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Mendeleev Commun., 2021, **31**, 251–253

Mendeleev Communications

An unusual acetylene–allene rearrangement in iodomethylates of cotarnine acetylene derivatives

Lev Yu. Ukhin,*[a] Lyudmila G. Kuz'mina,[b] Tatyana N. Gribanova,[a] Lyudmila V. Belousova,[a] Eugenii N. Shepelenko,[c] Gennadii S. Borodkin,[a] Olga I. Dmitrieva,[a] Vitaly A. Podshibyakin[a] and Natalia V. Stankevich[a]

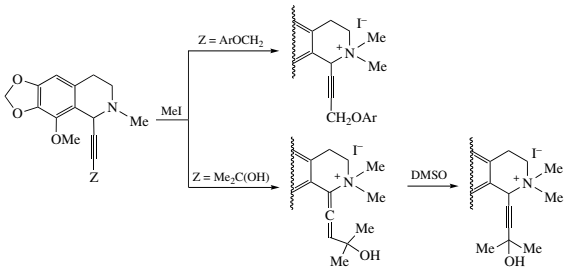
[a] *Institute of Physical and Organic Chemistry, Southern Federal University, 344090 Rostov-on-Don, Russian Federation. E-mail: lyukhin@ipoc.sfedu.ru*

[b] *N. S. Kurnakov Institute of General and Inorganic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation. E-mail: kuzmina@igic.ras.ru*

[c] *Southern Scientific Center of the Russian Academy of Sciences, 344006 Rostov-on-Don, Russian Federation. E-mail: dubon@ipoc.sfedu.ru*

DOI: 10.1016/j.mencom.2021.03.036

N-Methylation of cotarnine–phenol propargyl ethers conjugates with MeI affords the corresponding quaternary ammonium derivatives with retained acetylenic moiety. 3-Hydroxyalk-1-yn-1-yl analogues in the course of such iodomethylation undergo isomerization into allenic derivatives which are transformed into acetylenic ones upon dissolution in DMSO.



Keywords: cotarnine acetylene derivatives, isoquinolinium compounds, iodomethylation, acetylene–allene rearrangement, X-ray, quantum-chemical calculations.

Cotarnine, an isoquinoline-based alkaloid that was used until recently in gynecological practice,[1] invariably attracts the attention of chemists primarily due to the variety of possible transformations into new biologically active compounds.[2–7] Earlier, we reported a synthesis of 1-alkynyl derivatives of cotarnine from cotarnine chloride and Ag^{I} organoacetylenides[8–10] and from cotarnine chloride and terminal organoacetylenes catalyzed by the CuI–morpholine system.[11]

This study deals with an unusual acetylene–allene rearrangement that occurs upon iodomethylation of some acetylenic derivatives of cotarnine. In fact, 1-alkynyl derivatives of cotarnine **1a–d** smoothly react with iodomethane under mild conditions to give quaternary isoquinolinium derivatives, iodomethylates **2a–d** (Scheme 1). A single-crystal X-ray diffraction study showed that iodomethylates **2a**,**b** retain the acetylenic structure in reactions with derivatives of propargyl ethers of phenols **1a**,**b**, whereas iodomethylation of propargyl alcohol derivative **1d** is accompanied by isomerization into allene derivative **3d** (Figures 1 and 2).† These differences can be visible only in the crystal packing since both types of compounds possess acetylenic structures in DMSO solutions (see Scheme 1).

