Tetrahedron Letters No. 22, pp. 1955-1958, 1971. Pergamon Press. Printed in Great Britain.

Revised Structure and Stereochemistry of Coriolins

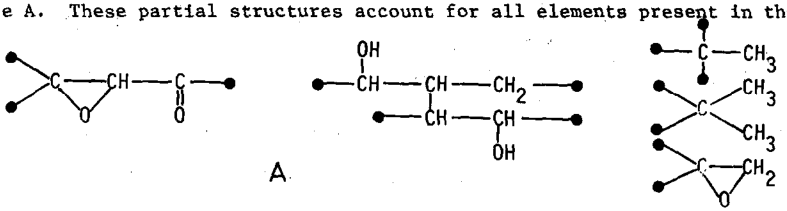
Shuji Takahashi, Hiroshi Naganawa, Hironobu Iinuma, Tomohisa Takita,
Kenji Maeda and Hamao Umezawa

Institute of Microbial Chemistry, Shinagawa-ku, Tokyo, Japan

(Received in Japan 1 April 1971; received in UK for publication 27 April 1971)

In the previous papers,[1,2)] we proposed the structures of coriolin, coriolin B and C based on spectroscopic analysis, biogenetic consideration and chemical transformations. We should revise these structures based on new evidences. In this paper we report the structures and stereochemistry as presented in I, II and III.

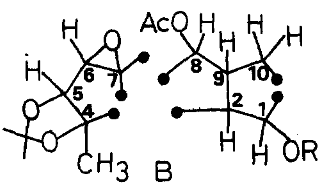
As already described,[1)] the NMR spectrum of coriolin suggested the presence of partial structure A. These partial structures account for all elements present in the molecule.



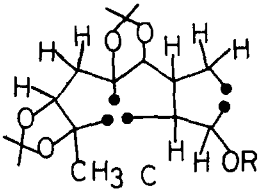
A

The former structures were deduced by biogenetic consideration, and spectroscopic analysis of hexahydrocoriolin and the tri-ketone derivative. The assignment of the IR absorption at 1782 cm^{-1} of the latter derivative (compound IV in the former report[1)]) to a cyclobutanone function led to these structures. In the further studies, it was found that the IR absorption at 1782 cm^{-1} came from a decomposed product which appeared in the course of the oxidation purposing to obtain the tri-ketone derivative.

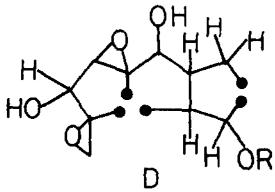
The new evidences are as follows. Reduction of coriolin, coriolin B and C with $LiAlH_4$ in tetrahydrofuran gave the same product, hexahydrocoriolin (IV).[2)] This indicates that coriolins have the same carbon skeleton and stereochemistry. Hydrogenation of coriolin B with PtO_2 in methanol gave dihydrocoriolin B (V) (m.p. 93-97°, $C_{23}H_{38}O_6$, m/e 410) and tetrahydrocoriolin B (VI) (m.p. 67-69°, $C_{23}H_{40}O_6$, m/e 412). The NMR spectrum of V in $CDCl_3$ solution revealed the presence of four tertiary methyl groups (a 3-H singlet at 1.05 δ and a 9-H singlet at 0.95δ) and an α-epoxy carbinol group [a pair of doublets (J=1.0 Hz) at 3.51 and 3.96δ, internal reference: TMS]. On treatment with p-toluenesulfonic acid in 2,2-dimethoxypropane, V afforded the mono-acetonide (VII) [m.p. 67-69°, $C_{26}H_{42}O_6$, m/e 450, $\nu_{max.}^{KBr}$ 3500 (OH), 1735 cm^{-1} (ester)]. These results suggest that V was derived by reductive ring-opening of the exocyclic ethylene oxide, yielding a tertiary methyl and a tertiary hydroxy groups. Acetylation of VII with acetic anhydride-pyridine gave the mono-acetate (VIII) (m.p. 92-94°, $C_{28}H_{44}O_7$, m/e 492, $\nu_{max.}^{KBr}$ 1745 (ester) no OH band). In the NMR spectrum of VIII, C_1-H (see partial structure B; R=$C_7H_{15}CO$) appeared at 5.26δ, which was coupled to C_2-H (2.37δ, J=6.5 Hz). C_2-H in turn was coupled to C_9-H (3.01δ, J=12.0 Hz). C_9-H was further coupled to C_8-H (4.92δ, J=6.3 Hz) and C_{10}-methylene (about 1.5δ). The characteristic NMR shift [3.92 δ ($C\underline{H}$-OH) $\longrightarrow$ 4.92 δ ($C\underline{H}OAc$)] of C_8-H confirmed the presence of acetoxy group at C_8. C_5-H (4.38δ) was coupled to C_6-H (3.39δ, 2.0 Hz). Then, the partial structure B was deduced for VIII.



