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

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ARTICLE INFO

Article history:

Received

Received in revised form

Accepted

Available online

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.

Keywords:

Acremolin

Antiaromatic heterocycles

*N*²,3-Ethenoguanines

NMR spectroscopy

Structural corrigendum

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 ≠ 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 cycloaddition⁴ or cycloreversion⁵ 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 intensities¹⁸ 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 *Acromonium 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 C₁₁H₁₃N₅O. Moreover, IR and UV spectra were recorded, and ¹H NMR and ¹³C NMR investigations including ¹H 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

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

Figure 1. Structure **4**, reported for acremolin in ref.¹⁹, and the assignment of the corresponding ¹³C NMR signals and some of the ¹H 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 ¹H NMR and ¹³C NMR spectra reported by Shin et al.¹⁹ The proton H-1' was said to generate a signal with $\delta = 7.37$, 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 ¹H NMR signal.²¹ Furthermore, the great value of $\Delta\delta(\text{C-2'/C-1'}) = 44.9$ 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}

Scheme 2. Structures of isomeric ethenoguanines with the formula C₁₁H₁₃NO.

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 ¹H COSY or HMBC

Figure 2. ¹³C NMR and ¹H 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 reported¹⁹ by Shin et al., both regioisomers of **5** are plausible candidates for a revised structure of acremolin. Fortunately, the complete ¹H NMR and ¹³C NMR data of compound **8** were published (Figure 2).²³ These data can now be utilized to calculate the ¹H and ¹³C 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 ¹³C NMR studies²⁴ 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

Figure 3. Calculated ¹³C NMR and ¹H 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 $\delta(\text{C-7})$ in **5a** and $\delta(\text{C-8})$ 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 $\delta(\text{C-8})$ of **5a** and $\delta(\text{C-7})$ 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 $\delta(\text{H-8})$ of **5a** and $\delta(\text{H-7})$ 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

$^1J(\text{C-5/H-5})$ of imidazoles.²⁷ For example, $^1J(\text{C-7/H-7}) = 191 \text{ Hz}$ was measured for **8**.^{23b} On the other hand, $^1J(^{13}\text{C}, ^1\text{H})$ is expected to be greater than 230 Hz for 1*H*-azirines such as **4** (compare also to $^1J(\text{C-3/H-3})$ in 2*H*-azirines²⁸).

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 $\text{N}^2,3$ -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, Acemolin, a stable natural product with an antiaromatic 1*H*-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>.

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Graphical Abstract

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marine fungus
Acremonium
strictum

metabolite
 $C_{11}H_{13}N_5O$

very short-lived
antiaromatic heterocycle

stable compound

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