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Synthesis of *dl*-Pumiliotoxin C Hydrochloride and Its Crystal Structure*,[1]

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Racemate of pumiliotoxin C which is a toxic constituent of skin extracts of Neotropical frogs, *Dendrobates pumilio* and *Dendrobates auratus*, was synthesized. The epoxy-lactam (**8**) was synthesized from octahydroquinolone (**4**) *via* the N-benzyl-*cis*-octahydroquinolone (**7**). The bromohydrin (**9**) from **8** was successively subject to Jones' oxidation, dehydrobromination, and the conjugated addition to give the methyl-ketone (**14**). The thio-lactam (**40**) was obtained from the methyl-ketone (**14**) *via* the decahydroquinolone (**39**). Using the Eschenmoser's procedure, the thio-lactam (**40**) was transformed to the vinylogous amide (**42**). Catalytic hydrogenation of **42**, followed by Jones' oxidation, gave the amino-ketone (**44**). Reductive desulfurization of the thioacetal (**45**) gave *dl*-pumiliotoxin C (**46**), the stereochemistry of which was confirmed by a single crystal X-ray analysis. Three stereoisomers, (**17**), (**19**), and (**36**), of the methyl-ketone (**14**) were also prepared.

Many amphibians produce irritating and unpleasant skin secretions that provide partial defense against predation. Compounds isolated from strikingly colored Neotropical frogs possess remarkably potent pharmacological activities.[3-9] Recent works of Witkop and his co-workers on the toxic constituents of *Dendrobates pumilio*[4] and *Dendrobates auratus*[4,6] have led to the isolation of three toxins, pumiliotoxin A, B, and C, and the novel *cis*-decahydroquinoline structure (**1**) of pumiliotoxin C has been established by a single crystal X-ray analysis of its hydrochloride.[4,10] The circumstances that the quantity of pumiliotoxin C having been isolated (15 mg from 250 frogs), was too small for permitting detailed pharmacological investigations[4] and the novel structure was assigned to this toxic principle, prompted us to synthesize *dl*-pumiliotoxin C. This paper deals with details of the synthesis of *dl*-pumiliotoxin C hydrochloride and its crystal structure.[1]

Syntheses of Four Stereoisomers of N-Benzyl-5-methyldecahydroquinol-2,7-dione, (14), (17), (19), and (36)

Condensation of *cis*-3a,4,7,7a-tetrahydro-1-indanone (**2**)[11] with hydroxylamine yielded the oxime (**3**) which was converted into *cis*-octahydroquinolone (**4**) by treatment with *p*-toluene-

* Dedicated to the memory of Prof. Eiji Ochiai.

1) All synthetic compounds reported in this paper were racemic and a preliminary communication of this work appeared in *Tetrahedron Letters*, **1975**, 323.

2) Location: *Yoshida-shimoadachi-cho, Sakyo-ku, Kyoto, 606, Japan.*

3) J.W. Daly and C.W. Myers, *Science*, **156**, 970 (1967).

4) J.W. Daly, T. Tokuyama, G. Harbermehl, I.L. Karle, and B. Witkop, *Ann.*, **729**, 198 (1969).

5) B. Witkop, *Experientia*, **27**, 1121 (1971).

6) D. Mebs, *Experientia*, **29**, 1328 (1973).

7) I.L. Karle, *J. Am. Chem. Soc.*, **95**, 4036 (1973).

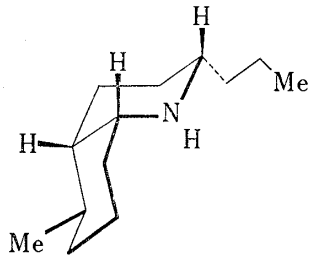
8) J.W. Daly, I.L. Karle, C.W. Myers, T. Tokuyama, J.A. Waters, and B. Witkop, *Proc. Natl. Acad. Sci., U.S.*, **68**, 1870 (1971).

9) G. Brown and B. Witkop, *Israel J. Chem.*, **12**, 697 (1974).

10) A. Private communication from Dr. B. Witkop, N.I.H., Bethesda, Maryland 20014, U.S.A.

