.8	81.0
6	5.57dq	5.57dq	109.0	108.1
7	6.48dq	6.35dq	147.5	147.0
8	1.88dd	1.96dd	19.1	16.7
OCH ₃	3.81s	3.81s	52.8	53.0

$J(\text{Hz})$: *5E* - $H_{6,7} = 16.0$; $H_{6,8} = 1.8$; $H_{7,8} = 6.9$; *5Z* - $H_{6,7} = 11.0$; $H_{6,8} = 1.6$; $H_{7,8} = 7.0$



1R=H 5R=CH₃

deviation occurs at the $-\text{COO}$ group where the discrepancies between the semi-empirical and *ab initio* methods are observed.

The AM1 atomic charges were calculated using the Mulliken population at the semi-empirical equilibrium geometry. A test was carried out in which Mulliken charges were also calculated at the *ab initio* equilibrium geometry, and no significant difference with respect to the atomic charges calculated using AM1 geometry was observed. The *ab initio* atomic charges were calculated at the respective theoretical equilibrium geometry using four different procedures: a) Mulliken charges⁸, b) charges derived from electrostatic potentials using Kollmann's criterion⁹, c) charges calculated from electrostatic potential using the CHELP procedure¹⁰, and d) the use of electrostatic potential applying the CHELP method¹¹. Table 2 shows the calculated charges using these five methods. A reasonable agreement among the atomic charge signals from the four heavier atoms is observed using any of the five methods. However, a comparison between the atomic charges and the $^{13}\text{C-NMR}$ chemical shifts shows that no direct correlation is possible between these two properties. The results for C-1, C-2 and C-3 indicate that, independent of the method used to calculate charges, the high positive the charge of C-1 suggests that this is the most unprotected atom of the structure. Its neighbor C-2, having a negative charge presents a more protected nucleus than C-3 and C-5, having positive atomic charges. The atomic charges for these three carbons are in agreement with the $^{13}\text{C-NMR}$ observations. The results for the other heavier atoms show

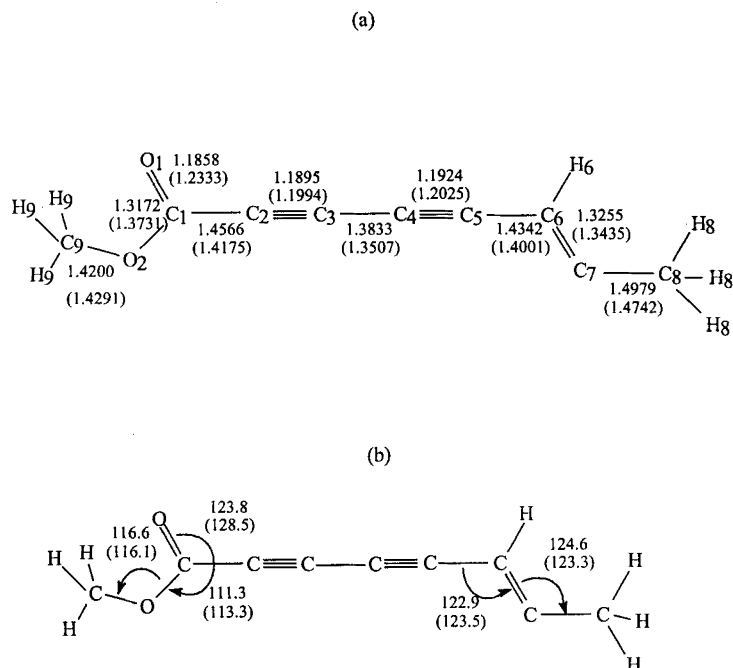


Figure 1. The optimized structure calculated at the Hartree-Fock level with the 6-3G** basis set and at the AM1 level of calculation (values in parentheses). Only (a) the bond lengths (in Å) and (b) the bond angles (in degrees) for the planar structure containing the heavier atoms are shown.

