Communications to the Editor

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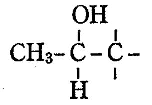
A Fungal Metabolite, Novel Isocyano Epoxide

The structure of a fungal metabolite isolated from *Trichoderma* sp. was determined.

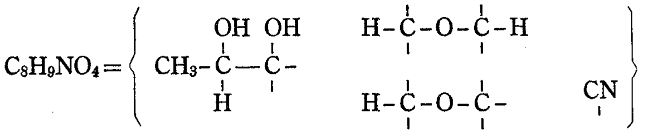
In continuing our studies on the search of biological active fungal metabolites, we have isolated a compound named 142B from the culture filtrate of *Trichoderma* sp. Compound 142B was purified on silica gel column, mp 102—104, $[\alpha]_D^{25}$ $-35.8°$ ($c=0.265$, CH_3OH). Correct analytical values for $C_8H_9O_4N$ were obtained.[1] These results and infrared (IR) spectrum showed that 142B is identical with trichoviridine.[2] 142B had IR absorption bands attributed to isocyano (or cyano, 2150 cm^{-1}) and hydroxyl(s) (3330 and 3510 cm^{-1}). Qualitative colour tests showed the absence of nitro, cyano, and carbonyls. The nuclear magnetic resonance (NMR) spectrum of 142B in D_2O and a monoacetate in $CDCl_3$ showed the presence of a partical structure,



$$CH_3-\overset{OH}{\underset{H}{C}}-\overset{|}{\underset{|}{C}}-$$

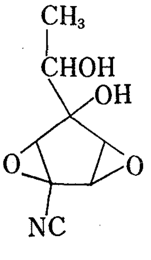
and an active hydrogen in the monoacetate, and three other hydrogens on carbons bearing oxygens.[3a]

142B consumed rapidly $NaIO_4$, showing the presence of vicinal diol.[3b] In an acidic condition, oxidation progressed further.[3c] These results gave the following partial structure for 142B.

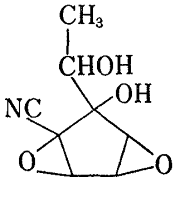


$$C_8H_9NO_4=\left\{ CH_3-\overset{OH}{\underset{H}{C}}-\overset{OH}{\underset{|}{C}}- \quad \begin{array}{c} H-\overset{|}{\underset{|}{C}}-O-\overset{|}{\underset{|}{C}}-H \\ H-\overset{|}{\underset{|}{C}}-O-\overset{|}{\underset{|}{C}}- \end{array} \quad \underset{|}{CN} \right\}$$

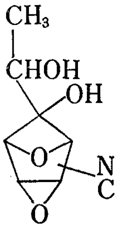
Among all the structures made by combinations of the unpaired bonds in the above partial structure,



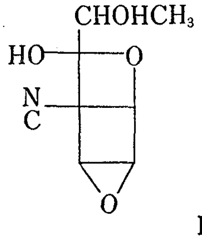
1a



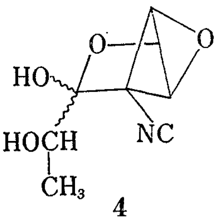
1b



2



3



4

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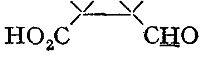
1) Mass spectrum did not give the molecular ion.

2) A. Tamura, H. Kotani, and S. Naruto *J. Antibiotics*. **28**, 161 (1975). Japan Pat. 45-15435 (1970).

3) *a)* Complex spin couplings of these three hydrogens were observed; *b)* When the reaction was monitored by NMR, the CH_3 signal of 142B disappeared. Instead, a broad absorption at δ 1.5—3 ppm appeared. *c)* The NMR spectrum of the final reaction solution showed only two absorptions at δ *ca.* 3.8 and 8.1, both as sharp singlets. Any oxidation products formed from structures **1b**—**4**, can not give such an NMR spectrum. Only the oxidation poduct from **1a**, probably



$$\underset{HO_2C}{\overset{H}{>}}\!\overset{O}{\triangle}\!\underset{CHO}{\overset{NC}{<}}$$

, explains the spectrum.

only **1a**,**1b**, **2**, **3** and **4** are the chemically possible structures.[3] However, we had no concluding evidence, and no chemical and spectroscopic information on the stereochemistry and absolute configuration, and therefore three dimensional X-ray crystallographic analysis has been carried out.