11) *a*) H.O. House and G.H. Rasmusson, *J. Org. Chem.*, **28**, 31 (1963); *b*) J.-C. Jallageas, A. Casadevall, and E. Casadevall, *Bull. Soc. Chim. France*, **1969**, 4047; *c*) E. Dane and K. Eder, *Ann.*, **539**, 207 (1939).

sulfonyl chloride in dry pyridine.[12] The *cis* ring junction of **4** was confirmed by the following chemical conversion. Thus, catalytic hydrogenation of **4** afforded decahydroquinol-2-one (**5**) and subsequent reduction with lithium aluminum hydride gave known *cis*-decahydroquinoline (**6**)[13] which was characterized as its crystalline hydrochloride. The N-benzyl compound (**7**) obtained by benzyltion of **4**, was oxidized with *m*-chloroperbenzoic acid (MCPBA) to yield the epoxy-lactam (**8**) as a single product.



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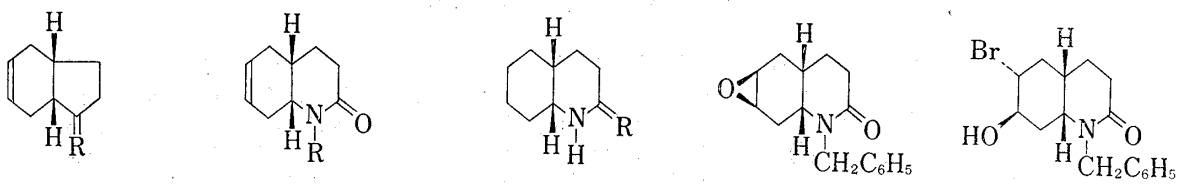


