Tetrahedron Letters No. 12, pp 1185 - 1188, 1972. Pergamon Press. Printed in Great Britain.

# IKARUGAMYCIN. II. STRUCTURE OF IKARUGAMYCIN

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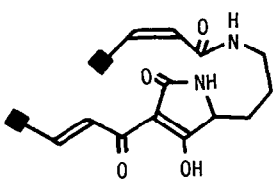
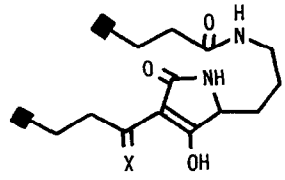
(Received in Japan 3 February 1972; received in UK for publication 16 February 1972)

In the preceding paper, we have revealed the partial structure I for an antibiotic, ikarugamycin (1).[1] We wish to report here the structure of the antibiotic on the basis of the following evidences.

Ikarugamycin (1) ($C_{29}H_{38}O_4N_2$) contains the functional groups shown in the partial structure I and an additional isolated double bond, indicating 1 to be a pentacyclic compound.




1(I)




2: X=O

3: $X=H_2$

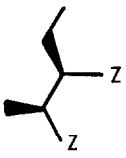
On alkaline hydrolysis of hexahydroikarugamycin (2)[1] (NaOH in $HOCH_2CH_2OH$-$H_2O$, 100°, 20 hr), the cleavage of an amido group and β-tricarbonyl system occurred to give a tricyclic dicarboxylic acid which was isolated as the dimethyl ester 4 [$C_{20}H_{34}(COOMe)_2$; m/e 392*[2]($M^+$)]. The same treatment of 1 yielded a hardly separable mixture of two isomeric diesters, 5a and 5b [$C_{20}H_{28}(COOMe)_2$; m/e 386*($M^+$); $\nu_{max}(CCl_4)$ 1732 and 1657 $cm^{-1}$; $\lambda_{max}$(MeOH) 225 nm (ε ca. 13,500) in 5a; $\nu_{max}(CCl_4)$ 1748, 1734, and 1658 $cm^{-1}$; $\lambda_{max}$(MeOH) 223 nm (ε ca. 8,800) in 5b]. The formation of the latter was probably due to partial deconjugation of one of the two conjugated double bonds shown in I. The mixture was directly used for catalytic hydrogenation giving only 4. The formations of these tricyclic diesters (5a and 5b from 1 and 4 from 2) indicate that ikarugamycin (1) contains the partial structure I as a part of a large-membered ring in 1.

Subsequent treatments of the mixture (5a and 5b) with $O_3$, $HCO_3H$, and then $CH_2N_2$ afforded two

bicyclic tetraesters, 6 [$C_{14}H_{22}(COOMe)_4$; m/e 426*($M^+$)] and 7 [$C_{13}H_{20}(COOMe)_4$; m/e 412 ($M^+$)], while the similar treatments of 1 yielded the compound 6 only. These facts can be explained by the presence of at least one methylene group adjacent to -CH=CH-CO- group in 1.

Structure of a carbocyclic part of ikarugamycin (1) was elucidated by the rather vigorous oxidations of 1 and its derivatives (2 and 3) as shown below.

Oxidation of 1 with $KMnO_4$ in pyridine-$H_2O$ (50°, 5 hr), followed by esterification of the resulting acids with $CH_2N_2$, afforded several methyl esters, 8,[3] 9,[3] 10, 11, 7, and 6 (Z=COOMe in all cases). In particular, the diester 10 has the following spectroscopic properties: $\nu_{max}$ ($CCl_4$) 1738 $cm^{-1}$; m/e 228 ($M^+$), 168 ($M^+$-HCOOMe), and 109 ($M^+$-HCOOMe-COOMe); $\delta_{ppm}$($CCl_4$) 0.85(3H, d, J=7.5Hz)($CH_3$CH-), 0.89(3H, t, J=6.7Hz)($CH_3$-$CH_2$-), 1.2∿1.7(3H, m), 1.8∿2.4(3H, m), 2.79(1H, t, J=8.0Hz)(-CH-COOMe), 3.09(1H, ddd, J=8.5, 8.0, 7.5Hz)(-CH-COOMe), 3.63(3H, s)(-COOMe), and 3.64 (3H, s)(-COOMe). Irradiation at 3.09 caused the triplet at 2.79 to collapse to a doublet (J=8.0 Hz), which indicated that the two carbomethoxy groups should be in a 1,2-relationship. From these data and the formation of 9, the structure of the diester can be represented by 10. Furthermore, the mass spectrum of the triester 11 [m/e 314*($M^+$), 169*(cleavage of α-β bond), 146 (McLafferty rearrangement, cleavage of α-β bond), and 109 (169-HCOOMe)] showed 11 to be represented by 11a or 11b.

