



CHAPTER II

[SUPPL Chapter II # 8]

Arabic compound numbers in TAPSOC,
Roman numerals in Supplementary material

HEDZ and LEDZ in DIMBOA, a natural herbicide

HEDZs and LEDZs within molecules are relatively easy to identify by studying the substitution pattern and EW/ED functional group interactions through conjugation and dipolar effects. DIMBOA (**I**) offers a good example of how the early recognition of the reactivity pattern of this curious natural herbicide can guide you through a full-fledged mechanistic strategy.

DIMBOA is unstable in water, understandably enough considering its functionally dense structure with lots of Lewis base sites for water association. But it is also a paradox taking into account its secretion by roots of several grass species, including maize and wheat, in moist soil. It sounds like a waste of metabolic resources.

A fast look at **I** shows a HEDZ on the western side of the molecule and a complex LEDZ on the east, all of it in the heterocyclic ring [Figure S(II)8.1]. This is where one might expect most reactions in hydrolytic media at least in its fundamental, unperturbed state.

While this quick analysis is a good start in understanding what might have happened in Scheme II.11 of your APSOC, it is certainly not enough [1]. Some measure of systematic problem analysis should help. Perhaps it would be a good idea if you proposed a few basic questions and build your arguments from there.

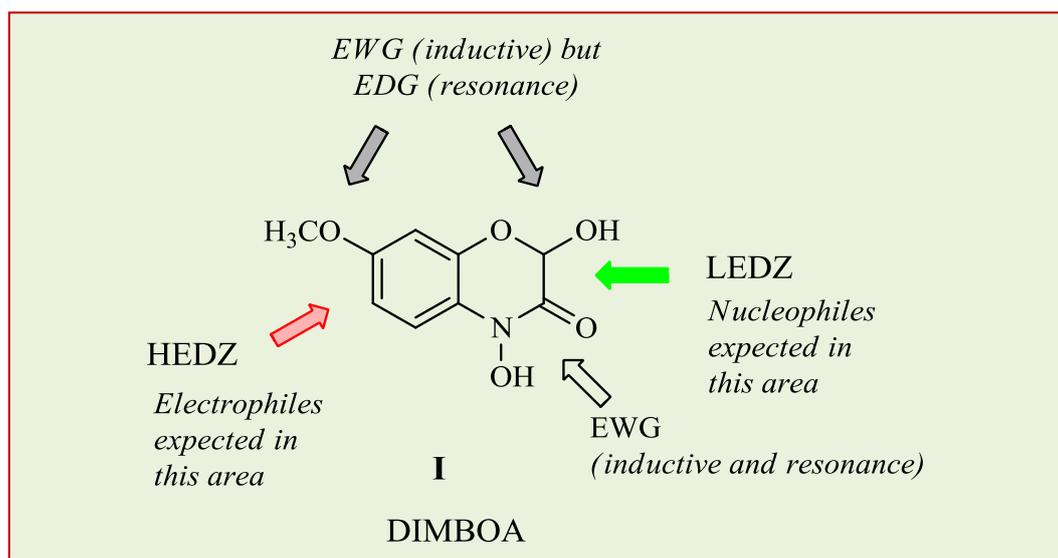


FIGURE S(II)8.1. Identification of zones of differential electron density (HEDZ/LEDZ) in DIMBOA, a natural herbicide of some commercial and wild grasses species.

Problem Analysis of Scheme II.11, the TAPSOC way:

a.- Apparent reaction? This is difficult to pinpoint offhand. All we can say with a broad brush is this: compound **I** undergoes a profound change ciphered in deconstructing the heterocycle. As well, loss of aromaticity with regioselective incorporation of ethyl sulfide in the anisol sector.

b.- HEDZ and LEDZ in **I** are separated by sp^3 atoms. For them to interact electronically, some sort of conjugational bridge should be erected along the way if electron flow between these two zones is deemed necessary. Otherwise, electron traffic is not expected between the two sections.

c.- Of the two electronically dynamic zones, LEDZ is seemingly the more active as there are EW functional groups clustered in a small space. The reaction is likely to begin here.

d.- There are clear signs of the spiro oxazolidone in target **65** (TAPSOC numbering) stemming from the elements of the heterocycle in **I** after fracture and reconstruction. No need for rearrangement involving C-C disconnection and reconnection. Heteroatoms are in charge of this job.

e.- Labeling atoms would be a good idea to follow the course of events. MeO stands as the only functional group probably not undergoing group shift and is thus our earmark (C^7) in **I**. This time the IUPAC nomenclature for this molecular skeleton is adopted (not so in others for practical reasons). Then, carbon labels are figured out in product **65** according to their minimal modification [Figure S(II).2].

