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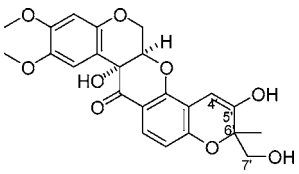
CORRESPONDENCE/REBUTTAL

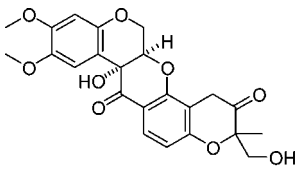
Comment on Cubé Resin Insecticide: Identification and Biological Activity of 29 Rotenoid Constituents

Sir: A recent survey on new rotenoid compounds brought to our attention the thorough paper from Fang and Casida (*1*) on the identification and biological activity of 29 rotenoid constituents of cubé resin insecticide. One among the 12 new compounds reported was described as 5′,7′-dihydroxytephrosin (**1**) (numbered **19** in ref *1*).



1 (**19** in *1*)

In fact, **1** is just the enol form of the corresponding 3-chromanone **2** (4′,5′-dihydro-7′-hydroxy-5′-oxotephrosin). Actually, a search for substructures of more complex structures with a specific 3-chromanone unit such as **3** as input structure returned three references (*1*−*3*) showing surprisingly the enol form **1**.



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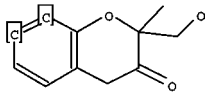

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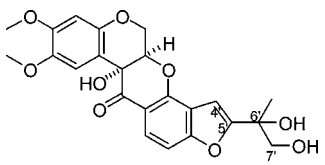
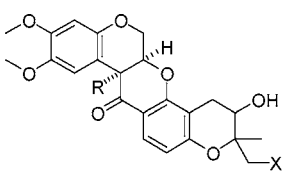
The rationale for the proposed structure **19** was based (in part) on the presence of NMR absorptions for a trisubstituted double bond (1H absorption at δ 6.84, s, H-4′; δ 100.8, d, C-4′; and δ 160.2, s, C-5′), implying an almost quantitative presence of the enol form **1**. However, the reported spectroscopic evidence for simple models of 3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-3-ones from our past experience (*4*, *5*) and other literature reports (*6*, *7*) describes the presence (for the corresponding H-4′ signal) of a 2H absorption at $\delta \sim 3.5$ and points out an almost quantitative presence of the keto form in the plausible keto−enol equilibrium. Because from these literature reports the keto form must be expected to be the preferred one, the question arose whether the enol tautomer was really so much favored in this particular case. Whereas the changes in substitution pattern were considered to be an unlikely rationale to account for such a shift of the equilibrium, a more plausible structural proposal to account for the reported NMR data would imply a change from the six-membered deguelin structure to a five-membered rotenone-type one. O-substitution in both positions 5′ and 6′ implies a potential ambiguity to assess the correct one involved in ring formation (rotenone- or deguelin-type derivatives) unless some data would point it out consistently. The unlikeliness of the enol form may be the answer in the present case to point out 6′,7′-dihydroxy-4′,5′-dehydrorotenolone (6′,7′-dihydroxy-isorotenolone) **4** (or **19R** for **19** revised structure) as the correct structure for the isolated rotenoid.



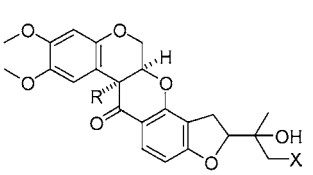
4 (**19R** for*1*)

Furthermore, this structure **4** was already discussed in the original paper as a plausible immediate precursor of another isolated new rotenoid, 7′-*nor*-6′-oxo-4′,5′-dehydrorotenolone (**18**) (*1*), by sequential oxidative aromatization of ring E, followed by oxidation, hydrolysis, and oxidative carbon−carbon bond cleavage. The structural change proposed would reinforce the mechanistic proposal and could be summarized as follows: To be 6′,7′-dihydroxy-4′,5′-dehydrorotenolone and not to be 5′,7′-dihydroxytephrosin, is that just an NMR question?

Two further examples of potential ambiguity in ref *1* deserve to be considered, because of O-substitution in both positions 5′ and 6′, among the reported new rotenoids. Thus, the NMR-based rationale for structural elucidation of 4′,5′-dihydro-5′,7′-dihydroxytephrosin (**20** in ref *1*) and 7′-chloro-4′,5′-dihydro-5′-hydroxydeguelin (**21** in ref *1*) (in this paper **5a**, R = X = OH; **5b**, R = H, X = Cl, respectively) would apply equally well to the corresponding rotenone-type derivatives 6′,7′-dihydro-6′,7′-dihydroxyrotenolone and 7′-chloro-6′,7′-dihydro-6′-hydroxyrotenolone (**6a**, R = X = OH; **6b**, R = H, X = Cl, respectively).



5 (**20,21**)



6 (**20R,21R**)

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However, because the cis and trans coupling constants for H-4′/H-5′ reported in ref *1* for the different isomers of 4′,5′-dihydro-4′,5′-dihydroxytephrosin (structure secured by X-ray crystal data) are 7.2, 6.7, 5.1, and 4.6 Hz, whereas for rotenolone structures these constants are in the range of 8−10 Hz, the assignment of type **6** structures appears to be more likely, considering the *J* values reported for **5a (20)** and **5b (21)** (*8*, *9*).

In conclusion, regular 1D and 2D NMR data for **1** (if it exists in such a 100% enol form) and **4**, **5a** and **6a**, and **5b** and **6b** should be very similar. To prove unambiguously correct one or the other requires further experiments, but the revised structures are a better rationale for the reported NMR data.

LITERATURE CITED

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(8) Reported data for **5a** (compound **20** in ref *1*) and **5b** (compound **21** in ref *1*; two isomers on NMR) should be revised: $4'_A,4'_B$-geminal coupling for **5a** and **5b** is not reported (outer bands only ca. $^1/_{10}$ the inner ones!?) and only one of the two H-4′ is shown for **5b**. Data (5′,*4′*,4′; *considered inconsistencies shown in italics*): for compound **4** in ref *1* (five-membered rotenoid model), 5.33 (dd, 9.7, 8.2), 3.38 (dd, 15.9, 9.7), 3.02 (dd, 15.9, 8.2); for **20** in ref *1* (**5a**), 4.86 (dd, 9.2, *8.7*), 3.16 (*d*, *8.2*), 3.15 (*d*, 9.2); for **21** in ref *1* (**5b**), 4.93 (*m*, 2H), 3.21 (*d*, *8.7*, 1H), 3.19 (*d*, *8.7*, 1H).

(9) Among the reviewer's reports, further experiments that would require access to the original compounds (likely available only in minute amounts) are proposed for unambiguous assignments: ^{1}H NOE difference for 7′ in **4** or $(IO_4)^-$ degradation to obtain **18**; $(IO_4)^-$ treatment of **6a** to obtain the 6′-norketone; convert **6b** to **6a** (Ag_2O?); ^{1}H−^{1}H COSY experiments in a polar aprotic solvent would yield any connections via scalar couplings distinguishing structures **5** or **6**. Acetylation or methylation of **1/4** has also been suggested.

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