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THE STRUCTURE OF TELEOCIDIN B

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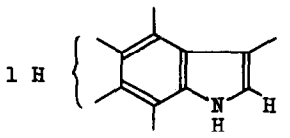
Teleocidin B (I), isolated from mycelia of several strains of Streptomyces (1,2), has a strong irritating action and causes severe eruptive vesications on human skin. It also shows a highly potent toxicity against aquatic animals. Since 1962 no chemical investigations have been reported, for teleocidin B and its derivatives must be handled only with extreme caution. We have re-examined the isolation and the characterization of this substance, and extended further the structure elucidation studies. The present paper mainly describes the evidences for the structure of a derivative, dihydro-teleocidin B (II).

Teleocidin B itself forms light brown powder (m.p. 135°, with decomposition) even by the purification with counter-current distribution, and several attempts to crystallize it were failed. This powdered material, however, rapidly absorbed one equivalent mole of hydrogen under the presence of platinum catalyst to afford crystalline dihydro-teleocidin B (II), $C_{28}H_{43}O_2N_3 \cdot H_2O$, m.p. 168°.

The molecular formula was confirmed by the mass spectral measurement (M^+: m/e 453). The IR spectrum of II suggests the following functional groups: ν_{max}^{KBr} 3600-3200 cm^{-1} (OH and NH), 1630 (-CONH-), 1598, 1555, and 1503 (aromatic ring), and 1060 (OH). A characteristic UV spectrum (λ_{max}^{EtOH} 232 mμ (log ε 4.53) and 287 mμ (3.98), with inflections at 276 and 297 mμ) shows the presence of a substituted indole chromophore (3), which was supported by the NMR data: 9.6 ppm (1H), 7.0 (1H), and 6.6 (1H)(in deuterated acetone)(4,5,6). Existence of an N-CH_3 group was also evident (2.9 ppm, 3H, singlet).

On treatment with dilute hydrochloric acid in alcohol, the hydrolysis of the amide group (lactam ring) of II took place, and there was obtained dihydro-teleocidin B amine (III), $C_{28}H_{43}O_2N_3$, m.p. 207 - 209°, pKa' 8.2 (-NH_2) in 50 % methanol. The amine III exhibited no hydroxyl absorption and its pKa' value showed the absence of a free carboxyl group. The produced carboxyl function, therefore, should re-cyclize to form a six-membered or larger lactone ring (IR: 1715 cm^{-1}). This amino-lactone (III) was easily re-converted into the hydroxy-lactam (II) with base, indicating that a skeletal rearrangement had not occurred during this hydrolytic isomerization. In the NMR spectrum, three protons of the indole ring (partial structure A) appeared at 8.3 ppm (1H), 7.1 (1H), and 6.9 (1H)(7,8), and the N-CH_3 group at 2.9 ppm (3H, singlet)(in $CDCl_3$).

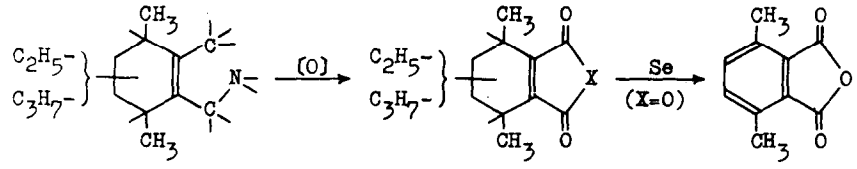


Partial Structure A

Oxidation of II or III under various conditions (2) gave two products: teleocidic anhydride (IV), $C_{15}H_{22}O_3$, m.p. 61 - 64°, and teleocidimide (V), $C_{15}H_{23}O_2N$, m.p. 118 - 119°. From the IR (1840, 1762, and 1635 cm^{-1}) and UV (λ_{max}^{EtOH} 258 mμ, log ε 3.85) of IV, a di-substituted maleic anhydride structure was assigned. The carbon skeleton was furnished from the fact that 3,6-dimethylphthalic anhydride was obtained by the selenium dehydrogenation. Thus, the structure of IV may be formulated as a substituted 3,6-dimethyl-1-cyclohexene-1,2-dicarboxylic acid anhydride.

The nature of the remained C_5-side chain has not been established from chemical degradations. However, in the mass spectrum of IV, a moderately intense peak at m/e 221 (M-29), as well as two strong peaks at m/e 208 (M-42) and 179 (M-42-29), was observed. The one-step fragmentation from the M-42 ion to the M-42-29 ion was confirmed by a prominent metastable ion peak at m/e 154.0. These results are accounted for only by assuming that the C_5-side chain contains a C_2H_5 group (29 mass units).

Conversion of teleocidic anhydride (IV) into teleocidimide (V) with methanolic ammonia indicates the latter being as an imide counterpart of the former. Teleocidimide (V) was also obtained even under the oxidation condition where the N-CH_3 group would not be attacked.