The crystals are monoclinic, space group $P2_1$, with lattice constants $a=10.712$ (5), $b=7.244$ (4), $c=5.545$ (3) Å, $\beta=90.51$, $Z=2$. The intensity data were collected on a Philips PW-1100 automatic diffractometer with monochromated by (a graphite monochromater) Cu $K\alpha$ radiation out to $2\theta=156°$. A total of 932 non-zero independent reflections were used in the structure determination. The structure was solved by the direct method and refined by several cycles of block-diagonal least-squares calculations. The final R-factor was 0.038 assuming anisotropic thermal motions for non-hydrogen atoms.

The assignment of nitrogen atom in the isonitrile group was made by comparing the temperature factors of N and C (8). This was further confirmed by the least-squares refinement in which a nitrile group was assumed in place of the isonitrile group. In this case, the structure could not be refined beyond $R=0.053$.

The absolute configuration was determined using the anomalous dispersion effect of the oxygen atoms. Two sets of least-squares refinement in which the imaginary term of the oxygen scattering factor ($\Delta f''=0.1$) was taken as $-\Delta f''$ and $+\Delta f''$, resulted in an R-factor of 0.0379 for the configuration shown in Fig. 1 and 0.0384 for the mirror image. This was further confirmed by comparing the observed ratio of each $|F(hkl)|^2/|F(\bar{h}\bar{k}\bar{l})|^2$ with the calculated one. Among the twenty pairs, of which both the ratios deviate more than 5% from unity and the observed $|F(hkl)|$' s greater than 2.0, fifteen pairs supported the above conclusion. An ORTEP drawing of the molecule is shown in Fig. 1, which also represents the absolute configuration.

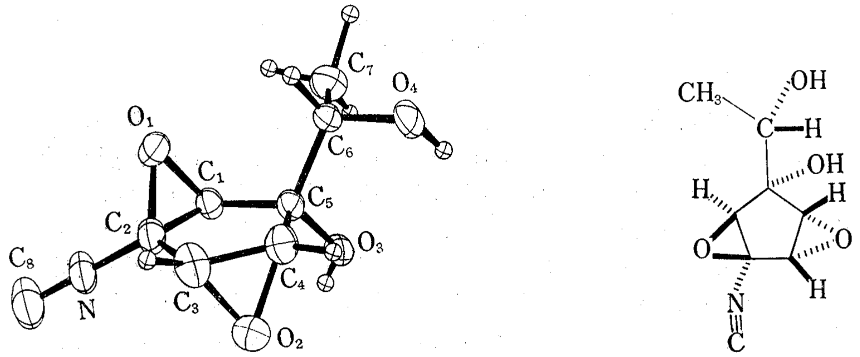


Fig. 1. Computer generated drawing and the chemical structure of 142 B (Trichoviridine). The absolute configuration is implied.

The chemical structure thus determined is a cyclopentane derivative having two epoxides on a ring.[4] The cyclopentane ring is very plane and the three hydrogens on carbons 1, 2, and 4 are in a favorable configuration for the long-length spin-coupling[3,4] The existence of the isonitrile group in natural products is a quite rare example and has been observed only in marine sponges[5] and a metabolite from *Penicillium notatum*[6] so far.

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4) *cis*-Diepoxycyclopentanes are known: W.R. Adams and D.J. Toecker *Tetrahedron*, **27**, 2631 (1971); G. Young, H.K. Hall, and S. Winstein *J. Am. Chem. Soc.*, **78**, 4338 (1956); B. Tolbert, R. Steyn, J.A. Franks, and H.Z. Sable, *Carbohyd. Res.*, **5**, 62 (1962).

