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ISOLATION AND STRUCTURE OF CITREOTHIOLACTONE, A NOVEL METABOLITE OF PENICILLIUM CITREO-VIRIDE B.

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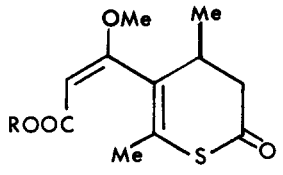
Summary: Citreothiolactone has been isolated from the mycelium of Penicillium citreo-viride B. and its structure also been elucidated on the basis of its spectral data coupled with some chemical evidence. Biogenetic relationship between citreothiolactone and citreopyrone is also presented.

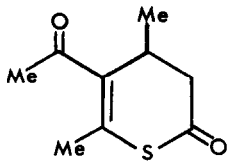
In connection with naturally occurring pyrones which are quite interesting from view points of their chemical reactivity as well as of biological activity, we have isolated three new metabolites from the mycelium of Penicillium citreo-viride B..[1,2] Further efforts have been made to find physiologically active substances, resulting in the isolation of a new metabolite, named citreothiolactone (1).

According to essentially the same procedure as described in the previous paper,[1] The AcOEt extract (9.97 g) of the yellow rice (300 g)[3] was roughly separated by column chromatography (Mallinckrodt 100 mesh, 200 g) using $CHCl_3$ and then 2% MeOH in $CHCl_3$ as eluant. After elution with $CHCl_3$,[4] further elution with 2% MeOH in $CHCl_3$ afforded a crude oil (251 mg) which was further separated by repeating preparative TLC (Kieselgel PF_{254}, 1) 5% MeOH in $CHCl_3$ 2) 8% MeOH in $CHCl_3$) to give citreothiolactone (41 mg) as needles: mp 154 - 156 °C (from ether); $C_{11}H_{14}O_4S$ [m/e 242(M^+)]; CD (MeOH) $[\theta]_{332}$ -1.1 x 10^3; IR (KBr) 3600 - 2500br., 1690sh., 1675sh., 1660, 1605 and 1570 cm^{-1}; ^1H NMR ($CDCl_3$) δ1.38 and 1.42(total 3H (relative ratio 1 : 1), each d, J= 7Hz), 2.02(3H, s), 2.4 - 2.9(2H, m), 3.3 - 3.8(1H, m), 3.72(3H, s) and 5.26(1H, s); ^{13}C NMR ($CDCl_3$) δ 19.7 and 19.9(each q), 21.6(q), 36.3(d), 44.7 and 45.3(each t), 56.1(q), 94.5(d), 156.0(s), 168.2 (s), 171.2(2 x s) and 191.2(s).

On the basis of elemental analysis, this compound has a molecular formula $C_{11}H_{14}O_4S$ or $C_{11}H_{14}O_6$. Of two possibilities, the former was confirmed by high resolution mass spectrum of its methyl ester (2), which was readily obtained on methylation with CH_2N_2 in ether [2 as a colorless oil: $C_{12}H_{16}O_4S$ (m/e 257.0766); IR (film) 1712, 1660, 1620 and 1565 cm^{-1}; ^1H NMR ($CDCl_3$) δ1.38 and 1.43(total 3H (relative ratio 1 : 1), each d, J= 6.5Hz), 2.02(3H, s), 2.5 - 3.0(2H, m), 3.61 (3H, s), 3.72(3H, s), 3.4 - 3.7(1H, overlapped with two MeO signals) and 5.30(1H, s)]. From the ^1H NMR spectra of both 1 and 2 (δ1.38 and 1.42 in 1; δ1.38 and 1.43 in 2) together with ^{13}C NMR signals at δ19.7, 19.9, 44.7 and 45.3 in 1, a sample of citreothiolactone or its methyl ester seems to be a mixture of two isomers. Actually, however, these signals are due to two atropisomers of 1 (or 2), as follows. In the variable temperature ^1H NMR spectrum of 2 at 70 °C, the two doublets at δ1.38 and 1.43 became a sharp doublet at δ1.41. Clearly, both 1 and 2 have a Me-$\overset{|}{C}$H-CH_2- grouping. Furthermore, citreothiolactone (1) has a MeO-$\overset{|}{C}$=CH-COOH grouping on



