Chemistry of F_1,F_0-ATPase Inhibitor. Photoisomerization of Citreoviridin and Isocitreoviridin and Structure of Isocitreoviridin

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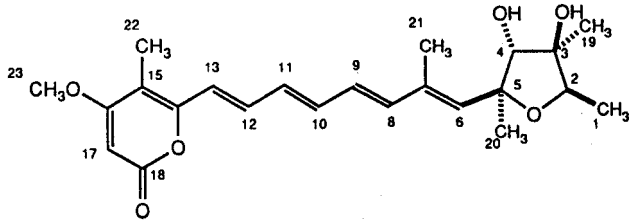
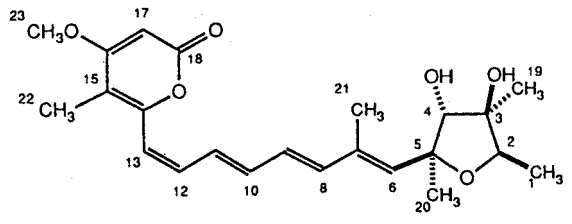
Citreoviridin is known as a F_1F_0-ATPase inhibitor that was first isolated from moldy rice by Hirata.[1] In our total syntheses of citreoviral and citreoviridin, the instability of citreoviridin has been revealed.[2] The synthetic citreoviridin was accompanied by an impurity which was at first quite difficult to remove. Successful separation followed the discovery that the impurity is a result of photoisomerization of the compound. Samples of synthetic citreoviridin or natural citreoviridin was exposed to normal room illumination (incandescent, fluorescent, or sun light) and analyzed by HPLC to generate two well resolved major components, with a ratio of 3 : 2.[3] The material corresponding to either peak was kept under normal fluorescent room illumination and reinjected into the HPLC which recreated the 3 : 2 mixture as determined by refractive index detection and NMR stectroscopy.

These two peaks were separated under red light by using HPLC. Since Nagel reported that the citreoviridin sample contained 40% of another isomer, and we found a 3 : 2 ratio of citreoviridin and isocitreoviridin, we conclude that this is the isomeric material Nagel found and named isocitreoviridin.[4] In Figure 2, the olefinic region of proton NMR spectrum of isocitreoviridin is compared with that of citreoviridin. Since the H-8, 9, 10, 12 peaks of isocitreoviridin appear between 6.30-6.54 ppm and of second order, it is very difficult to assign exact coupling constants and chemical shifts. A



CITREOVIRIDIN



ISOCITREOVIRIDIN

Figure 1.

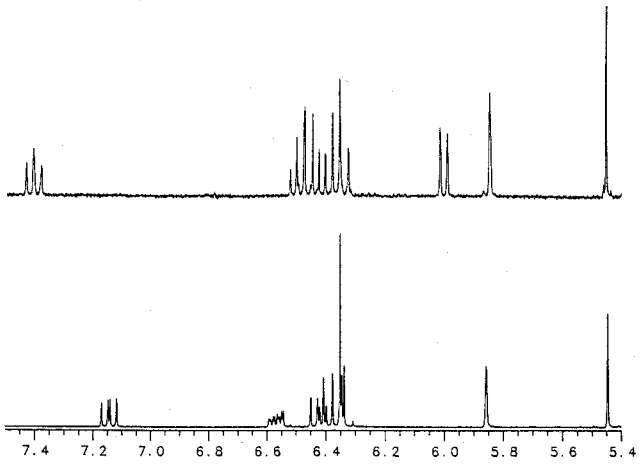


Figure 2. Plot of the Olefinic Region of ^1H NMR spectra of Isocitreoviridin (above) and Citreoviridin (below).