5) F. Cafieri, E. Faitorusso, S. Magno, C. Sartacroce, and D. Sica, *Tetrahedron*, **29**, 4259 (1973); L. Minale, R. Riccio, and G. Sodano, *Tetrahedron*, **30**, 1341 (1974); B.J. Burreson, P.J. Scheuer, J. Finer, and J. Clardy, *J. Am. Chem. Soc.*, **97**, 4763 (1975).

6) I. Hagedorn and H. Tonjes., *Pharmazie*, **12**, 567 (1957).

Isocyano-epoxide may be the organic functional moiety reported for the first time in organic chemistry as far as we know. Concerning biogenetic problem, we can see some relation to pentenomycins[7] and crotoepoxide.[8]

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[7] T. Date, K. Aoe, K. Kotera, and K. Umino, *Chem. Pharm. Bull.* (Tokyo), **22**, 1963 (1974).
[8] S.M. Kupchan, R.J. Hemingway, P. Coggon, A.T. McPhail, and G.A. Sim, *J. Am. Chem. Soc.*, **90**, 2982 (1968).

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Acid-Catalyzed Methanolysis of optically Active N-Cyclohexyl Methylphenylphosphinamide——A Stereochemical Evidence for A-2 Mechanism——

A stereochemical study of the acid-catalyzed methanolysis of N-cyclohexyl methylphenylphosphinamide shows that the reaction proceeds by almost pure A-2 mechanism irrespective of the acidity of the reaction medium.

One of the authors (T. K) previously suggested[1] that the acid-catalyzed hydrolysis of phosphinamides proceeds by a continuous spectrum of mechanisms ranging from direct nucleophilic substitution (A-2) mechanism to unimolecular dissociation (A-1) mechanism and the degree of blending of the two extremes depends on the nucleophilicity of the leaving groups and the substituents at phosphorus. Our recent finding[2] that the acid-catalyzed methanolysis of optically active methylphenylphosphinanilide (**1**) proceeds by the acidity dependent merged A-1 and A-2 mechanisms strongly supported the above concept from the stereochemical point of view. However, the lack of the stereochemical evidences for the existence of the two extreme cases (pure A-1 or pure A-2) still leaves the concept rather ambiguous, though there have been recent papers[3] suggesting A-2 mechanism from kinetic data only.

We would report here our result on the acid-catalyzed methanolysis of (+)-N-cyclohexyl methylphenylphosphinamide (**2**), which clearly indicates that the almost pure A-2 mechanism is operative in this case irrespective of the change of the acidity of the medium.

(S)-Menthyl methylphenylphosphinate prepared by the Nudelman's procedure[4] was treated with lithium salt of cyclohexylamine in benzene to yield N-cyclohexyl methylphenylphosphinamide (**2**) (mp 117.0—118.5° $[\alpha]_D=53.0°$ (MeOH)[5]). The optical purity of **2** is considered

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[1] T. Koizumi and P. Haake, *J. Am. Chem. Soc.*, **95**, 8073 (1973).
[2] T. Koizumi, Y. Kobayashi, and E. Yoshii, *J. Chem. Soc. Chem. Comm.*, **1974**, 678.
[3] M.J.P. Harger, A.J. Macpherson, and D. Pickering, *Tetrahedron Letters*, **1975**, 1797; M.J.P. Harger, *J. Chem. Soc. Chem. Comm.*, **1973**, 774.
[4] A. Nudelman and D.J. Cram, *J. Org. Chem.*, **36**, 335 (1971).
[5] All compounds listed in this paper gave satisfactory elemental analysis and spectral data. Optical rotations were measured on a JASCO DIP-4 Automatic polarimeter and refer to solvent MeOH.