1 (R = H)
2 (R = Me)



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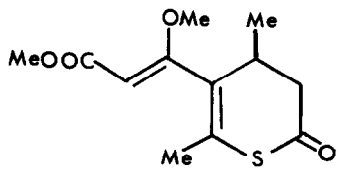

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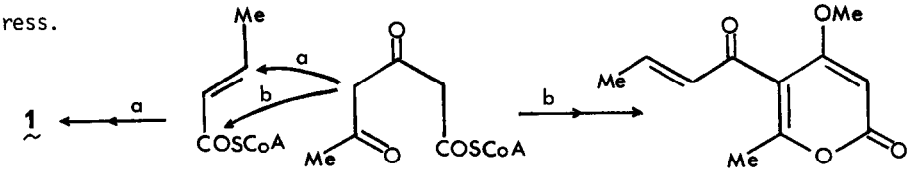
the basis of some chemical evidence. When treated with $AlCl_3$ in $CHCl_3$ (room temp., 8 h), citreothiolactone was readily converted into a methyl ketone (3)[5] via a β-keto carboxylic acid which was produced on demethylation. In the ^1H NMR spectrum of 3, there are two methyl singlets at δ 2.17 and 2.36, one of which is due to the newly formed CH_3CO group, in addition to a sharp doublet at δ 1.39.

From these data together with ^{13}C NMR spectrum of citreothiolactone, this compound is regarded as a thiolactone (δ 191.2; ν_{max} 1660 cm^{-1}) having a tetra-substituted double bond [δ 156.0 and 171.2 (or 168.2)], to which a methyl group (δ 2.02) must be attached. Thus, the most reasonable structure (1) must be given to citreothiolactone, by which two possible atropisomers can be explained well.[6] This result was further confirmed by the following spectral and chemical evidence.

When allowed to stand at room temperature for 2 months, the methyl ester (2) as an oil was spontaneously converted into a mixture of two isomers (2 and 4[7]; 2/4 = 4/1). The newly formed isomer (4) as an oil was also converted into 2 in ca. 33% yield (room temp., 2 months). In comparison of ^1H NMR spectra between 2 and 4, the former has the NMR signal due to an olefinic proton in lower magnetic field than that in 4 (δ 5.30 in 2; δ 4.84 in 4). Furthermore, low-intensity irradiation at δ 3.72 caused a 13% increase in the integrated intensity of the olefinic proton signal at δ 5.30 in 2, while any enhancement of the corresponding signal intensity at δ 4.84 was not detected in 4. Finally, it is noted that the trans isomer (4) is not present as two atropisomers, as judged from its ^1H NMR spectrum.

From a biogenetic point of view, both citreothiolactone (1) and citreopyrone (5)[1] may be produced from the common intermediate, as shown below. Biosynthetic study of these metabolites is in progress.



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References

1. M. Niwa, S. Ogiso, T. Endo, H. Furukawa, and S. Yamamura, Tetrahedron Lett., 21, 4481 (1980).
2. M. Niwa, T. Endo, S. Ogiso, H. Furukawa, and S. Yamamura, Chem. Lett., 1981, 1285.
3. Incubated stationarily at 24 °C for 23 days.
4. Citreopyrone (5) has been obtained from the $CHCl_3$ fraction.
5. 3 as a colorless oil: $C_9H_{12}O_2S$ (m/e 184.0555); IR (film) 1690, 1650 and 1550 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39(3H, d, J= 7Hz), 2.17(3H, s), 2.36(3H, s), 2.70(2H, m) and 3.4 - 3.7(1H, m).
6. In the case of another possibility, in which the secondary methyl group is attached to the α-position of the thiolactone CO group, two possible atropisomers must not be detected.
7. 4 as a colorless oil: $C_{12}H_{16}O_4S$ (m/e 256.0757); IR (film) 1720, 1695sh., 1655, 1625 and 1560 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40(3H, d, J= 6.5Hz), 2.19(3H, s), 2.54(1H, dd, J= 11, 16Hz), 2.85 (1H, dd, J= 4, 16Hz), 3.4 - 3.7(1H, overlapped with two MeO signals), 3.60(3H, s), 3.67(3H, s) and 4.84(1H, s).

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