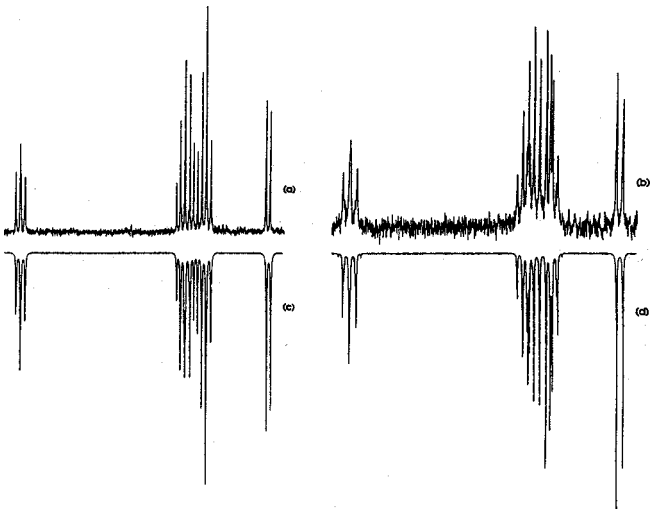


Figure 3. Plot of Experimental and Calculated ^1H NMR Spectra for Olefinic Protons of Isocitreoviridin in CD_2Cl_2. (a) experimental, 500 MHz; (b) experimental, 360 MHz; (c) calculated, 500 MHz; (d) calculated, 360 MHz.

proton NMR study using COSY and NOE experiments provided the coupling constants and chemical shifts of this isocitreoviridin. To confirm this data, it was necessary to compare the observed second order spectrum and the calculated spectrum. As shown in Figure 3, the olefinic region of the real spectrum and the calculated region from the data matched very well. Using these values, the match between calculated and observed spectra is excellent for both 500 MHz and 360 MHz.[5] Same method has been used for the assignment of the coupling constants and chemical shifts of citreoviridin as was illustrated in our previous report.[2] The structure of citreoviridin was originally identified by X-ray.[6]

It was proposed by Nagel that isocitreoviridin has one Z double bond between C-10 and C-11.[4] But, the coupling constant between H-12 and H-13, $J_{12,13}$, infers that isocitreoviridin has one Z double bond between C-12 and C-13. To reaffirm Z structure between C-12 and C-13, NOE experiment was carried out. When the H-13 peak was irradiated, H-12 and

Table 1. Selected ^1H NMR Data for Isocitreoviridin

C#	δ ^1H[a]	COSY[b]
6	5.86, s	
8	6.34, d, $J_{8,9}$=14.40 Hz	H9
9	6.45, dd, $J_{8,9}$=14.40 Hz, $J_{9,10}$=11.10 Hz	H8, 10
10	6.50, dd, $J_{9,10}$=11.10 Hz, $J_{10,11}$=13.32 Hz	H9, 11
11	7.41, dd, $J_{10,11}$=13.32 Hz, $J_{11,12}$=12.22 Hz	H10, 12
12	6.38, dd, $J_{11,12}$=12.22 Hz, $J_{12,13}$=11.86 Hz	H11, 13
13	6.00, d, $J_{12,13}$=11.86 Hz	H12

[a]Recorded in CD_2Cl_2 at 500 MHz. [b]Recorded in CD_2Cl_2 at 360 MHz.

H-22 peak showed NOE. This result reconfirms the facts that the double bond between C-12 and C-13 is Z and C-13 is connected to the pyrone moiety. In addition, when the H-6 peak was irradiated, H-4 and H-8 peaks showed NOE. This result verifies the connectivity between C-6 and C-8.

Our discovery that when citreoviridin was exposed to incandescent, fluorescent, or sun light for brief period of time, there was a significant amount of another isomer, isocitreoviridin, generates question of which isomer, citreoviridin, or isocitreoviridin, is the real inhibitor.[2] In a different account, we reported that citreoviridin is an inhibitor of ATP hydrolysis and ATP synthesis catalyzed by beef heart mitochondrial enzyme F1-ATPase, but isocitreoviridin has no effect on either activity of the enzyme.[7]