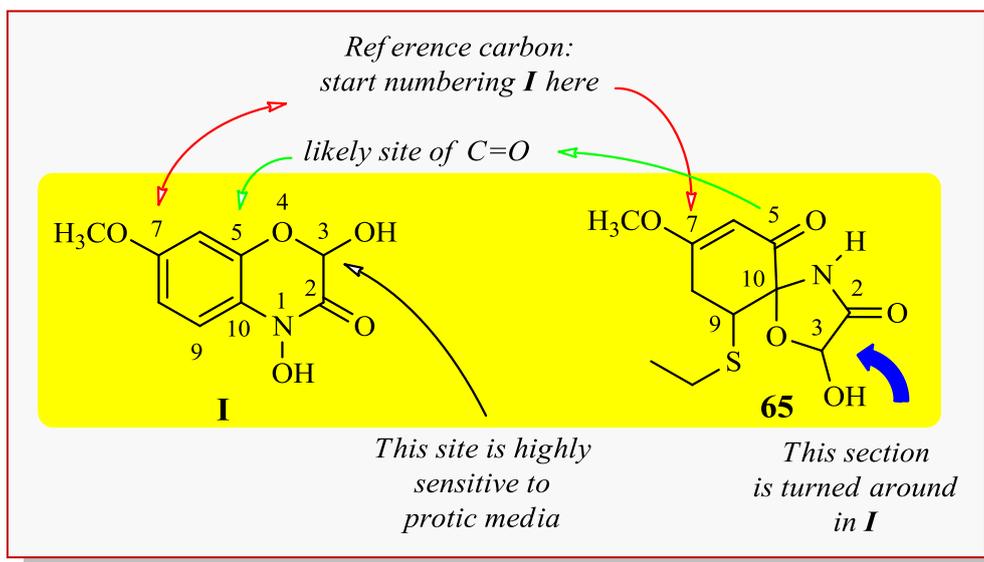


FIGURE S(II)8.2. A mechanistic strategy begins to take shape.

f.- From this figure it is now easy to pin down atoms undergoing bond changes; C⁵, C⁹ and C¹⁰: C³-O⁴ is broken, probably by β elimination of the hemiacetal. As a result O⁴ becomes part of the ketone. *This is a EWG which would activate the western (anisole) ring as electrophile to receive nucleophilic ethyl sulfide.*

g.- EtSH would attack C⁹ owing to its being δ relative to the conjugated ketone at C⁵, and hence, part of the desired LEDZ.

