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TOTAL SYNTHESIS OF dl-PUMILIOTOXIN C HYDROCHLORIDE AND ITS CRYSTAL STRUCTURE

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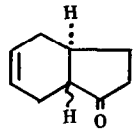
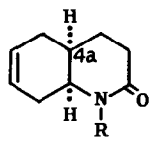
Pumiliotoxin C, a novel toxic cis-decahydroquinoline alkaloid, was isolated from the skin extract of Dendrobates pumilio, a strikingly colored Panamanian frog, and the complete constitution of the base except for the absolute configuration was established by a single crystal x-ray analysis of the base hydrochloride.[1] This communication concerns with the total synthesis of dl-pumiliotoxin C hydrochloride and its crystal structure.*1

A mixture of cis- and trans-tetrahydro-1-indanone (I)[2] in the ratio 9:1 was condensed with hydroxylamine and subsequent treatment with p-TsCl yielded the cis-octahydroquinolone (II)*2, m.p. 113°, and the trans-compound (IV)*2, m.p. 165-167°, in 53 and 6% yields, respectively. Oxidation of the N-benzyl compound (III), prepared from II, with m-chloroperbenzoic acid afforded the epoxy-lactam (V), m.p. 98°, in a 84% yield. The bromohydrin (VI), formed in a high yield by treatment of V with 48% HBr, was oxidized with Jones' reagent to give the bromo-ketone (VII), ν: 1724 (ketone); 1632 (lactam), in a 99% yield. Dehydrobromination of the bromo-ketone (VII) in DMF with LiBr-Li_2CO_3 afforded the α,β-unsaturated ketone (VIII) in a 43% yield, m.p. 133-134°, ν: 1680 (α,β-unsat. ketone); 1635 (lactam), δ: 6.86 (1H, dd, J=10.0, 6.0 Hz, C_5-H); 5.97 (1H, d, J=10.0 Hz, C_6-H), without epimerization at the C_{4a}-center.

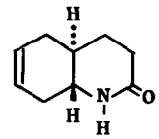
The stereoselective conjugate addition of lithium dimethylcopper[3] to the compound (VIII) cleanly afforded the methyl ketone (IX)*3, δ: 0.92 (3H, d, J=7 Hz, C_5-CH_3), in greater than 86% yield as a sole product. The thioacetal (X), derived from IX, was reduced with Raney W-2 nickel to afford the N-benzylquinolone (XI) in a 82% yield. Reductive debenzylation[4] of XI gave 5-methylquinolone (XII), m.p. 152°, in a 71% yield, and subsequent treatment of XII with P_2S_5 afforded the thiolactam (XIII), m.p. 130°, in a 79% yield.



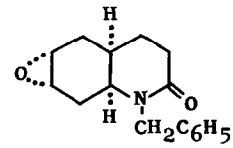
(I)



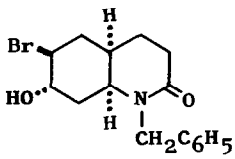
(II) R=H
(III) R=$CH_2C_6H_5$



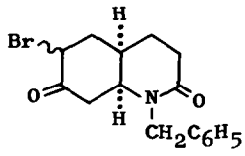
(IV)



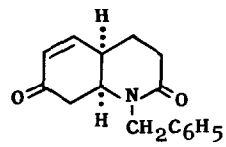
(V)



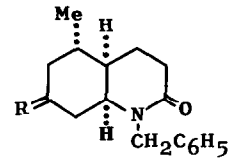
(VI)



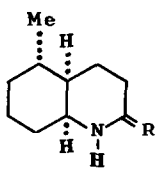
(VII)



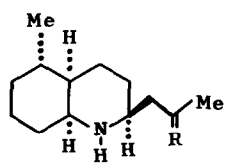
(VIII)