Table 2. The atomic charges calculated at the Hartree-Fock level with the 6-31G** basis set, and at the AM1 level at the respective theoretical equilibrium geometries using different methods (see Fig. 1).

	AM1 ^a Mulliken	6-31G** ^a (Mulliken)	6-31G** ^b (MK)	6-31G** ^c (CHELP)	6-31G** ^d (CHELPG)
O1	-0.3595	-0.5412	-0.6333	-0.6043	-0.6496
C 1	0.4717	0.8236	1.2109	0.9112	1.1710
C 2	-0.1574	-0.6388	-0.6773	-0.2666	-0.5371
C 3	0.0811	0.5051	0.4454	0.0822	0.3070
C 4	-0.0892	0.5427	-0.3371	-0.437	-0.2170
C 5	-0.0286	-0.7213	0.1544	-0.0710	0.0669
C 6	-0.1657	-0.0541	-0.3294	-0.0764	0.1955
C 7	0.1708	-0.0776	0.0435	0.0609	-0.0307
C 8	-0.3355	-0.3650	-0.2601	-0.0681	-0.0547
O 2	-0.3086	-0.6007	0.4552	-0.4959	-0.5076
C 9	-0.1966	-0.0389	0.0882	0.5367	0.0889
H 9	0.1580	0.1435	0.1310	-0.0592	0.0800
H 9	0.1380	0.1417	0.0889	-0.0698	0.0474
H 9	0.1380	0.1416	0.0889	-0.0697	0.0485
H 7	0.1950	0.1599	0.1213	0.0440	0.1094
H 8	0.1328	0.1325	0.0868	0.0402	0.0318
H 8	0.1425	0.1383	0.0960	0.0346	0.0416
H 8	0.1425	0.1383	0.0960	0.0346	0.0408
H 6	0.2122	0.1704	0.2178	0.0803	0.1589

a) Mulliken charges⁸; b) charges derived from the electrostatic potentials using Kollmann's criterion⁹; c) charges derived from the electrostatic potential using the CHELP method¹⁰; d) charges derived from the electrostatic potential using the CHELPG procedure¹¹.

divergence either in the charge signal or in its magnitude and no suggestion for protection can be made with certainty. The reasonable agreement between the atomic charges for the first three carbon atoms and the ^{13}C -NMR chemical shifts may be associated with the high difference in the electronegativity of the atoms connected to the ester group. The results suggest that the minimization of this effect with atomic distance does not provide a significant separation of the charges, and consequently a possible correlation with ^{13}C -NMR chemical shifts.

Finally, by comparing the spectral data of the synthetic product (*E* configuration) with those of the natural product methyl ester, we can now confirm that both have the same configuration.

Experimental

UV and IR spectra were obtained in Perkin-Elmer spectrophotometers, Lambda 3A (in CH_2Cl_2 solution) and 1600 FTIR series (film, NaCl cells), respectively. NMR data were registered in Bruker ACP-300 equipment (^1H at 300 MHz and ^{13}C at 75.5 MHz). Mass spectra were obtained in a HP GC-MS, model P5970. *E* and *Z* methyl ester derivatives were separated by Chromatotron¹² (elution in CH_2Cl_2) and purified by continuous PLC¹² (7 h, run with hexane: AcOEt, 99:1).

(*E/Z*) - Penta-3-ene-1-yne (4). Starting from propargyl alcohol, propargyl bromide was prepared and further reacted with acetaldehyde following the procedure described by Whiting *et al.*³, where (\pm)-4-pentyn-2-ol was obtained in 44% yield. Spectral data were identical to the literature. After tosylation and heating (135 °C), the mixture of 4 was obtained in a 71% yield: $\nu_{\text{max}}^{\text{film}}$ (cm^{-1}): 3 313 ($\equiv\delta\text{C-H}$), 2 103 ($\text{C}\equiv\text{C}$), 1 599 and 1 442 ($\text{C}=\text{C}$), 934 ($\text{C}=\text{C-trans}$), 812 ($\text{C}=\text{C-cis}$).