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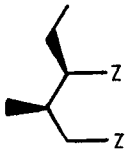


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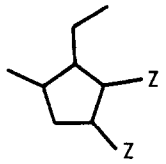


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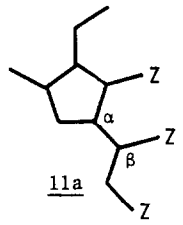
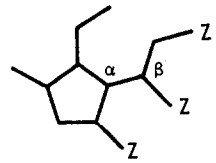
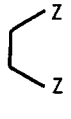



11a




11b

Oxidation of 1 with $CrO_3$ in 6N $H_2SO_4$ (80°, 14 hr), followed by esterification with $CH_2N_2$, afforded methyl esters, 12,[3] 8, 9, 10, 11, 13,[3] 14 [m/e 302*($M^+$)],[3] and 15 [m/e 316*($M^+$)].[4]

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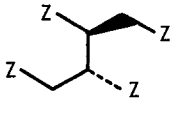


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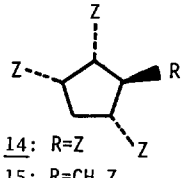
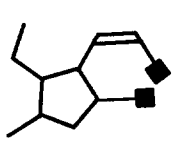


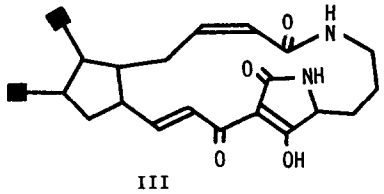

14: R=Z
15: R=$CH_2Z$

The formation of 11 and 15 from 1 can lead to the following four tentative structures (6a∿6d) for the tetraester 6 (7a and 7b for 7). In fact, treatment of 6 with NaOMe-MeOD yielded the

formation of 15 coupled with the structural relationships not only among 13, 21, and 23, but also between 17 and 22, the partial structure I can be extended to III.

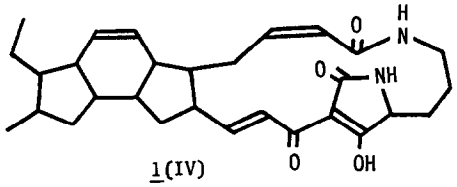


II




III

Since the partial structure III is incompatible with 6b, the structure 6a is the only possible one for the tetraester 6. From the combination of II, III, and 6a, the full structure of ikarugamycin (1) can be deduced as IV. The structure IV can account for the formations of all the oxidation products described herein and the spectroscopic properties of 1.[1] Studies on the stereochemistry of ikarugamycin (1) are in progress.




1(IV)

Acknowledgments

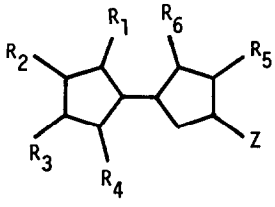
We thank the Fujisawa pharmaceutical company for the gift of ikarugamycin and Mr.T.Kondo (Dept. of Agr. Chem., Nagoya Univ.) for the measurements of NMR (100MHz) spectra.

## REFERENCE AND FOOTNOTES

1. S.Ito and Y.Hirata, Tetrahedron Letters, this issue.

2. The compositions of all asterisk-peaks were secured by high resolution mass spectrometry.
3. These esters were identical with the corresponding authentic specimens (IR, mass, and NMR spectra and GLC).
4. The structures of these new esters were suggested by their spectral data, especially mass and NMR spectra, and finally confirmed by the direct comparisons with the synthetic samples (IR, mass, and NMR spectra and GLC).
5. These structures were further supported by their syntheses: although the synthetic esters were inseparable mixtures of diastereomers, both natural and synthetic esters have the same behaviors on GLC and TLC. Furthermore, their mass spectra are superimpossable to each other. The preparation of these esters (15, 18, 19, 20, 21, and 23) will be reported in near future.