As shown by quantum chemical calculations, compound **1c** also should undergo isomerization into allene derivative **3c** upon iodomethylation. As a rule, such prototropic isomerization occurs under the action of strong bases, for example, $NaNH_2$.[12,13(a)] However, examples of the use of weaker bases such as NaOH,[14,15] and $Bu_4N^+F^-$ (ref. 16) are known. Detailed data on the acetylene–allene rearrangement were recently reviewed.[17] In our case one may assume that the iodine anion plays a role of the proton carrying catalyst. It is known that,

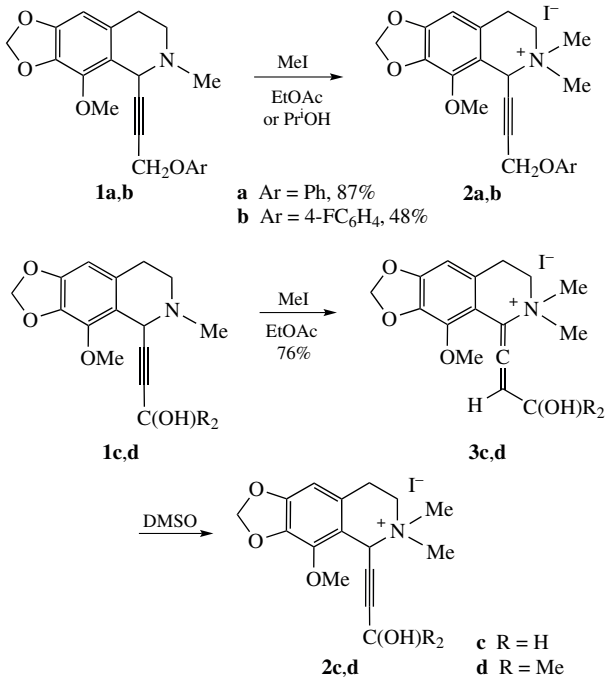
† Single crystals of compounds **2a**,**b** and **3d** were mounted on a CCD area Bruker SMART APEX-II diffractometer [MoKα radiation (λ = 0.71073)] where crystallographic parameters and diffraction reflections were measured at room temperature. Using Olex2, the structures were solved with the ShelXT structure solution program using Intrinsic Phasing and refined with the olex2.refine refinement package using Gauss–Newton minimization.

Crystal data for **2a**. $C_{22}H_{24}INO_4$ (M = 493.34 g mol^{-1}), triclinic, space group $P\bar{1}$ (no. 2), a = 8.5664(2), b = 10.3893(2) and c = 13.2519(3) Å, α = 112.9340(10)°, β = 94.0460(10)°, γ = 96.9030(10)°, V = 1069.38(4) Å^3, Z = 2, T = 296 K, μ(MoKα) = 1.524 mm^{-1}, d_{calc} = 1.5320 g cm^{-3}, 18699 reflections measured (4.28 ⩽ 2θ ⩽ 54.24°), 4654 unique (R_{int} = 0.0260, R_σ = 0.0234) which were used in all calculations. The final R_1 was 0.0323 [$I \geqslant 2\sigma(I)$] and wR_2 was 0.0692 (all data).

Crystal data for **2b**. $C_{22}H_{23}FINO_4$ (M = 511.34 g mol^{-1}), triclinic, space group $P\bar{1}$ (no. 2), a = 8.5800(2), b = 10.3125(2) and c = 13.2384(3) Å, α = 112.3980(10)°, β = 93.3120(10)°, γ = 95.1800(10)°, V = 1073.14(4) Å^3, Z = 2, T = 296.15 K, μ(MoKα) = 1.528 mm^{-1}, d_{calc} = 1.5823 g cm^{-3}, 18613 reflections measured (4.3 ⩽ 2θ ⩽ 54.24°), 4694 unique (R_{int} = 0.0283, R_σ = 0.0257) which were used in all calculations. The final R_1 was 0.0287 [$I \geqslant 2\sigma(I)$] and wR_2 was 0.0616 (all data).

Crystal data for **3d**. $C_{18}H_{25}INO_{4.5}$ (M = 453.28 g mol^{-1}), monoclinic, space group $C2/c$ (no. 15), a = 30.958(4), b = 9.5031(12) and c = 15.0514(18) Å, β = 117.682(4)°, V = 3921.2(8) Å^3, Z = 8, T = 296 K, μ(MoKα) = 1.656 mm^{-1}, d_{calc} = 1.536 g cm^{-3}, 31867 reflections measured (5.92 ⩽ 2θ ⩽ 54.28°), 4252 unique (R_{int} = 0.0198, R_σ = 0.0115) which were used in all calculations. The final R_1 was 0.0368 [$I \geqslant 2\sigma(I)$] and wR_2 was 0.0997 (all data).