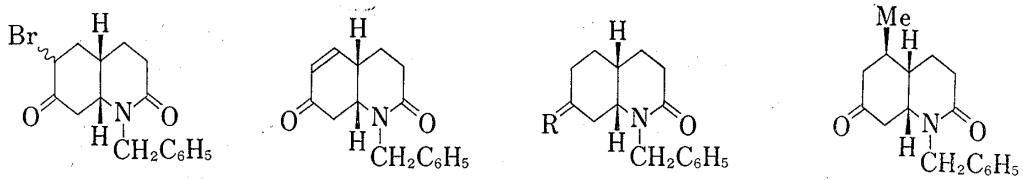
2 : R=O
3 : R=NOH

4 : R=H
7 : R=$CH_2C_6H_5$

5 : R=O
6 : R=H_2

8

9



10

11

12 : R=O
13 : R=H_2

14

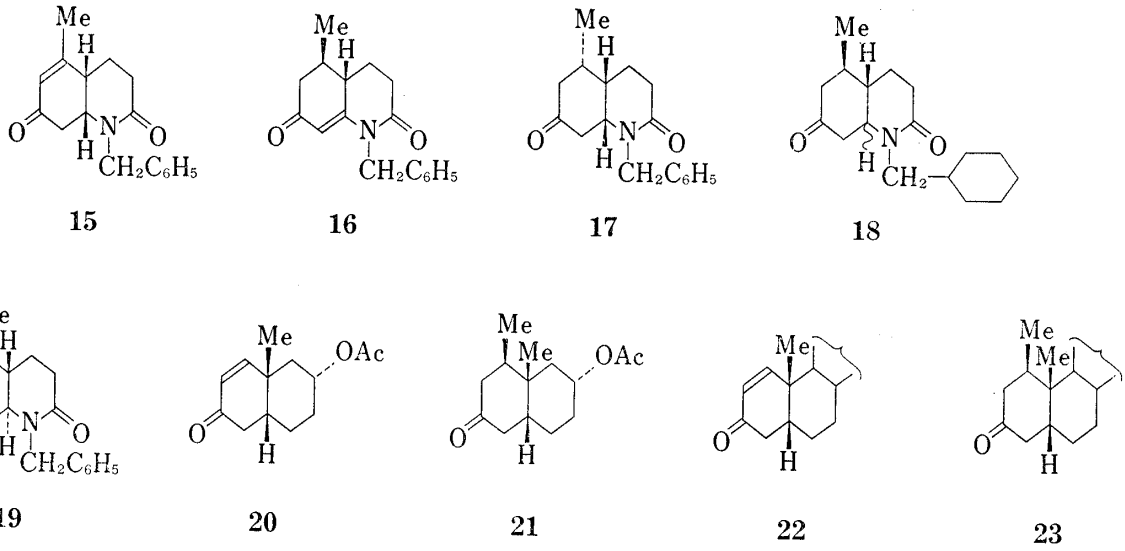
Chart 1

The configurational assignment of the β-epoxy ring in the epoxy-lactam (**8**) was based on the generally accepted principle that the per-acid attacks the double bond from the less hindered "convex" face to produce the less hindered epoxide.[14] When treated with 48% hydrobromic acid, the epoxy ring of **8** was subject to the regioselective attack of a bromide anion to yield the bromohydrin (**9**).[15] The bromo-ketone (**10**) obtained from **9** by Jones' oxidation was dehydrobrominated with lithium bromide-lithium carbonate in N,N-dimethylformamide (DMF) to give the α,β-unsaturated ketone (**11**). The *cis* ring junction of **11** was substantiated by the following evidence. Thus, N-benzyl-*cis*-decahydroquinolone (**13**) derived from the enone (**11**) by catalytic hydrogenation, followed by Huang-Minlon reduction, was found to be identical with the compound (**13**) which was obtained from N-benzyl-*cis*-octahydroquinolone (**7**) by catalytic hydrogenation.

The next step of the present synthesis required the stereoselective conjugate addition of methyl group to the enone (**11**). It is well known that cyclic enones react with alkylcopper reagent to give the conjugated addition product.[16] This type of reaction has been effectively employed for introduction of methyl group to a number of α,β-unsaturated ketones.[16] Treatment of the enone (**11**) with lithium dimethylcopper[16,17] gave the methyl-ketone (**14**) in more

12) R.K. Hill and O.T. Chortyk, *J. Am. Chem. Soc.*, **84**, 1065 (1962).
13) W.L.F. Armarego, *J. Chem. Soc.* (*C*), **1967**, 377.
14) H.O. House, "Modern Synthetic Reactions," 2nd ed., W.A. Benjamin, Inc., Calif., 1972, pp. 302—304.
15) J.G. Buchanan and H.Z. Sable, "Selective Organic Transformations," Vol. 2, John Wiley & Sons, Inc., New York, 1972, pp. 1—51.
16) G.H. Posner, "Organic Reactions," Vol. 19, John Wiley & Sons, Inc., New York, 1972, pp. 3—110.
17) H.O. House, W.L. Respess, and G.M. Whitesides, *J. Org. Chem.*, **31**, 3128 (1966).

than 86% yield as a sole product. The β configuration of the newly introduced methyl group was inferred from analogy with the results that reactions of the *cis*-octalone (**20**) and coprost-1-en-3-one (**22**) with the same reagent gave the 1β-methyl-*cis*-decalone (**21**)[18] and 1β-methyl-coprostan-3-one (**23**),[19] respectively. Prior to put forward the synthetic step of *dl*-pumiliotoxin C, attempts were made to synthesize other three possible isomers (**17**), (**19**), and (**36**), of **14** with the intention of confirming the stereochemistry of the methyl-ketone (**14**).



15 **16** **17** **18**

19 **20** **21** **22** **23**

Chart 2

The methyl-ketone (**14**) was brominated and the resulting crude bromo-ketone was dehydrobrominated with lithium bromide-lithium carbonate in DMF to yield the enone (**15**) (11%), the nuclear magnetic resonance (NMR) of which revealed signals at δ 5.88 (1H, diffused s., C_6–H), 2.00 (3H, d., J=1 Hz, C_5–Me), and the enone (**16**) [20% yield; NMR δ 1.12 (3H, d., J=6 Hz, C_5–Me)]. Catalytic hydrogenation of the enone (**15**) afforded the methyl-ketone (**17**) as a single product. In this case, hydrogen attack to the double bond may occur preferentially from the less hindered side leading to the assumption that the methyl group of the methyl-ketone (**17**) is α-oriented, and hence the C_5-methyl of the methyl-ketone (**14**) is β-oriented. This assumption will be chemically confirmed by the following fact. Thus, synthesis of *dl*-pumiliotoxin C in which the β configuration of the methyl group had been established, was completed using this methyl-ketone (**14**) as stated later.

