Tetrahedron Letters,Vol.26,No.50,pp 6239-6242,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

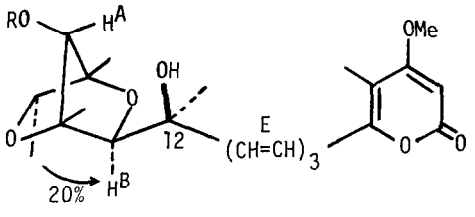
ISOLATION AND STEREOSTRUCTURES OF NEOCITREOVIRIDINOL AND EPINEOCITREOVIRIDINOL

Shigeru Nishiyama, Yoshikazu Shizuri, and Shosuke Yamamura*
Department of Chemistry, Faculty of Science and Technology, Keio University
Hiyoshi, Yokohama, Japan
Yukimasa Terada, Kazuaki Kawai, and Hideyuki Furukawa
Faculty of Pharmacy, Meijo University, Tempaku-ku, Nagoya, Japan

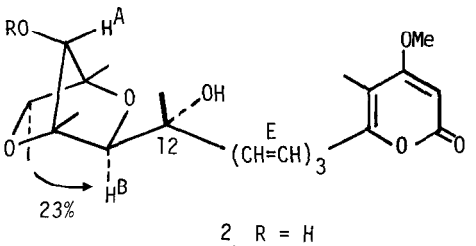
Summary: Both neocitreoviridinol and epineocitreoviridinol with a 2,5-dioxabicyclo[2.2.1]-heptane ring have been isolated as new metabolites of Penicillium citreo-viride B., and their stereostructures have also been elucidated on the basis of their spectral data coupled with molecular mechanics calculations. In addition, a promising synthetic intermediate for neocitreoviridinol has been made.

Of mycotoxins, citreoviridin[1] and verrucosidin[2] have a polysubstituted tetrahydrofuran ring in addition to a conjugated pyrone system, while aurovertin B[3] and citreoviridinol[4] contain a 2,6-dioxabicyclo[3.2.1]octane ring in their structures. In the present paper, we wish to describe the stereostructures of neocitreoviridinol (1) and epineocitreoviridinol (2) which have a new 2,5-dioxabicyclo[2.2.1]heptane ring. Furthermore, the 2,5-dioxabicyclo[2.2.1]-heptane has been made as a promising synthetic intermediate of 1.

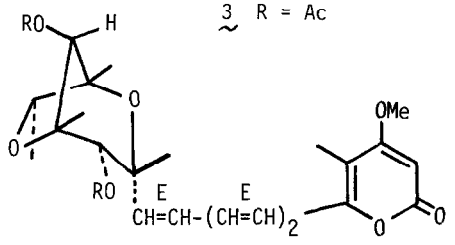
According to essentially the same procedure as described in the previous paper,[4] the AcOEt extract of the yellow rice was chromatographed on silica gel (Mallinckrodt, 100 mesh) using AcOEt and then further separated by repeating preparative TLC [Kieselgel PF_{254}; benzene - AcOEt (1 : 10)] to give both citreoviridinol and isocitreoviridinol from the relatively nonpolar fractions. From one of the more polar fractions, an inseparable mixture of neocitreoviridinol (1) and epineocitreoviridinol (2) was obtained in ca. 0.1% (relative ratio: 1/2 = 3/4). These two metabolites were characterized as the corresponding acetates (3 and 4), in pure state, which were quantitatively produced on acetylation with Ac_2O - pyridine (room temp., overnight) [3 as a syrup: $C_{25}H_{32}O_8$ (m/z 460.2105(M^+)); $[\alpha]_D^{30}$ +49° (c 0.11, $CHCl_3$); IR (film) 3450, 1730, 1700, 1620, 1575, and 1535 cm^{-1}; $\delta(CDCl_3)$ 1.18(3H, s), 1.20(3H, s), 1.22(3H, d, J= 6Hz), 1.33(3H, s), 1.95(3H, s), 2.12(3H, s), 3.70(1H, s), 3.80(3H, s), 4.07(1H, q, J= 6Hz), 5.20(1H, s), 5.47(1H, s), and 5.8 - 6.6(6H, complex). 4 as a syrup: $C_{25}H_{32}O_8$ (m/z 460.2096 (M^+)); $[\alpha]_D^{30}$ -57.4° (c 0.41, $CHCl_3$); IR (film) 3430, 1740, 1695, 1615, 1570, and 1535 cm^{-1}; $\delta(CDCl_3)$ 1.23(3H, d, J= 6Hz), 1.25(3H, s), 1.30(3H, s), 1.38(3H, s), 1.98(3H, s), 2.15(3H, s), 3.75(1H, s), 3.83(3H, s), 4.07(1H, q, J= 6Hz), 5.07(1H, s), 5.48(1H, s), and 5.9 - 6.6(6H, complex)]. On hydrolysis with K_2CO_3 in MeOH (0 °C, 2 h), the two acetates (3 and 4) were quantitatively reconverted to neocitreoviridinol (1) and epineocitreoviridinol (2) [1 as a