CCDC 2009290, 2009291 and 2009292 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center *via* http://www.ccdc.cam.ac.uk.



Scheme 1

along with metals such as Zn and Mg, the iodide anion is used as the Lewis base in dihalogen elimination reactions.[13(*b*)] In the aliphatic series, the allene group is less stable than the acetylenic one because it is stabilized by strong electron-withdrawing substituents.[12] In our system, the role of such a substituent belongs to a positively charged nitrogen conjugated with the cyclic carbon C^1. The latter simultaneously is the terminal carbon of the allenic moiety, which precludes isomerization into a new acetylenic derivative. However, the positive charge on nitrogen is not sufficient to stabilize the

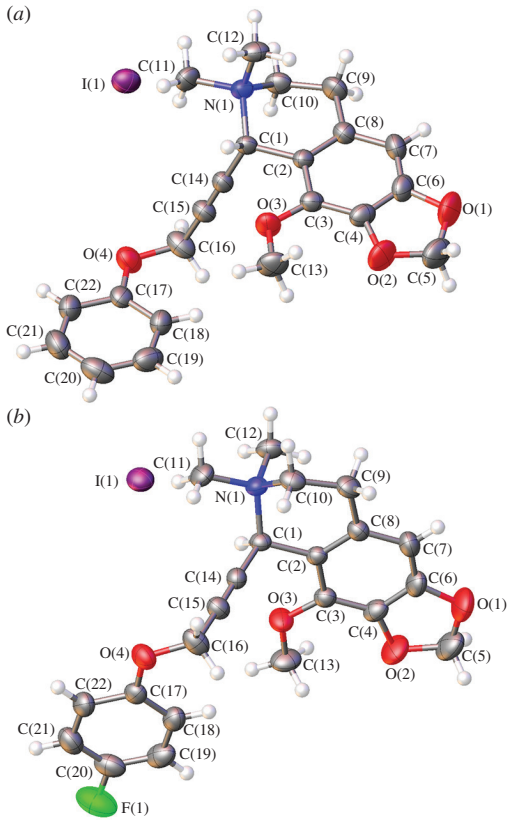


Figure 1 Structures of the formula units of isostructural compounds (*a*) **2a** and (*b*) **2b**. Thermal ellipsoids are given at a 50% probability level.

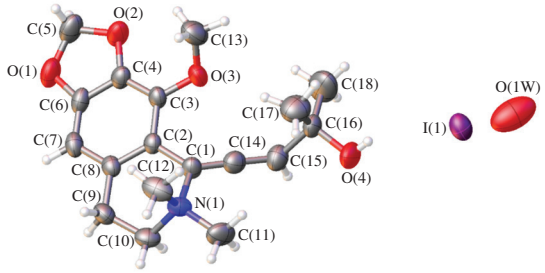


Figure 2 Molecular structure of **3d**. Thermal ellipsoids are given at a 50% probability level.

allenic structure. Only compound **1c** with a hydroxy group at $C^{3'}$ undergoes the rearrangement.

Quantum-chemical calculations by the MO62X/Def2TZVP method showed that the allenic form of crystalline compound **3d** is 2.3 kcal mol^{-1} more favorable than the acetylenic form, whereas the acetylenic form of derivative **2a** is 1.7 kcal mol^{-1} more favorable than the allenic one. The higher stability of the allenic form of **3d** is due to the formation of a bridge between the iodide ion and the hydroxy group. The calculation results agree with X-ray diffraction data revealing that compound **3d** exists in hydrated form. The OH···I$^-$···H$_2$O···I$^-$···HO dimer is found in crystalline **3d** (Figure 3).