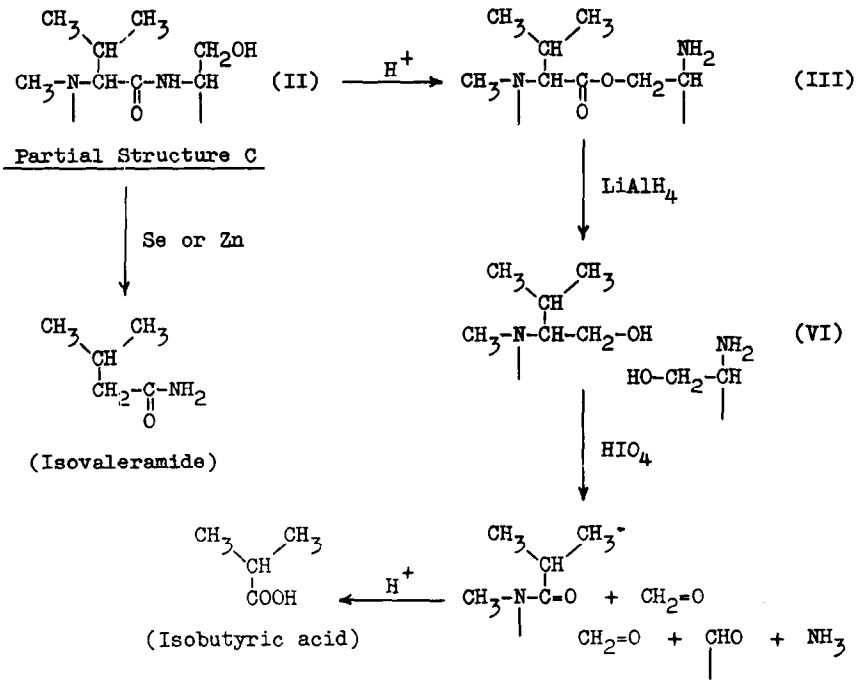


Partial Structure B

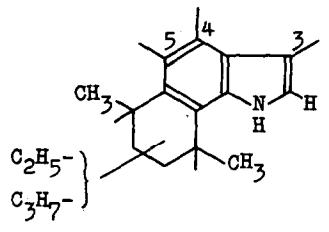
IV: X = O

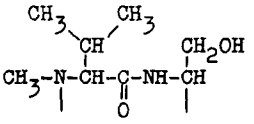
V: X = NH

Reduction of dihydro-teleocidin B amine (III) with lithium aluminum hydride yielded an amino-diol derivative (VI). The UV spectrum shows the indole chromophore remains intact. This amino-diol (VI) consumed two moles of periodic acid and afforded ammonia and two moles of formaldehyde, the latter being identified as its dimedone derivative. Isobutyric acid was also detected after the acid hydrolysis of the periodate oxidation mixture. These results are accommodated to the partial structures and the reaction sequence shown below. This structural unit for the lactam bridge was also supported by the fact that selenium dehydrogenation or zinc dust distillation of II gave isovaleramide.



In the partial structures A, B, and C above for dihydroteleocidin B (II), we have three carbon atoms and one nitrogen atom more than those actually involved in II. It is immediately obvious that the structures A and B should have these dupulicate atoms since neither carbon nor nitrogen atom in A and C can overlap each other. Any other combinations are easily excluded from the available data. The structure of II is, therefore, represented as D.



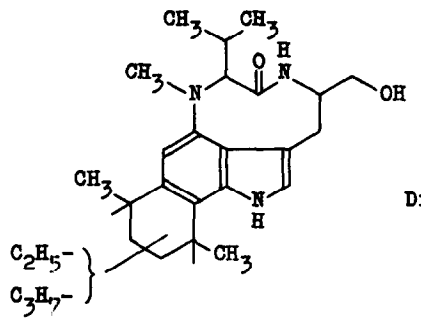


-H (aromatic, at C_4 or C_5)

$-CH_2-$

Partial Structure D

That the benzene ring of II is very much susceptible to oxidations may probably be due to the presence of a hetero-atom substituent (nitrogen atom, in this case) on the indole nucleus. The enhancement of absorption intensity for indole ring vibrations in the IR spectra (1598, 1555, 1503 cm^{-1} in II, and 1597, 1545, 1500 cm^{-1} in III) would also be ascribable to the hetro-atom substitution (9). In fact, the UV spectrum of II agrees well with those of 4-amino or 5-amino indole derivatives (10,11,12). On the other hand, examination of molecular models and bond length calculations show that the ring formation between C_3 and C_5 with the lactam bridge is sterically impossible. Thus, the following structure remains as the most probable formulation of dihydroteleocidin B (II).



Dihydro-teleocidin B (II)

Since the UV spectrum of teleocidin B (I) is superimposable on that of the above dihydro derivative (II), it is clear that the catalytic hydrogenation of I would proceed on a double bond of a side chain. The IR absorptions at 978 and 910 cm^{-1}, presumably originated from a mono-substituted double bond (vinyl group), disappeared on the reduction, and this observation further suggests the structural correlation between I and II ($-CH=CH_2 \longrightarrow -CH_2CH_3$). However, the assignment is still tentative and the rigorous structure proof of I will be dealt with in a future publication. The more detailed discussions of the present results are reported elsewhere (13).

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