References

1. Hirata, Y.; Goto, T.; Sakabe, N. *Tetrahedron Lett.* **1964**, 1825.
2. Suh, H.; Wilcox, C. S. *J. Am. Chem. Soc.* **1988**, *110*, 470.
3. To isolate isocitreoviridin from the mixture of citreoviridin and isocitreoviridin, normal phase HPLC was used with 3.5% MeOH/CH_2Cl_2. CH_2Cl_2 was filtered through Al_2O_3 column before using.
4. Nagel, D. W.; Steyn, P. S.; Scott, D. B. *Phytochemistry* **1972**, *11*, 627.
5. ^1H NMR (500 MHz, CD_2Cl_2) (CH_2Cl_2, internal standard) δ 7.41 (dd, 1H, $J_{10,11}$=13.3 Hz, $J'_{11,12}$=12.2 Hz, H11), 6.50 (1H, $J_{10,11}$=13.3 Hz, $J'_{9,10}$=11.1 Hz, H10), 6.45 (1H, $J_{8,9}$=14.4 Hz, $J'_{9,10}$=11.1 Hz, H9), 6.38 (1H, $J_{12,13}$=11.9 Hz, $J'_{11,12}$=12.2 Hz, H12), 6.34 (1H, $J_{8,9}$=14.4 Hz, H8), 6.00 (d, 1H, $J_{12,13}$=11.9 Hz, H13), 5.86 (s, 1H, H6), 5.46 (s, 1H, H17), 3.93 (br s, 1H, H4), 3.82 (s, 3H, H23), 3.77 (q, 1H, J=6.3 Hz, H2), 1.96 (s, 3H, H22), 1.93 (br s, 3H, H21), 1.33 (s, 3H, H20), 1.16 (s, 3H, H19), 1.13 (d, 3H, J=6.3 Hz, H1).
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Unusual Rearrangement of 2-Amino-1-Substituted Phenyl-1-Alkanol to 1-Substituted phenyl-2-Alkanone

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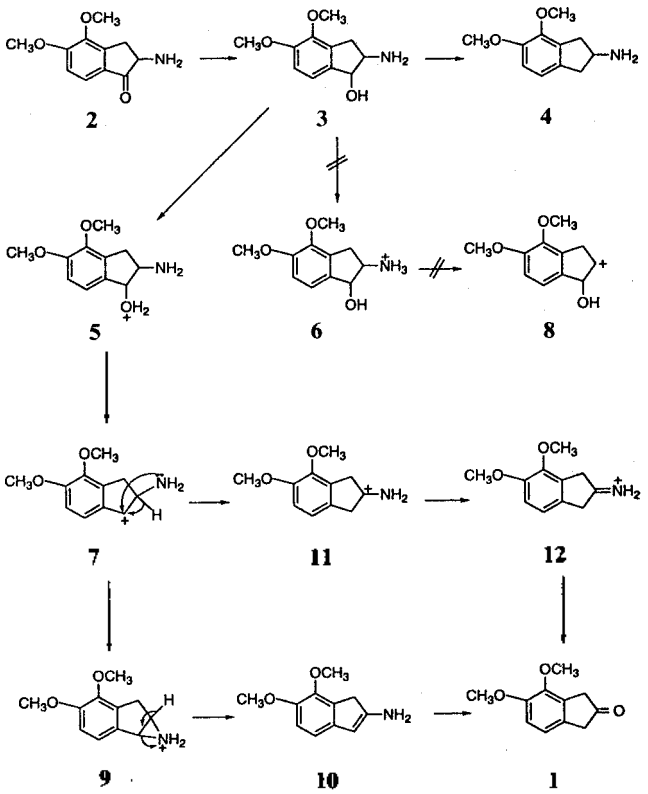
Illustrating the previously reported results,[1-3] in brief (scheme), the carbonyl group to the benzene ring of the aminoketone **2** was easily removed by the hydrogenolysis in the presence of 10% palladium on charcoa; the intermediate aminoalcohol, 2-amino-4,5-dimethoxy-1-indanol **3** was not isolated, but **3** was continously hydrogenated in the presence of $HClO_4$ in glacial acetic acid at 70 ℃ for 24 hours, to bring about hydrogenolysis of the benzylic hydroxyl group[4] directly to give 2-amino-4,5-dimethoxy-indane **4**. However, the catalytic reduction of **2** gave exclusively the desired reduction product **4** along with a small amount of a white solid, having a higher mobility than that of **4** on thin layer chromatogram. The white compound was thus believed to be a 4,5-dimethoxy-2-indanone **1** in view of the spectral characteristics (^1H and ^{13}C NMR, Mass, IR) and analytical data.[1,3]



Scheme 1. Plausible Mechanism for the Rearrangement Product Formation of Ketone **1** from the Aminoalcohol **3**.