The iodide anion in this dimer forms two hydrogen bonds, I$^-$···H–O(4) and I$^-$···H–O(1W), with an OH group and a water molecule. The distance between I$^-$ and the hydroxy group corresponds to a somewhat stronger interaction. The water molecule occupies a particular position on the crystal axis 2. Geometric parameters of compounds **2a**,**b** and **3d** are given in Table S1 (see Online Supplementary Materials). The mechanism of isomerization of the acetylenic forms **2c**,**d** to the allenic forms **3c**,**d** is outlined in Scheme 2. The positive charge on nitrogen polarizes the C^1–H bond, while the iodide ion catalyzes the proton elimination and its transfer to the triple bond. Calculations also showed that the allenic structure **3c** is 4.4. kcal mol^{-1} more favorable than its acetylenic form **2c**. It is also confirmed by the similarity of the IR spectra of **3c** and **3d** in Nujol (see Online Supplementary Materials). Compound **3d** is very inert to electrophilic reagents. It is soluble in boiling Ac_2O and precipitates unchanged on cooling. The structure of **3d** complies with the rules corresponding to chiral allenes. Both of its parts are asymmetrical.[13(*c*)]

The crystals of **2a** and **2b** are built of isolated molecules that interact through van der Waals forces. The iodide anion is the only particle capable of forming weak directional interactions. A fragment of the crystal packing in **2a** showing the crystal environment of iodide is depicted in Figure S1 (see Online Supplementary Materials). A similar environment of an iodide anion with similar interatomic distances also exists in a crystal of **2b** (see Online Supplementary Materials for the complete list of values).

The NMR spectra of compounds **2a**, **2b** and **2d** manifest a long-range spin–spin coupling between the C^1H and $C^{3'}H_2$ protons, a significant contribution to which is provided by

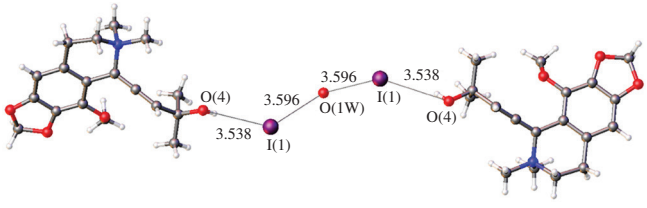
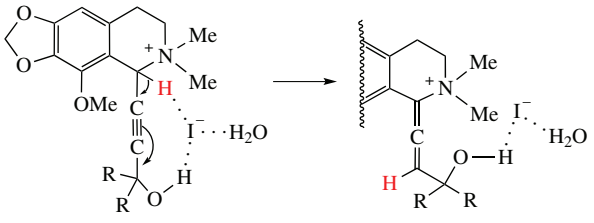


Figure 3 The hydrated form of the dimer in a crystal of **3d**; the distances are given in Å.



2c,**d** **3c**,**d**

Scheme 2

acetylenic moieties *via* the π-mechanism. Long-range spin–spin coupling was also found between the C^1H proton and one of the protons (presumably equatorial) of the C^3H_2 group. This is evident from the COSY spectrum of compound **2a** recorded in $CDCl_3$ (see Online Supplementary Materials). The chemical shifts of the C^3H_2 protons differ by 0.8 ppm in this solvent. This long-range coupling between the C^1H protons and one of the C^3H_2 protons exists in all the compounds **2a–d**. The additional splits of the C^1H signals in compounds **2a**, **2b** and **2d** is explained by a combination of the long-range spin–spin coupling described above.

This study was supported by the Ministry of Science and Higher Education of the Russian Federation (State assignment in the field of scientific activity of Southern Federal University, 2020, project FENW-2020-0031 no. 0852-2020-0031). To prove the structure of the compounds obtained, we used the equipment of the Center for Molecular Spectroscopy of the Southern Federal University (Rostov-on-Don).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2021.03.036.