B



C

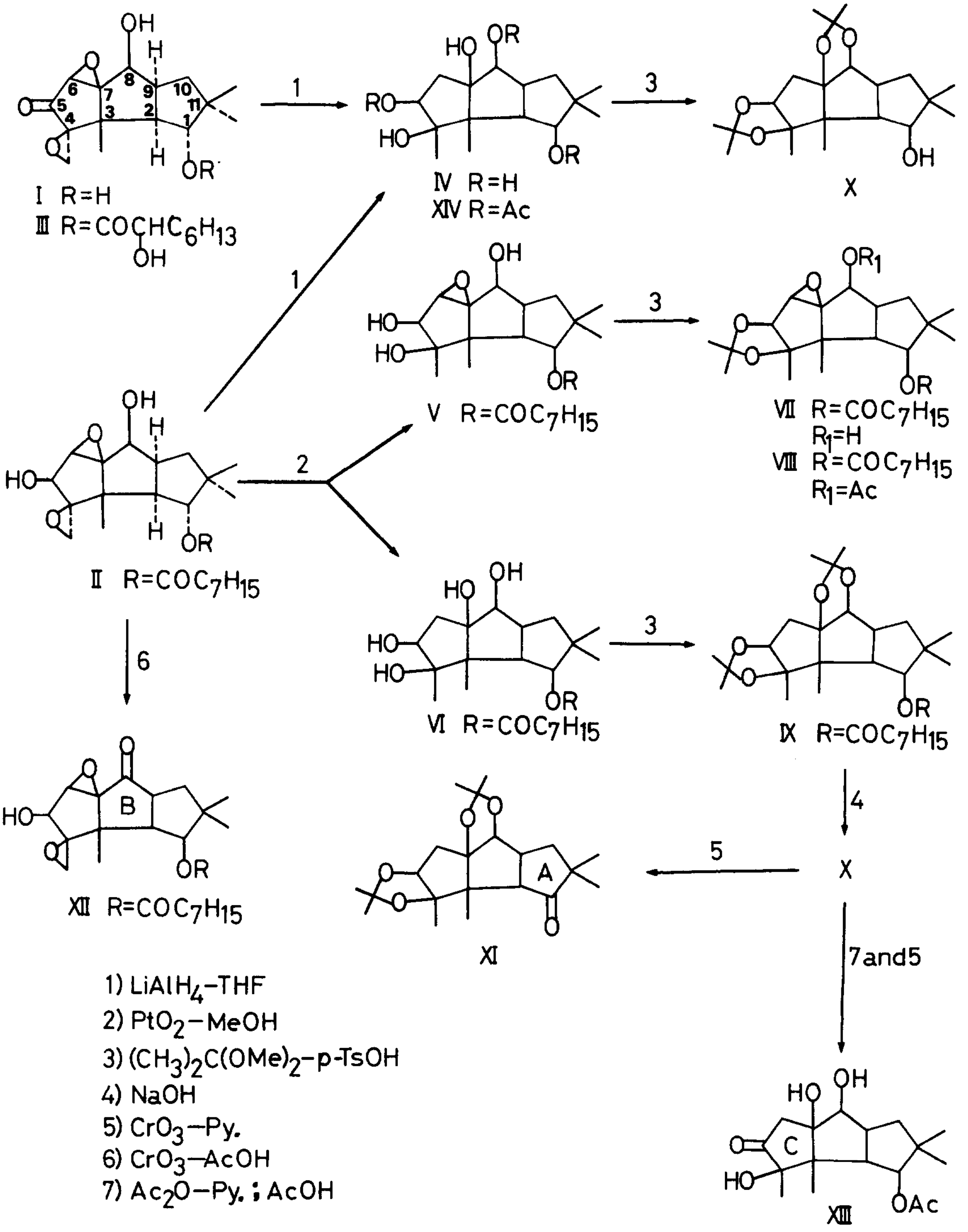


D

Treatment of VI with p-toluenesulfonic acid in 2,2-dimethoxypropane afforded the diacetonide (IX) [$\nu_{max.}^{liq.}$ 1740 cm^{-1} (ester), no OH band, m/e 492]. In the NMR of IX, C_5-H (4.28δ) appeared as triplet. On the other hand IV gave the other diacetonide (X) (m.p. 112-114°, $C_{21}H_{34}O_5$, m/e 366) by the same treatment, which was also derived from IX by alkali hydrolysis. These results led to the partial structure (depicted in C) of IX (R=$C_7H_{15}CO$) and X (R=H), and to the partial structure (D; R=$C_7H_{15}CO$) of II.