N-Benzyl-5β-methyl-*trans*-decahydroquinol-2,7-dione (**19**) was synthesized from the enone (**16**). Catalytic hydrogenation of **16** using 10% Pd-C catalyst did not proceed because of its vinylogous amide structure. Then, the enone (**16**) was catalytically hydrogenated over Adams' PtO_2 in methanol, and the crude reduction mixture was oxidized with Jones' reagent. Chromatographic separation of the oxidation products afforded the methyl-ketone (**14**: 6% yield), the methyl-ketone (**18**: 9% yield), and the methyl-ketone (**19**: 21% yield). Since the thin-layer chromatography (TLC) behavior, infrared spectrum (IR) and NMR spectra of **19** were different from those of the methyl-ketone (**14**), the ring juction of **19** should be *trans* and C_{8a}–H should be α-oriented. Finally, synthesis of the last isomer, the methyl-ketone (**36**), was accomplished by the following sequences. When treated with *p*-toluenesulfonyl chloride, the oxime (**25**) prepared from *trans*-3a,4,7,7a-tetrahydro-1-indanone (**24**),[11] gave

18) J.A. Marshall and J.M. Cohen, *J. Org. Chem.*, **36**, 887 (1971).
19) *a*) W.J. Wechter, G. Slomp, F.A. MacKellar, R. Wiechert, and U. Kerb, *Tetrahedron*, **21**, 1625 (1965); *b*) W.J. Wechter, *J. Org. Chem.*, **29**, 163 (1964): *c*) L. Decaux and R. Vessiere, *Compt. Rend.*, **267**, 738 (1968).

trans-octahydroquinolone (**26**). The *trans* ring junction of **26** was established by the following experiments. Thus, octahydroquinolone (**26**) was catalytically hydrogenated to give the compound (**27**). Treatment of **27** with $LiAlH_4$ yielded oily known *trans*-decahydroquinoline (**28**)[13] which was characterized as its crystalline hydrochloride. The N-benzyl derivative (**29**) derived from **26** by benzylation was oxidized with MCPBA to give a separable mixture consisting of the epoxides, (**30**) and (**31**), in a *ca.* 1:1 ratio. The α configuration of the epoxide ring in the epoxy-lactam (**31**) and hence the β configuration of that in the epoxy-lactam (**30**) were proved by the following evidence.

