Acremolin, a stable natural product with an antiaromatic 1*H*-azirine moiety? A structural reorientation

Klaus Banert*

Organic Chemistry, Chemnitz University of Technology, Strasse der Nationen 62, 09111 Chemnitz, Germany

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

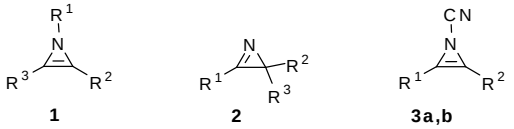
Keywords:
Acremolin
Antiaromatic heterocycles
N^2,3-Ethenoguanines
NMR spectroscopy
Structural corrigendum

ABSTRACT

Recently, acremolin (**4**), a novel modified base, was isolated from a marine-derived fungus and claimed to possess a structure with a 1*H*-azirine moiety. It is shown now that the reported NMR data are not compatible with this antiaromatic heterocycle, which should be an extremely unstable compound. An isomeric, substituted N^2,3-ethenoguanine is presented as a plausible alternative structure of acremolin that is consistent with all spectroscopic data. Thus, 1*H*-azirines keep their classification as very short-lived intermediates.

Strained compounds are of special interest because of their increased energy content and the enhanced reactivity, which frequently results from this. For 1*H*-azirines **1** and 2*H*-azirines **2**, it is obvious that both types of heterocycles include considerable ring strain (Scheme 1). However, the properties of **1** and **2** are quite different.[1] A great number of 2*H*-azirines **2**, especially those with $R^1 \neq H$, were isolated and characterized by spectroscopic methods in solution or even by X-ray crystallographic structure determination. Although compounds of type **2** are highly reactive, the 2*H*-azirine unit has been found in a few natural products.[2] On the other hand, only five examples of short-lived 1*H*-azirines **3a**,**b** were photochemically generated and detected at very low temperatures by IR spectroscopy, which indicated absorptions in the region of 1867–1890 cm^{-1} attributed to C=C valence vibration.[3] Most probably, the push-pull substitution pattern of **3a**,**b** diminishes the antiaromatic character of the 1*H*-azirine structure and increases the relative stability. Thus, attempts to isolate or observe the parent compound (**1** with $R^1 = R^2 = R^3 = H$) by cycloaddition[4] or cyclorevision[5] approaches and by using argon-matrix isolation technique were unsuccessful and yielded unsubstituted **2** and other isomeric species. Elusive 1*H*-azirine intermediates were merely postulated in several other reactions, which finally led to 2*H*-azirines,[6] pyrroles,[7] indoles,[8] oxazoles,[9] isoquinolines,[10] ketenimines,[11] nitriles,[12] or anilines.[13] Furthermore, many quantum chemical calculations, that analyzed the energy content,[14] the molecular geometry,[15] the nitrogen inversion barrier,[16] the basicity,[17] and the vibrational frequencies and IR intensities[18] of the parent 1*H*-azirine **1**, have been published. All experimental and theoretical results emphasize the properties of the antiaromatic heterocycles **1** as short-lived intermediates, which cannot be isolated at room temperature.

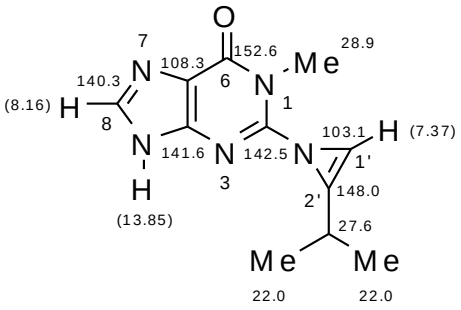
Recently, Shin et al. reported on the isolation of a novel modified base from the culture broth of the marine fungus *Acremonium strictum*.[19] They called this compound acremolin and analyzed the white amorphous solid with the help of HR-FAB-MS to get the molecular formula $C_{11}H_{13}N_5O$. Moreover, IR and UV spectra were recorded, and ^{1}H NMR and ^{13}C NMR investigations including ^{1}H COSY, HSQC, and long-range HMBC methods were performed. This led to the surprising structure **4** (Figure 1). The authors emphasized that the presence of a 1*H*-azirine moiety is unprecedented among natural products.[19] However, such an antiaromatic heterocycle has never



a $R^1 = NPh_2$, $R^2 = P(O)Ph_2$
b R^1 = OMe, O*i*Pr, OCHMeEt, $OCHEt_2$, $R^2 = H$

Scheme 1. Structures of 1*H*-azirines and 2*H*-azirines.

