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# THE ABSOLUTE CONFIGURATIONS OF LONGITUBINE (7-O-ACETYL-9-O-LATIFOLYLRETRONECINE) AND LATIFOLIC ACID

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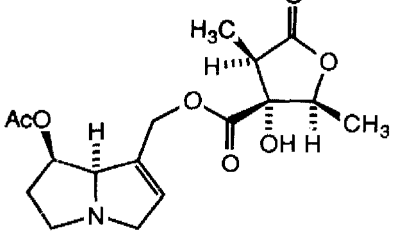
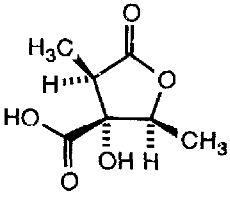
**SUMMARY:** A single crystal X-ray study established the absolute configuration of longitubine (7-O-acetyl-9-O-latifolylretronecine) and hence that of latifolic acid. The absolute configuration of latifolic acid conforms with that established chemically by Matsumoto, Okabe and Fukui, and consequently is not in agreement with that purportedly established through an X-ray study by Roitman and Wong.

A new pyrrolizidine alkaloid, assigned structure 1 and named longitubine, was reported[1] from *Hackelia longituba*. The same structure was independently assigned[2] to a new alkaloid (named 7-O-acetyl-9-O-latifolylretronecine) from *H. californica*. The alkaloid from *H. californica* was reported[2] to be an oil, but it solidified upon long standing in the cold and was recrystallized from EtOAc/hexane to yield needles or prisms, depending on crystallization conditions. All data ($^1$H and $^{13}$C nmr and mass spectra, mp and direction of optical rotation) were identical to those reported[1] for longitubine, assuring identity of the two substances.

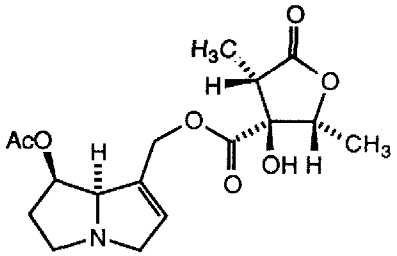


1

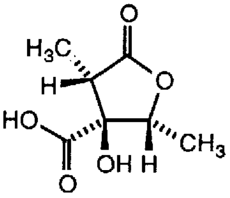


2

In a related study[3], the known alkaloid latifoline[4] (also isolated from *H. longituba*) was hydrogenolyzed to yield crystalline (+)-latifolic acid, whose absolute stereochemistry was reported[3] as **2**, based upon X-ray crystallography. This determination is in disagreement with the absolute configuration for (+)-latifolic acid *determined chemically*[5]*, which indicated the enantiomer* **3**. Although absolute configurations can be established by careful X-ray crystallography without incorporation of a heavy atom[6,7,8], the reported data[3] do not meet the criteria for an unambiguous determination. Specifically, the R ratio (1.314) on which the assignment was based cannot possibly be correct; it is much too high for the small anomalous effects involved. A reasonable ratio would be in the range 1.01-1.04.[7,8] Moreover, the R index (0.072) is too high for a safe determination by the R ratio method.[9] Finally, as emphasized before[7,8], only a selected set of enantiomer sensitive reflections should be used in the determination. This was not done.



**4**



**3**

In order to resolve the question of latifolic acid stereochemistry and to confirm *the structure of longitubine, an X-ray structure determination was performed on a* crystal of the the isolate from *H. californica*. Since the absolute configuration of retronecine is known without doubt[10,11,12,13,14] and its presence as the necine base in latifoline[4,15] and longitubine[1,2] not under question, the absolute configurations at the latifolic acid centers can be determined in reference to those of the retronecine moiety. The results of our X-ray study[16] (Figure 1) show conclusively that the proper structure for longitubine is that represented by **4**, not **1**, and hence the original chemical establishment[5] of the (+)-latifolic acid structure as **3** is correct. Roitman and Wong speculated[3] that "an error such as interchanged samples may have occurred" in the synthesis study,[5] but the error must instead have been in the X-ray procedures.

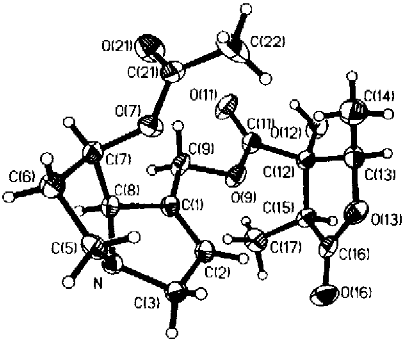


Figure 1. X-Ray structure of longitubine, showing the absolute configuration **4**.

The results of an X-ray study are generally regarded as irrefutable. Because of experimental and mathematical complexity it is very difficult for the uninitiated to detect flaws. This incident may serve as a reminder to the chemical community that even the most reliable methods can lead to erroneous results if appropriate standards are not maintained.

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