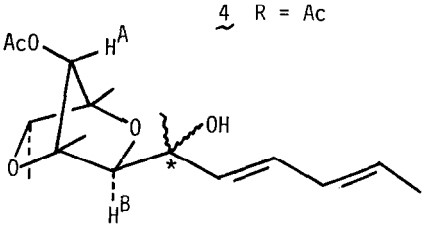
1 R = H
3 R = Ac



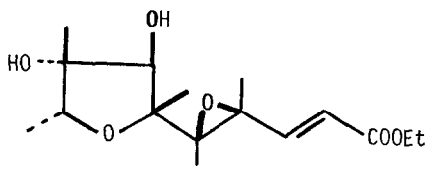
2 R = H
4 R = Ac



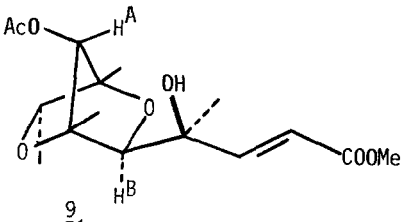
5 R = Ac
6 R = H



7a (S configuration)
7b (R configuration)



8



9

syrup: $C_{23}H_{30}O_7$ (m/z 418.1988(M^+)); IR (film) 3430, 1690br., 1615, 1600sh., 1570, and 1530 cm^{-1}. 2 as a syrup: $C_{23}H_{30}O_7$ (m/z 418.2018(M^+)); IR (film) 3430, 1690, 1615, 1600sh., 1570, and 1530 cm^{-1}],[5] respectively. The IR spectra of these metabolites (1 and 2) are almost identical to each other. Furthermore, the spectral data of the acetates (3 and 4) are quite similar to those of citreoviridinol diacetate (5)[4] except for some points. Particularly, all of them have the same conjugated pyrone system. In addition, the NMR signals assignable to the remaining moiety correspond to one another. However, as judged from the acetylation experiments, both 1 and 2 have two OH groups, one of which must be a tertiary one, while citreoviridinol (6)[4] has two secondary OH groups. In the light of the above facts together with co-occurrence of 6, some NOE experiments of the acetates (see 3 and 4)[6] indicate that the two newly isolated metabolites have such a structure as 1 except for their stereochemistry at C_{12}-position. Finally, the stereochemistry at C_{12}-position was determined by a combination of ^1H NMR spectral data with molecular mechanics calculations, as follows.

In comparison of the NMR spectra of the two acetates (3 and 4), the signal due to H^A in the former is observed in lower magnetic field as compared with that in 4 (3: δ5.20; 4: δ 5.07),[7] whereas the singlet due to H^B in 3 is found in slightly higher magnetic field (3: δ3.70; 4: δ3.75). Presumably, these differences are attributable to the stereochemistry at C_{12}-position. Thus, molecular mechanics calculations[8] of model compounds (7a and 7b) have