* Tel.: + 49 37153131463; fax: + 49 37153121229;
E-mail address: klaus.banert@chemie.tu-chemnitz.de

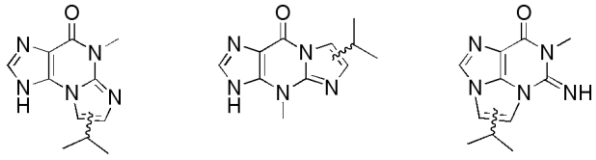


4

Figure 1. Structure **4**, reported for acremolin in ref.[19], and the assignment of the corresponding ^{13}C NMR signals and some of the ^{1}H NMR signals (δ values, DMSO-d_6).

been isolated as a pure compound or characterized in solution although this was tried many times.[1]

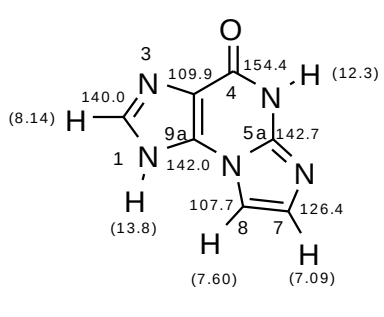
Some doubts about the structure **4** already resulted from the chemical shifts in the ^{1}H NMR and ^{13}C NMR spectra reported by Shin et al.[19] The proton H-1' was said to generate a signal with δ = 7.37, which is within the typical region of aromatic compounds (Figure 1).[20] But the antiaromatic properties of the 1*H*-azirine moiety should induce a shielding effect for the perimeter proton (H-1') and an upfield shift for the corresponding ^{1}H NMR signal.[21] Furthermore, the great value of $\Delta\delta$(C-2'/C-1') = 44.9 ppm cannot be explained by the usual α-effect of an isopropyl group on the adjacent olefinic carbon atom (+20.3 ppm) and the corresponding β-effect (–11.5 ppm),[22] because the sum only reaches a value of 31.8 ppm. Instead of **4**, an alternative structure, in which C-1' and C-2' are intrinsically (even without isopropyl group) different, should be discussed. However, the strongest argument against the structure **4** is the isolation of acremolin at room temperature, which is absolutely incompatible with an antiaromatic 1*H*-azirine moiety.[1,3–18]



5 **6** **7**

Scheme 2. Structures of isomeric ethenoguanines with the formula $C_{11}H_{13}NO$.

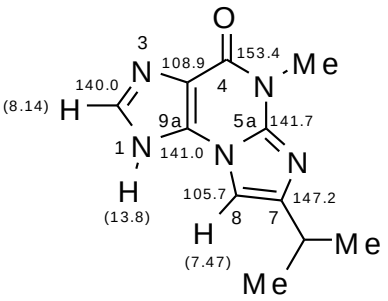
When the three-membered ring of **4** is omitted and a second fused five-membered cyclic system is introduced, the isomeric etheno-bridged guanines **5**, **6**, and **7** can result (Scheme 2). Whereas **6** and **7** are not compatible with ^{1}H COSY or HMBC



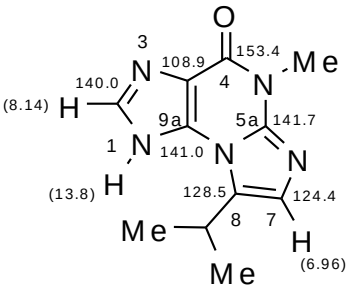
8

Figure 2. ^{13}C NMR and ^{1}H NMR data of 1*H*-imidazo[2,1-b]-purine-4(5*H*)-one (**8**) reported in ref. [23a,d] (δ values, DMSO-d_6).

experiments reported[19] by Shin et al., both regioisomers of **5** are plausible candidates for a revised structure of acremolin. Fortunately, the complete ^{1}H NMR and ^{13}C NMR data of compound **8** were published (Figure 2).[23] These data can now be utilized to calculate the ^{1}H and ^{13}C NMR δ values of **5a** and **5b** (Figure 3). The additional methyl group at N-5 should induce small upfield shifts for the four carbon atoms of the six-membered ring. This assumption is based on ^{13}C NMR studies[24] with uracil and 3-methyluracil, which show little shielding effects due to the methyl group ($\Delta\delta$ = 0.4 – 3.4 ppm). In the case of 2-thiouracil and 3-methyl-2-thiouracil, the changes of the chemical shifts are even smaller ($\Delta\delta$ = 0.5 – 1.5 ppm).[24]



5a



5b

Figure 3. Calculated ^{13}C NMR and ^{1}H NMR data of **5a** and **5b** (δ values, DMSO-d_6) based on the corresponding data of **8** and increments for the additional methyl group at N-5 and the isopropyl group at C-7 or C-8.