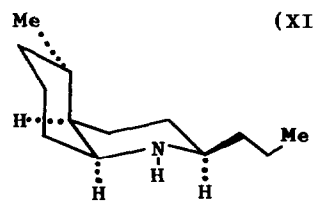
(IX) R=O
(X) R= 
(XI) R=H_2



(XII) R=O
(XIII) R=S
(XIV) R=CHCOMe



(XV) R=O
(XVI) R= 

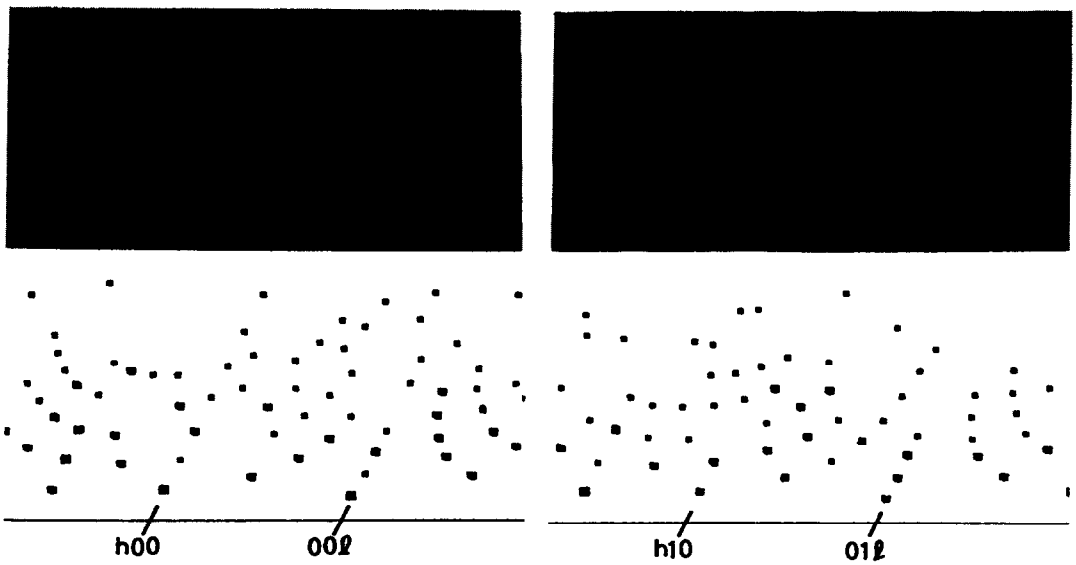


(XVII)

Next, using the Eschenmoser's method[5], condensation of XIII with bromoacetone in methylene chloride, followed by treatment with triphenylphosphine afforded the vinylogous amide (XIV), ν: 1603, 1558 (vinylogous amide), in a 71% yield. Catalytic reduction of XIV over PtO_2 in AcOH, and successive oxidation with Jones' reagent gave the keto-amine (XV), ν: 1704, in a 37% yield

Finally, the thioacetal (XVI), derived from the keto-amine (XV), was reduced with Raney W-2 nickel to yield dl-pumiliotoxin C (XVII) as a colorless oil, which was characterized as its hydrochloride,[*4] m.p. 232°, mass spectrum: m/e 195 (M^+), 194 (M-1), and 152 (base peak). The NMR spectrum (in $CDCl_3$, 100 MHz) of dl-pumiliotoxin C hydrochloride was superimposable with that of reported spectrum[1a].

Single crystals of dl-pumiliotoxin C hydrochloride, recrystallized from ethanol-ethyl acetate solution, are monoclinic colorless needles elongated



Equator(left) and the first layer(right) Weissenberg photographs of synthetic pumiliotoxin C hydrochloride(up) and calculated plots of natural one(down).

Fig. 1

along the b-axis. The largest of those minute crystals, 0.04 x 0.005 x 0.4^{mm}, was selected for the x-ray examination using Cu Kα radiation. Oscillation and zeroth and first layer equi-inclination Weissenberg photographs taken around the b-axis showed the unit-cell dimensions and the intensity distribution for the crystals matched perfectly with that of the reported values for naturally extracted pumiliotoxin C hydrochloride[1a] within the experimental error. Unit-cell dimensions are a=8.61, b=7.58, c=11.60A and β=109.8°. X-ray photographs, (h0ℓ) and (h1ℓ), compared with the calculated plots are shown in Fig. 1, where the area of the each spot in the calculated plot is depicted as proporticnal to the logarithm of the intensity calculated from the reported positional and thermal parameters using Lorentz and polarization factors. It was confirmed that the structure of the synthetic molecules including their conformation should be the same as that of the naturally extracted molecules as formula XVII.

As the space group is non-centrosymmetric $P2_1$ and two molecules are in the unit-cell, dl-pumiliotoxin C hydrochloride crystallizes as a conglomerate and

not a racemate, like glutamic acid hydrochloride[6]. Therefore it is expected the infrared spectra of the crystal and the melting point agree with that of the natural product. No significant differnces in crystal habit and in the optical rotation under the polarized microscope were observed for each crystal Three of the largest crystals gave no significant differences in x-ray photographs. The solution of the crystals gave no optical rotation. Therefore whether the crystal bathed in the x-ray beam is the true single crystal or composite of D and L-domains like dl-dimethylglyoximo-diamine-cobaltic chloride pentahydrate[7] are still unknown.

Footnotes and References

*1 All new compounds gave satisfactory analytical and spectroscopic data to support the structures. IR and NMR spectra were measured in $CHCl_3$ and $CDCl_3$, respectively.

*2 The cis and trans ring junction of II and IV were established as follows. Catalytic hydrogenation of II over palladized charcoal and subsequent $LiAlH_4$ reduction gave the known cis-decahydroquinoline, and the same treatments of IV yielded the known trans-decahydroquinoline (cf. W. L. F. Armarego: J. Chem. Soc., (C), 1967, 377).

*3 The stereochemistry with regard to the C_5-methyl group will be stated in a separate paper.

*4 The authors are indebted to Dr. B. Witkop, N. I. H., Bethesda, Maryland, U. S. A., for his suggestion on the identification of dl-pumiliotoxin C.

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