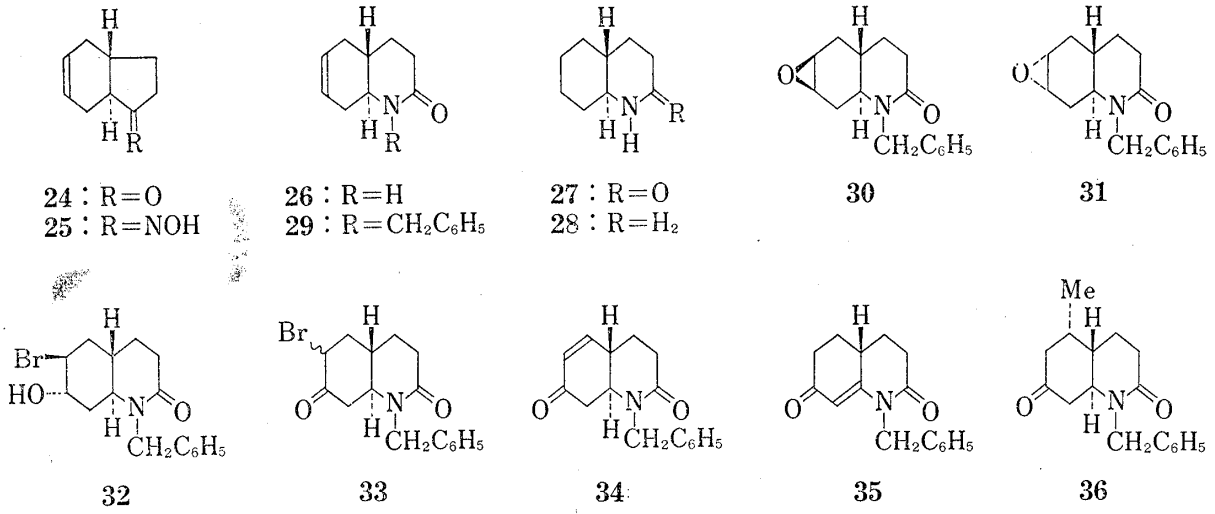


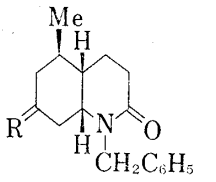
Chart 3

Regioselective diaxial cleavage of the epoxy ring[15] of **31** with 48% hydrobromic acid yielded the bromohydrin (**32**). Treatment of **32** with Jones' reagent gave the bromo-ketone (**33**) which was subject to dehydrobromination to yield the enone [**34**: ν cm^{-1}: 1678 (α,β-unsaturated ketone), 1640 (lactam CO); NMR δ 6.80 (1H, q., J_A=10 Hz, J_B=2 Hz, C_5–H), 6.01 (1H, q., J_A=10 Hz, J_B=3 Hz, C_6–H] and the enone [**35**: ν cm^{-1}: 1691, 1644, and 1583 (vinylogous amide); NMR δ: 5.56 (1H, d., J=1.5 Hz, C_8–H) in a 9:1 ratio. The latter enone was supposed to arise from the bromo-ketone (**33**) by the rearrangement of C_6–Br to C_8 and subsequent dehydrobromination.[20] From the spectral data above, it is obvious that the carbonyl groups of **34** and **35** were located at C_2 and C_7 positions. Consequently, a ketonic function of the bromo-ketone (**33**) and a hydroxyl group of the bromohydrin (**32**) should be at C_7 position and the bromo group at C_6 position. Since the bromohydrin (**32**) arised from the epoxy-lactam (**31**) of the *trans* ring junction by *trans* diaxial epoxide ring-opening, the β-axial conformation of C_6–Br and the α-axial conformation of C_7–OH could be deduced.[15] These assignments indicated in turn that the epoxy ring of the epoxy-lactam (**31**) is α-oriented and that of the isomeric epoxy-lactam (**30**) is β-oriented. The conjugated addition of lithium dimethylcopper to the enone (**34**) yielded N-benzyl-5α-methyl-*trans*-decahydroquinol-2,7-dione (**36**) as a single product. Thus, four stereoisomers of N-benzyl-5-methyldecahydroquinol-2,7-dione, (**14**), (**17**), (**19**), and (**36**), were synthesized.

Synthesis of *dl*-Pumiliotoxin C (46)

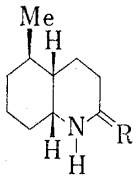
On the basis of the results described thus far, synthesis of *dl*-pumiliotoxin C from N-benzyl-5β-methyl-*cis*-decahydroquinol-2,7-dione (**14**) was undertaken. In our synthetic scheme, the problems to be solved were reduction of the C_7-carbonyl group, removal of the N-benzyl group, and introduction of *n*-propyl group at C_2 position.

20) H.O. House and R.W. Bashe, *J. Org. Chem.*, **30**, 2942 (1965).



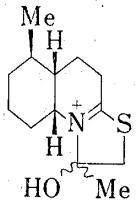
37 : R= 

38 : R=H_2

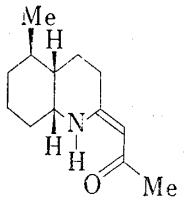


39 : R=O

40 : R=S



41



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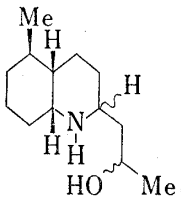

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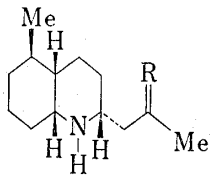

44 : R=O

45 : R=

46 : R=H_2

Chart 4

In an attempt to reduce the C_7-carbonyl function of the methyl-ketone (**14**), **14** was treated with a mixture of hydrazine hydrate and potassium hydroxide in diethylene glycol to give an inseparable mixture. Then, the thioacetal (**37**) obtained from the methyl-ketone (**14**) was refluxed in ethanol with Raney nickel to yield the decahydroquinolone (**38**) in an 82% yield and the debenzylated compound (**39**) in a 5% yield. Reductive debenzylation[21] of **38** in liquid ammonia at −33° with metallic sodium gave also the decahydroquinolone (**39**) in a high yield.

Next synthetic step was the carbon-carbon bond formation at C_2 position of **39**. The decahydroquinolone (**39**) was treated with phosphorous pentasulfide, and then the resulted thiolactam (**40**) was converted into the thiazole derivative (**41**) by the Eschenmoser's procedure.[22] After the thiazole derivative (**41**) was treated with aqueous sodium bicarbonate, the reaction product was heated with a mixture of triphenylphosphine, *tert*-butanol, and potassium *tert*-butoxide to give the vinylogous amide (**42**) in a 71% yield. Catalytic hydrogenation of **42** under the presence of platinum dioxide gave the oily amino-alcohol (**43**) which was then oxidized with Jones' reagent to give the β-amino-ketone (**44**) as a sole product. Finally, the thioacetal (**45**) derived from **44** was reduced with Raney W-2 nickel to yield *dl*-pumiliotoxin C (**46**)[23] as a colorless oil. The oil was characterized as its hydrochloride, mp 232° (in a sealed tube). The NMR and Mass spectra of the synthetic racemate (**46**) were identical with those of natural pumiliotoxin C reported by Witkop, *et al.*[4] The present synthesis is the first total synthesis of racemic pumiliotoxin C.