Thus, upfield shifts of $\Delta\delta$ = 1.0 ppm due to the additional methyl group were included when the δ values of C-3a, C-4, C-5a, and C-9a of **5a**,**b** were calculated from the corresponding data of **8** (Figure 3). Greater effects should be induced by the isopropyl group, which is known to produce a downfield shift of $\Delta\delta$ = 20.2 or 21.4 ppm for the *ipso* carbon in benzene or pyridine, respectively.[25] An average value of $\Delta\delta$ = 20.8 ppm was used in the calculation of δ(C-7) in **5a** and δ(C-8) of **5b**. Furthermore, isopropyl groups cause moderate shielding effects for carbon atoms in "*ortho*" position, for example, $\Delta\delta$ = 2.2 ppm in benzene and $\Delta\delta$ = 1.8 ppm in pyridine.[25] Thus, an upfield shift of $\Delta\delta$ = 2.0 ppm was included when δ(C-8) of **5a** and δ(C-7) of **5b** were calculated from the corresponding data of **8**. Finally, isopropyl groups also induce a small shielding effect for protons in "*ortho*" position ($\Delta\delta$ = 0.13 ppm in the case of cumene).[25] This is taken into consideration for δ(H-8) of **5a** and δ(H-7) of **5b** (Figure 3). The calculated results exclude **5b** as a potential candidate, but the NMR data estimated for **5a** are nearly identical with those measured for acremolin, which should no longer be characterized by structure **4**. Both structures, **4** and **5a**, can easily be distinguished when the coupling constants ^{1}J(C-1'/H-1') of **4**[26] or ^{1}J(C-8/H-8) of **5a** are known. In the case of **5a**, the value of ^{1}J should be about 190 Hz, which is quite typical for ^{1}J(C-4/H-4) or

^1J(C-5/H-5) of imidazoles.[27] For example, ^1J(C-7/H-7) = 191 Hz was measured for **8**.[23b] On the other hand, $^1J(^{13}C,^1H)$ is expected to be greater than 230 Hz for 1*H*-azirines such as **4** (compare also to ^1J(C-3/H-3) in 2*H*-azirines[28]).[27]

In summary, it has been demonstrated now that there is no necessity to assign the very unlikely antiaromatic structure **4** to the natural product acremolin. Instead, this compound shows stability and spectroscopic data, which are highly compatible with the structure of N^2,3-ethenoguanine **5a**. Thus, 1*H*-azirines keep their classification as very short-lived intermediates.

Acknowledgments

The author thanks Dr. A. Ihle for assistance with the manuscript. This is a post-peer-review version from Tetrahedron Letters, 53, K. Banert, Acremolin, a stable natural product with an antiaromatic 1H-azirine moiety? A structural reorientation, 6443-6445, 2012, with permission from Elsevier, self-archived on http://monarch.qucosa.de in 2014. The definitive publisher-authenticated version is available online at: http://dx.doi.org/10.1016/j.tetlet.2012.09.061 - See more at: http://www.sciencedirect.com/science/journal/00404039.