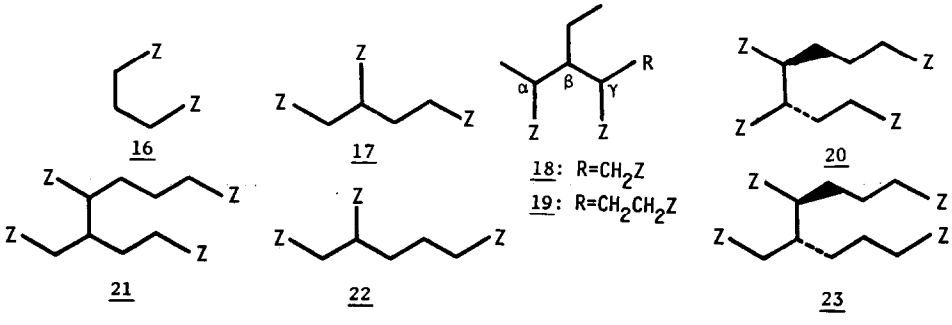
corresponding $d_5$-derivative.



| | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ |
|---|---|---|---|---|---|---|
| 6a | Z | Et | Me | H | $CH_2Z$ | Z |
| 6b | Z | Et | Me | H | Z | $CH_2Z$ |
| 6c | Et | Me | H | Z | $CH_2Z$ | Z |
| 6d | Et | Me | H | Z | Z | $CH_2Z$ |
| 7a | Z | Et | Me | H | Z | Z |
| 7b | Et | Me | H | Z | Z | Z |

On the other hand, chromic acid oxidation of hexahydroikarugamycin (2)[1] (in 6N $H_2SO_4$, 80°, 8 hr) gave many kinds of acids, which on esterification with $CH_2N_2$ yielded methyl esters, 12, 16,[3] 9, 10, 17,[3] 18, 19, 20, and 21. The structures of 18[5] and 19[5] were deduced by the following spectral data: 18 [$\nu_{max}(CCl_4)$ 1746 $cm^{-1}$; m/e 243*($M^+$-OMe), 187*(cleavage of α-β bond), 146 (McLafferty rearrangement, cleavage of β-γ bond), and 129 (cleavage of β-γ bond); $\delta_{ppm}(CCl_4)$ 0.88(3H, t, J=7.0Hz), 1.20(3H, d, J=7.0Hz), 3.69(3H, s), 3.71(3H, s), and 3.73(3H, s)]; 19 [$\nu_{max}$ ($CCl_4$) 1746 $cm^{-1}$; m/e 257*($M^+$), 201*(cleavage of α-β bond), 160*(McLafferty rearrangement, cleavage of β-γ bond), and 129 (cleavage of β-γ bond); $\delta_{ppm}(CCl_4)$ 0.89(3H, t, J=7.6Hz), 1.18(3H, d, J=7.2Hz), 3.68(6H, s), and 3.70(3H, s)]. Furthermore, the structure of 21[5] was determined by the following spectral data coupled with the formation of 17 and 20 from the same compound: m/e 315*($M^+$-OMe) and 174*(McLafferty rearrangement); $\delta_{ppm}(CCl_4)$ 1.1∿2.7(14H, m), 3.62(9H, s), and 3.66(3H, s).

In the case of deoxyoctahydroikarugamycin (3),[1] the above esters (12, 16, 9, 10, 17, 18, 19, 20, and 21) were also obtained. In addition, we could obtain two expected esters, 22[3] and 23 [m/e 329*($M^+$)],[4] which were homologues of 17 and 21, respectively.




The formation of 10 and 19 from 2 indicates the presence of the partial structure II in 1. This excludes the possible structure 11b for the triester 11. Accordingly, the two tentative structures 6c and 6d for the tetraester 6 (7b for 7) were also discarded. In the light of the