Single crystal X-ray analysis of *dl*-pumiliotoxin C hydrochloride provided unequivocal proof of the stereochemistry of the synthetic base. Single crystals of *dl*-pumiliotoxin C hydrochloride, recrystallized from ethanol-ethyl acetate, were monoclinic colorless needles elongated along the *b*-axis. The largest of those minute crystals, 0.04×0.005×0.4 mm, was selected for the X-ray examination using Cu $K\alpha$ radiation. Oscillation and zeroth and first layer equi-

21) J.P. Greenstein and M. Winitz, "The Chemistry of the Amino Acids," Vol. 2, John Wiley & Sons, Inc., New York, 1969, p. 1239.

22) M. Roth, P. Dubs, and A. Eshchenmoser, *Helv. Chim. Acta*, **54**, 710 (1971).

23) Most recently, we learned from Dr. B. Witkop by his private commiuncation that Dr. W. Oppolzer has completed a total synthesis of *dl*-pumiliotoxin C by his elegant synthetic scheme.

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 occurring pumiliotoxin C hydrochloride[4] within the experimental error. Unit-cell dimensions were $a=8.61$, $b=7.58$, $C=11.60$Å and $\beta=109.8°$. X-ray photographs, (ho*l*) and (hl*l*), compared with the calculated plots are shown in Fig. 1, where the area of the each spot in the calculated spot is depicted as proportional 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 occurring molecules as formula (**1**). As the space

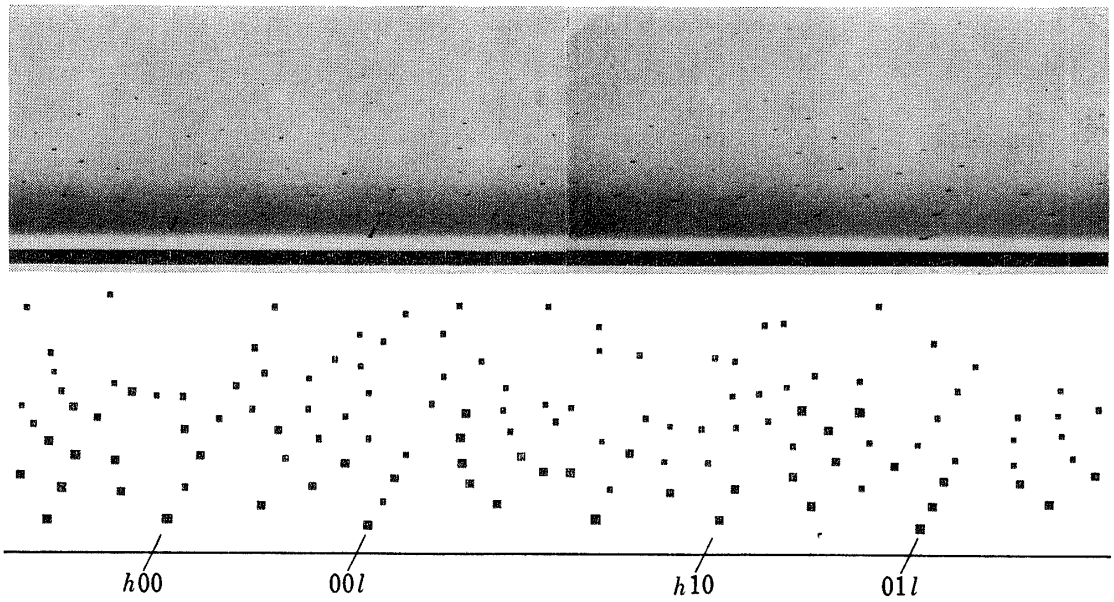

Fig. 1. Equator (left) and the first layer (right) Weissenberg photographs of synthetic pumiliotoxin C hydrochloride(up) and calculated plots of natural one (down).

group was non-centrosymmetric $P2_1$ and two molecules were in the unit-cell, *dl*-pumiliotoxin C hydrochloride crystallized as a conglomerate and not a racemate, like glutamic acid hydrochloride.[24] Therefore, it is expected the infrared spectrum of the crystal and the melting point agree with that of the natural product. No significant differences 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 di-dimethylgluoximino-diamine-cobaltic chloride penta hydrate[25] are still unknown.