References and Notes

1. Reviews on 1*H*-azirines and 2*H*-azirines: (a) Backes, J. In *Houben-Weyl, Vol. E16c;* Klamann, D., Ed.; Thieme: Stuttgart, 1992, pp 321–369; (b) Nair, V. In *The Chemistry of Heterocyclic Compounds, Small-Ring Heterocycles, Vol. 42, Part 1*; Hassner, A., Ed.; Wiley: New York, 1983, pp 215–332; (c) Pearson, W. H.; Lian, B. W.; Bergmeier, S. C. In *Comprehensive Heterocyclic Chemistry II, Vol. 1A*; Padwa, A., Ed.; Pergamon: New York, 1996, pp 1–60; (d) Palacios, F.; Ochoa de Retana, A. N.; Martinez de Marigorta, E.; de Los Santos, J. M. *Eur. J. Org. Chem.* **2001**, 2401–2414; (e) Gilchrist, T. L. *Aldrichimica Acta* **2001**, *34*, 51–55; (f) Rai, K. M. L.; Hassner, A. In *Advances in Strained and Interesting Organic Molecules, Vol. 8;* Halton, B., Ed.; Jai Press: Greenwich, 2000, pp 187–257; (g) Fowler, F. W. *Adv. Heterocycl. Chem.* **1971**, *13*, 45–76; (h) Wentrup, C. *Adv. Heterocycl. Chem.* **1981**, *28*, 231–361.
2. a) Miller, T. W.; Tristram, E. W.; Wolf, F. J. *J. Antibiot.* **1971**, *24*, 48–50; (b) Molinski, T. F.; Ireland, C. M. *J. Org. Chem.* **1988**, *53*, 2103–2105; (c) Salomon, C. E.; Williams, D. H.; Faulkner, D. J. *J. Nat. Prod.* **1995**, *58*, 1463–1466; (d) Stapley, E. O.; Hendlin, D.; Jackson, M.; Miller, A. K.; Hernandez, S.; Mata, J. M. *J. Antibiot.* **1971**, *24*, 42–47; (e) Davis, F. A.; Reddy, G. V.; Liu, H. *J. Am. Chem. Soc.* **1995**, *117*, 3651–3652; (f) Davis, F. A.; Liu, H.; Liang, C.-H.; Reddy, G. V.; Zhang, Y.; Fang, T.; Titus, D. D. *J. Org. Chem.* **1999**, *64*, 8929–8935.
3. Regitz, M.; Arnold, B.; Danion, D.; Schubert, H.; Fusser, G. *Bull. Soc. Chim. Belg.* **1981**, *90*, 615–631.
4. (a) Jacox, M. E.; Milligan, D. E. *J. Am. Chem. Soc.* **1963**, *85*, 278–282; (b) Kodama, S. *J. Phys. Chem.* **1988**, *92*, 5019–5024.
5. Maier, G.; Schmidt, C.; Reisenauer, H. P.; Endlein, E.; Becker, D.; Eckwert, J.; Hess, B. A.; Schaad, L. J. *Chem. Ber.* **1993**, *126*, 2337–2352.
6. (a) Fowler, F. W.; Hassner, A. *J. Am. Chem. Soc.* **1968**, 90, 2875–2881; (b) Anderson, D. J.; Gilchrist, T. L.; Rees, C. W. *Chem. Commun.* **1969**, 147; (c) Gilchrist, T. L.; Gymer, G. E.; Rees, C. W. *Chem. Commun.* **1971**, 1519–1520; (d) Anderson, D. J.; Gilchrist, T. L.; Gymer, G. E.; Rees, C. W. *J. Chem. Soc., Perkin Trans. 1* **1973**, 550–555; (e) Gilchrist, T. L.; Gymer, G. E.; Rees, C. W. *J. Chem. Soc., Perkin Trans. 1* **1973**, 555–561; (f) Atkinson, R. S.; Grimshire, M. J. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1215–1224.
7. Gilchrist, T. L.; Gymer, G. E.; Rees, C. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1–8.
8. (a) Mitchell, G.; Rees, C. W. *J. Chem. Soc., Chem. Commun.* **1986**, 399–401; (b) Mitchell, G.; Rees, C. W. *J. Chem. Soc., Perkin Trans. 1* **1987**, 413–422.
9. (a) Huisgen, R.; Blaschke, H. *Chem. Ber.* **1965**, *98*, 2985–2997; (b) Meinwald, J.; Aue, D. H. *J. Am. Chem. Soc.* **1966**, *88*, 2849–2850.
10. Gilchrist, T. L.; Gymer, G. E.; Rees, C. W. *J. Chem. Soc., Chem. Commun.* **1973**, 835–836.
11. Gilchrist, T. L.; Rees, C. W.; Thomas, C. *J. Chem. Soc., Perkin Trans. 1* **1975**, 8–11.
12. (a) Wentrup, C.; Crow, W. D. *Tetrahedron* **1970**, *26*, 3965–3981; (b) Thétaz, C.; Wentrup, C. *J. Am. Chem. Soc.* **1976**, *98*, 1258–1259.