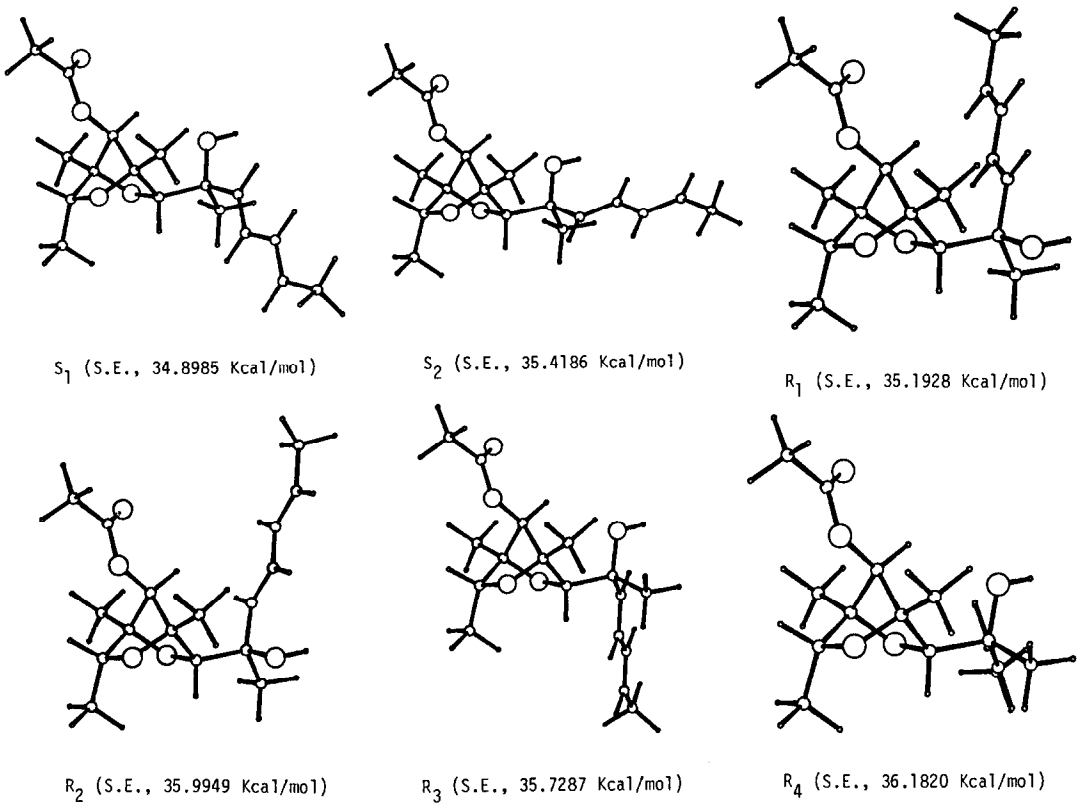


Fig. 1. The main stable conformations of 7a and 7b.
The relative ratio at 25 °C: S_1/S_2/others = 62.7 : 26.1 : 11.2 in 7a.
$R_1/R_2/R_3/R_4$/others = 50.5 : 13.0 : 20.4 : 9.5 : 6.6 in 7b.

been carried out, and the results are shown in Fig. 1. In the case of S configuration, 7a adopts two main conformations (S_1 and S_2), in which the the tertiary OH group is close to H^A. On the other hand, four conformers (R_1 - R_4) are mainly present in 7b with R configuration. Among them, The R_1 conformer occupies a half of total population. As judged from these data, neocitreoviridinol (1) and its epimer (2) adopt S and R configurations at C_{12}-position, respectively. This is also supported by the following chemical evidence: the epoxide (8), which was produced in 72% yield from the known synthetic intermediate of citreoviridin on mCPBA oxidation in CH_2Cl_2,[4] was readily converted into the corresponding 2,5-dioxabicyclo-[2.2.1]heptane (9),[9] in 3 steps [1) 0.5M NaOEt/EtOH (70 °C, 3 h); 2) excess MeI - K_2CO_3 (room temp., 2 h); 3) Ac_2O - pyridine (room temp., overnight) (71% overall yield)], which showed the same δ-value (5.20) due to H^A as observed in 3 (δ5.20). The bicyclic compound (9) is regarded as a synthetic intermediate for neocitreoviridinol (1).

The authors wish to thank Dr. S. Mihashi and Mr. S. Kosemura (Tobishi Pharmaceutical Co. Ltd.) for measurements of ^1H NMR (200 MHz) spectra. Calculations were performed at

Nagoya University Computation Center.

References and Notes

1. N. Sakabe, T. Goto, and Y. Hirata, Tetrahedron Lett., 1964, 1825; Tetrahedron, 33, 3077 (1977).
2. L. T. Burka, M. Ganguli, and B. J. Wilson, J. Chem. Soc., Chem. Commun., 1983, 544; M. Ganguli, L. T. Burka, and T. M. Harris, J. Org. Chem., 49, 3762 (1984).
3. L. J. Mulheirn, R. B. Beechey, and D. P. Leworthy, J. Chem. Soc., Chem. Commun., 1974, 874.
4. M. Niwa, T. Endo, S. Ogiso, H. Furukawa, and S. Yamamura, Chem. Lett., 1981, 1285: S. Nishiyama, Y. Shizuri, D. Imai, S. Yamamura, Y. Terada, M. Niwa, K. Kawai, and H. Furukawa, Tetrahedron Lett., 26, 3243 (1985).
5. On acetylation with Ac_2O - pyridine, both 1 and 2 were converted again to 3 and 4, respectively.
6. Any nuclear Overhauser effect was not observed between H^A and H^B.
7. The same differences are observed in the case of C_6D_6 as solvent.
8. Program MM2: N. L. Allinger, J. Am. Chem. Soc., 99, 8127 (1977); QCPE #395.
9. 9 as a colourless oil: $C_{16}H_{24}O_7$ [m/z 328.1518(M^+)]; IR (film) 3500, 1730, 1720, and 1650 cm^{-1}; δ($CDCl_3$) 1.17(3H, s), 1.22(3H, s), 1.23(3H, d, J= 6Hz), 1.36(3H, s), 2.13 (3H, s), 3.77(4H, s)*, 4.10(1H, q, J= 6Hz), 5.20(1H, s), 6.15(1H, d, J= 15Hz), and 7.00 (1H, d, J= 15Hz).
   * The signal due to H^B is overlapped with MeO signal.

(Received in Japan 12 October 1985)