Bromopropargylic acid (3). Propargyl alcohol was submitted to Jones oxidation and furnished the corresponding acid. Spectral data were identical to the literature. After reaction with NaOBr, bromopropargylic acid was obtained in a 43% yield: ^{13}C -NMR (CDCl_3): δ 156.3 (C-1), 72.2 (C-2) and 55.8 (C-3).

Methyl, (*E/Z*)-octa-6-ene-2,4-dienoate (5)-Cadiot-Chodkiewicz reaction of 3 and 4 according to the procedure by Bohlmann *et al.*⁴, followed by methylation (MeOH , H_2SO_4) furnished the mixtures *E* and *Z* of the methyl ester derivatives (5), which were separated by chromatography as mentioned above. ^1H and ^{13}C -NMR (Table 1); *E* isomer:

$\nu_{\text{max}}^{\text{CH}_2\text{Cl}_2}$ (nm) 232, 253, 276, 292 and 340; $\nu_{\text{max}}^{\text{film}}$ (cm^{-1}) 2945, 2221, 1713, 1624, 1436, 1295, 1200, 950; GC-MS[R_t 20.7 min; m/z (%)] 148 (M^+ , 79), 117(100), 105(6), 90(58), 77(35), 63(33), 51(9). *Z* isomer: $\nu_{\text{max}}^{\text{CH}_2\text{Cl}_2}$ (nm) 234, 2677, 276, 292, 309, 339; $\nu_{\text{max}}^{\text{film}}$ (cm^{-1}) 2954, 2845, 2220, 1713, 1654, 1438, 1298, 722; GC-MS[R_t 19.4 min; m/z (%)] 148 (M^+ , 70), 117(100), 105(9), 90(58), 77(35), 63(40), 51(9).

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References

1. A.F. Magalhães, D.M. Vieira and E.G. Magalhães, *Química Nova* **13**, 65 (1990).
2. J.B. Jones, *J. Chem. Soc.* 5759 (1963).
3. G. Eglington and M.C. Whiting, *J. Chem. Soc.* 3650 (1950).
4. F. Bohlmann, W. Sucrow and I. Queck, *Chem. Ber.* **97**, 2586 (1964).
5. G.C. Levy, R.L. Lichter and G.L. Nelson, *Carbon-13 nuclear magnetic resonance spectroscopy* (Wiley, 1980), p. 94; E. Breitmeier and W. Voelter, *Carbon-13 NMR spectroscopy* (VCH Verlagsgesellschaft, 1990), p.144.
6. M.J. Frish, G.W. Trucks, M. Head-Gordon, P.M.W. Gill, M.W. Wong, J.B. Foresman, B.G. Johnson, H.B. Schlegel, M.A. Robb, E.S. Replogle, R. Gomperts, J.L. Andres, K. Raghavachari, J.S. Binkley, C. Gonzalez, R.L. Martin, D.J. Fox, D.J. Defrees, J. Baker, J.J.P. Stewart and J.A. Pople, GAUSSIAN 92 (Revision A, Inc., Pittsburgh, 1992).
7. M.J.S. Dewar, E.G. Zoebisch, E.F. Healy and J.J.P. Stewart, *J. Am. Chem. Soc.* **107**, 3902 (1985).
8. R.S. Mulliken, *J. Chem. Phys.* **23**, 1833 and 1841 (1955).
9. a) B.H. Besler, K.M. Merz and P. Kollmann, *J. Comp. Chem.* **11**, 431 (1990); b) U.C. Singh and P.A. Kollmann, *J. Comp. Chem.* **5**, 129 (1984).
10. L.E. Chirlian and M.M. Francl, *J. Comp. Chem.* **8**, 894 (1987).
11. C.M. Brenemann and K.B. Wiberg, *J. Comp. Chem.* **11**, 361 (1990).
12. E. Stahl, *Angew. Chem. (International Ed.)* **22**, 507 (1983).

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