13. Wentrup, C. *Helv. Chim. Acta* **1972**, *55*, 1613–1617.
14. (a) Clark, D. T. *Theoret. Chim. Acta (Berl.)* **1969**, *15*, 225–234; (b) Hopkinson, A. C.; Lien, M. H.; Yates, K.; Csizmadia, I. G. *Int. J. Quantum Chem.* **1977**, *12*, 355–368; (c) Bock, H.; Dammel, R. *Chem. Ber.* **1987**, *120*, 1971–1985; (d) Alcami, M.; Mó, O.; Yáñez, M. *J. Am. Chem. Soc.* **1993**, *115*, 11074–11083; (e) Lathan, W. A.; Radom, L.; Hariharan, P. C.; Hehre, W. J.; Pople, J. A. *Top. Curr. Chem.* **1973**, *40*, 1–45.
15. (a) Mó, O.; Yáñez, M.; Elguero, J. *J. Mol. Struct. (Theochem)* **1989**, *201*, 17–37; (b) Byun, Y.-G.; Saebo, S.; Pittman, C. U. *J. Am. Chem. Soc.* **1991**, *113*, 3689–3696; (c) Malar, E. J. P. *Tetrahedron* **1996**, *52*, 4709–4718.
16. (a) Budzelaar, P. H. M.; Cremer, D.; Wallasch, M.; Würthwein, E.-U.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1987**, *109*, 6290–6299; (b) Alcami, M.; de Paz, J. L. G.; Yáñez, M. *J. Comp. Chem.* **1989**, *10*, 468–478.
17. (a) Würthwein, E.-U. *J. Org. Chem.* **1984**, *49*, 2971–2978; (b) Mó, O.; de Paz, J. L. G.; Yáñez, M. *J. Phys. Chem.* **1987**, *91*, 6484–6490.
18. Čársky, P.; Hess, B. A.; Schaad, L. J. *J. Am. Chem. Soc.* **1983**, *105*, 396–402.
19. Julianti, E.; Oh, H.; Lee, H.-S.; Oh, D.-C.; Oh, K.-B.; Shin, J. *Tetrahedron Letters* **2012**, *53*, 2885–2886.
20. The numbering for H-1'/H-2' and C-1'/C-2' is borrowed from Shin et al.[19] although it is not logical to give the substituted carbon atom a higher number than the unsubstituted carbon.
21. (a) Günther, H. *NMR Spektroskopie*, 3rd ed., Thieme: Stuttgart 1992, pp. 83–91; (b) Balci, M. *Basic ^1H-^{13}C-NMR-Spectroscopy*, Elsevier: Amsterdam, 2005, pp. 47–48.
22. Hesse, M.; Meier, H.; Zeeh, B. *Spektroskopische Methoden in der organischen Chemie*, 6th ed., Thieme: Stuttgart, 2002, pp. 169–170.
23. (a) Fedtke, N.; Boucheron, J. A.; Turner, M. J.; Swenberg, J. A. *Carcinogenesis* **1990**, *11*, 1279–1285; (b) Guengerich, F. P.; Persmark, M.; Humphreys, W. G. *Chem. Res. Toxicol.* **1993**, *6*, 635–648; (c) Kuśmierek, J. T.; Jensen, D. E.; Spengler, S. J.; Stolarski, R.; Singer, B. *J. Org. Chem.* **1987**, *52*, 2374–2378; (d) Lee, S. H.; Oe, T.; Blair, I. A. *Chem. Res. Toxicol.* **2002**, *15*, 300–304; (e) Sattsangi, P. D.; Leonard, N. J.; Frihart, C. R. *J. Org. Chem.* **1977**, *42*, 3292–3296.
24. Still, I. W. J.; Plavac, N.; McKinnon, D. M.; Chauhan, M. S. *Can. J. Chem.* **1978**, *56*, 725–729.
25. Pretsch, E.; Seibl, J.; Simon, W.; Clerc, T. *Tabellen zur Strukturaufklärung organischer Verbindungen mit spektroskopischen Methoden*, 3rd ed., Springer: Berlin, 1990.
26. Unfortunately, Shin et al.[19] did not give values for $^1J(^{13}C,^1H)$, especially for the ^{13}C NMR signal of acremolin with δ = 103.1.
27. Kalinowski, H.-O.; Berger, S.; Braun, S. *^{13}C-NMR-Spektroskopie*, Thieme: Stuttgart, 1984.
28. (a) Isomura, K.; Taniguchi, H.; Mishima, M.; Fujio, M.; Tsuno, Y. *Org. Magnet. Reson.* **1977**, *9*, 559–562; (b) Guillemin, J.-C.; Denis, J.-M.; Lasne, M.-C.; Ripoll, J.-L. *Tetrahedron* **1988**, *44*, 4447–4455.

Graphical Abstract

Acremolin, a stable natural product with an antiaromatic 1*H*-azirine moiety? A structural reorientation

Klaus Banert

Leave this area blank for abstract info.