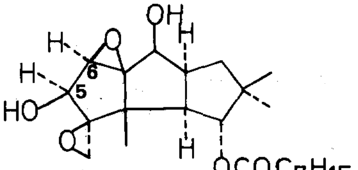
From the above-mentioned results, it is evident that coriolins have tricyclic carbon skeleton. The ring size was determined by IR absorption of the following three derivatives which had a keto-group on different ring respectively. XI (m.p. 128-130°, $C_{21}H_{32}O_5$, m/e 364, 1740 cm^{-1}), XII (m.p. 90-91°, $C_{23}H_{34}O_6$, m/e 406, 1753 cm^{-1}) and XIII (m.p. 199-200°, $C_{17}H_{26}O_6$, m/e 326, 1755 cm^{-1}). The IR absorptions indicated that all rings are five membered ring.

The hydroxy groups at C_4 and C_5, and C_7 and C_8 of IV must have cis-disposition, because the di-isopropyridene derivative (X) was obtained. The ring junction of ring A, B and C must be cis-anti-cis or cis-syn-cis configuration, because all rings are five-membered. The ring junction was studied by NMR analysis. We found that triacetyl hexahydrocoriolin (XIV) [m.p. 159-161°, $C_{21}H_{32}O_8$, m/e 352 (M^+ - 60)], derived from IV by acetylation, was one of the most adequate derivatives for this study. The NMR spectrum of XIV in D_6-benzene showed four tertiary methyl signals at 0.96, 1.21, 1.38 and 1.56δ. The long range coupling was observed between

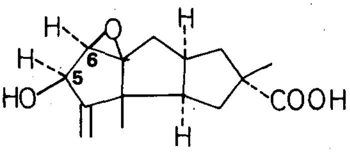


1) LiAlH$_4$–THF
2) PtO$_2$–MeOH
3) (CH$_3$)$_2$C(OMe)$_2$–p-TsOH
4) NaOH
5) CrO$_3$–Py.
6) CrO$_3$–AcOH
7) Ac$_2$O–Py. ; AcOH

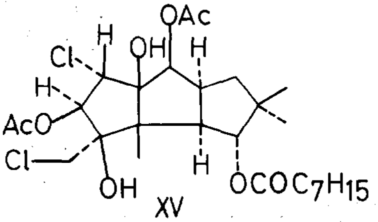
signals at 0.96 and 1.21δ. Therefore, these were assigned to the gem-dimethyl group. When II was reduced with $LiAlD_4$, the signal at 1.38 δ of XIV was broadened and diminished. Then, this signal was assigned to C_4-methyl, and the signal at 1.56δ as C_3-methyl. The nuclear Overhauser effect was observed between C_3-methyl and C_1-H (ca. 12% increase in the integrated intensity). This means that C_3-methyl and C_1-H present very near in the molecule, and indicates that the junction of ring A, B and C must be cis-anti-cis configuration.



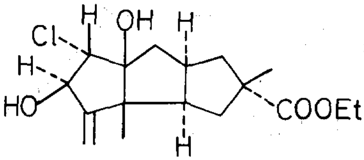
II



XVI



XV



XVII

The stereochemistry of C_5 and C_6 was assigned by comparative study of NMR spectra of coriolin B and hirsutic acid (XVI)[3] which has the same carbon skeleton. Coupling constant between C_5-H and C_6-H ($J_{5,6}$) of XVI is 2.0 Hz and $J_{5,6}$ of its chlorohydrin ethylester (XVII) is 9 Hz. On the other hand, $J_{5,6}$ of II was 1.5 Hz and $J_{5,6}$ of the di-chlorohydrin di-acetate (XV) (m.p. 107°, $C_{27}H_{42}O_8Cl_2$, m/e 564, 566 and 568), which was derived from II by hydrochlorination and acetylation, was 9 Hz. This suggests that C_5 and C_6 of coriolin B has the same stereochemistry as hirsutic acid.

From all of the above-mentioned results, the stereochemistry of coriolin, coriolin B and C was assigned to I, II and III, respectively.

References

1) S. Takahashi, H. Iinuma, T. Takita, K. Maeda and H. Umezawa, Tetrahedron Letters, 4663 (1969).

2) S. Takahashi, H. Iinuma, T. Takita, K. Maeda and H. Umezawa, ibid., 1637 (1970).

3) F. W. Comer, F. McCappa, H. Qureshi and A. I. Scott, Tetrahedron, 23, 4761 (1967).