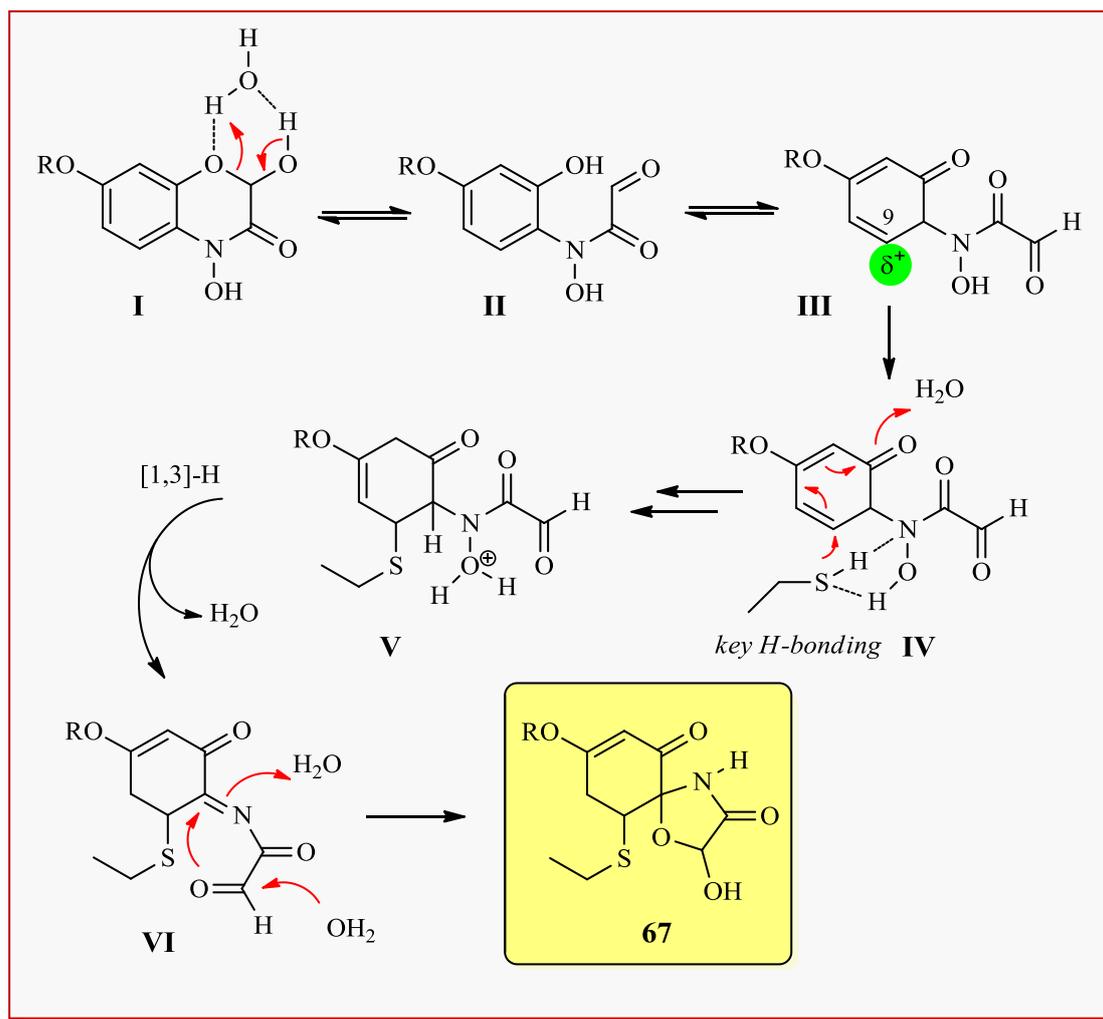
h.- MeO plays no role in the above proposal.

Based on this analysis, an operational plan can be blueprinted [Scheme S(II)8.1].

A key step is the critical bonding of ethyl sulfide in **III** → **V**. There are two independent LEDZs for it to go: aldehyde in the highly polarized α-dicarbonyl, and the δ carbon (C⁹) of the dienone ring. Hydrogen bonding in molecular assemblage **IV** would tether EtSH towards C⁹ [2].

Further, the crucial spirocyclization occurs in **VI** as a result of the strong electrophilic character of the imine carbon which in turn is the consequence of the electronic pull of the vicinal LED functions.

There are probably no better alternatives to this scheme. Experimental proof may be gathered by the isolation of aldehyde **III** at lower temperatures in the absence of nucleophiles other than water. But the intriguing hydrosulfide tethering in **IV** may prove much more difficult to assess unless DFT or other calculations are applied [2].



SCHEME S(II)8.1. Adapted from Dixon DP, Sellars JD, Kenwright AM, Steel PG. *Phytochemistry* 2012;77:171-178. Copyright ©2012 Elsevier, by permission, license N° 3094100598962.

REFERENCES

[1] Dixon DP, Sellars JD, Kenwright AM, Steel PG. *Phytochemistry* 2012;77:171-178.

[2] Molecular aggregations like **IV** have a strong effect on the kinetics of some bimolecular reactions, according to recent findings in Diels Alder cycloadditions. Check up: Robertson A, Philp D, Spencer N. *Tetrahedron* 1999;55:11365-11384. DOI: 10.1016/S0040-4020(99)00633-X; Domingo LR, Aurell MJ, Arnó M, Sáez JA. *J. Org. Chem.* 2007;72:4220-4227. DOI: 10.1021/jo070373j. See also problem 5.