References

1 M. D. Mashkovsky, *Lekarstvennye sredstva (Medicines)*, Novaya volna, Moscow, 2005 (in Russian).
2 Y. Mao, S. Song, D. Zhao and M. Cheng, *Heterocycles*, 2013, **87**, 2633.
3 A. A. Zubenko, V. G. Kartsev, A. S. Morkovnik, L. N. Divaeva, D. V. Alexeenko, K. Yu. Suponitsky, G. S. Borodkin and A. I. Klimenko, *Tetrahedron Lett.*, 2017, **58**, 1233.
4 L. T. Anh, A. A. Titov, R. Samavati, L. G. Voskressensky, A. V. Varlamov and V. N. Khrustalev, *Acta Crystallogr.*, 2017, **E73**, 1732.
5 L. Rout, B. B. Parida, G. Phaomei, B. Emmanuel and A. K. Sahoo, *Org. Synth.*, 2018, **95**, 455.
6 P. K. Reddy Nagireddy, V. K. Kommalapati, N. K. Manchukonda, B. Sridhar, A. D. Tangutur and S. Kantevari, *ChemistrySelect*, 2019, **4**, 4092.
7 V. G. Kartsev, A. A. Zubenko, L. N. Divaeva, A. S. Morkovnik, T. K. Baryshnikova and V. Z. Shirinian, *Russ. J. Gen. Chem.*, 2020, **90**, 238 (*Zh. Obshch. Khim.*, 2020, **90**, 261).
8 L. Yu. Ukhin, K. Yu. Suponitskii and V. G. Kartsev, in *Abstracts of the First International Conference 'Chemistry and Biological Activity of Nitrogen Heterocycles and Alkaloids'*, Moscow, 2001, vol. 1, p. 552.
9 L. Yu. Ukhin, K. Yu. Suponitskii and V. G. Kartsev, *Chem. Nat. Compd.*, 2003, **39**, 482 (*Khim. Prir. Soedin.*, 2003, 395).
10 L. Yu. Ukhin, I. R. Gol'ding and V. G. Kartsev, *Chem. Nat. Compd.*, 2004, **40**, 156 (*Khim. Prir. Soedin.*, 2004, 133).
11 L. Yu. Ukhin, E. N. Shepelenko, L. V. Belousova, O. S. Popova and D. V. Alekseenko, *Russ. Chem. Bull., Int. Ed.*, 2016, **65**, 831 (*Izv. Akad. Nauk, Ser. Khim.*, 2016, 831).
12 T. I. Temnikova and S. N. Semenova, *Molekulyarnye peregruppirovki v organicheskoi khimii* (*Molecular Rearrangements in Organic Chemistry*), Khimiya, Leningrad, USSR, 1983 (in Russian).
13 S. Phadtare, D. Kessel, T. H. Corbett, H. E. Renis, B. A. Court and J. Zemlicka, *J. Med. Chem.*, 1991, **34**, 421.
14 S. Phadtare and J. Zemlicka, *J. Org. Chem.*, 1989, **54**, 3675.
15 Y. Chen, L. Wang, N. Sun, X. Xie, X. Zhou, H. Chen, Y. Li and Y. Liu, *Chem. – Eur. J.*, 2014, **20**, 12015.
16 (*a*) M. B. Smith and J. March, *March's Advanced Organic Chemistry: Reactions*, *Mechanisms, and Structure*, 6th edn., John Wiley & Sons, Hoboken, NJ, 2007, ch. 12–2, p. 767; (*b*) M. B. Smith and J. March, *March's Advanced Organic Chemistry: Reactions*, *Mechanisms, and Structure*, 6th edn., John Wiley & Sons, Hoboken, NJ, 2007, ch. 17–22, p. 1539; (*c*) M. B. Smith and J. March, *March's Advanced Organic Chemistry: Reactions*, *Mechanisms, and Structure*, 6th edn., John Wiley & Sons, Hoboken, NJ, 2007, ch. 4, p. 149.
17 N. A. Danilkina, A. A. Vasileva and I. A. Balova, *Russ. Chem. Rev.*, 2020, **89**, 125.

Received: 22nd October 2020; Com. 20/6345