Pharmacological activity of the synthetic *dl*-pumiliotoxin C hydrochloride was similar to that of methanol extracts reported by Daly and Myers.[3] Thus, after the subcutaneous injection of the synthetic base hydrochloride (2.5 mg/20 g of the mouse), the albino mouse (ddK) showed locomotor difficulty with paralysis of the hind limbs. Then, salivation, extensor movements of the hind limbs, and finally, convulsions and death occurred within ten minutes.

Experimental

All melting points were taken on a Yanagimoto melting point apparatus and were uncorrected. Unless otherwise specified, IR spectra were obtained for solutions in chloroform with a Hitachi EPI-S spectrometer. Unless otherwise stated, NMR spectra were measured on a Varian A-60 or HA-100 spectrometer in deuterio-

24) *a*) W.C. Quene and F. Jellinek, *Acta Cryst.*, **12**, 349 (1959); *b*) B. Dawson, *Acta Cryst.*, **6**, 81 (1953).
25) A. Nakahara, Y. Saito, and H. Kuroya, *J. Inst. of Polytechniques* (Osaka City University), **1**, 19 (1950).

chloroform with tetramethylsilane as an internal standard and chemical shifts were given in δ values. The abbreviations, s., d., t., q., and m. in the NMR spectra signify singlet, doublet, triplet, quartet, and multiplet and the coupling constant (J) is measured in Hz. Mass spectra were determined at 80 eV on a Hitachi RMU-6D spectrometer, and abbreviation M^+ signifies the molecular ion. TLC was performed on Kieselgel G nach Stahl using acetone–chloroform (1: 4) as a developing solvent. Unless otherwise specified, the extracts were dried over anhydrous magnesium sulfate and column chromatographies were effected using Mallinckrodt silicic acid (100 mesh).

***cis*-Octahydroquinolone (4)**——To a solution of *cis*-2a,4,7,7a-tetrahydro-1-indanone (**2**) (272 mg) in 10 ml of MeOH were added hydroxylamine hydrochloride (420 mg) and sodium acetate (500 mg) under stirring, and the mixture was stirred at room temperature for 13 hr. The reaction mixture was poured into 5% HCl and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with H_2O, dried and evaporated to give 310 mg of the yellow oily oxime (**3**). A solution of 310 mg of the oxime (**3**) in 5 ml of dry pyridine was added 600 mg of *p*-toluenesulfonyl chloride under stirring and the mixture was stirred at room temperature for 10 hr The reaction mixture was poured into 5% HCl and extracted with $CHCl_3$, and the extract was washed with H_2O, dried and evaporated to yield 420 mg of a reddish oil. Purification of the oil by preparative TLC (Silica gel GF_{254}) and recrystallization from acetone–ether (1: 4) gave 161 mg (53% yield) of *cis*-octahydroquinolone (**4**) as colorless prisms, mp 113°. IR ν_{max} cm^{-1}: 3420, 3320, 3230 (NH), 1654 (lactam CO). NMR δ: 6.6—7.3 (1H, broad s., NH) 5.45—5.75 (2H, m,. C_6 and C_7 olefinic protons), 3.38—3.78 (1H, m., $W_{1/2}$= 12 Hz, C_{8a}–H). *Anal.* Calcd. for $C_9H_{13}ON$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.54; H, 8.77; N, 9.42.

***cis*-Decahydroquinol-2-one (5)**——A solution of 150 mg of the compound (**4**) in 20 ml of MeOH was hydrogenated at atmospheric pressure over 50 mg of 10% Pd-C at room temperature. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue in $CHCl_3$ was purified over an alumina column (0.8 × 2.0 cm) and the column was eluted with the same solvent. The crystalline residue was recrystallized from acetone–ether (1: 3) to give 110 mg of *cis*-decahydroquinol-2-one (**5**) as colorless pillars, mp 127—128°. IR ν_{max} cm^{-1}: 3410, 3320, 3230 (NH), 1650 (lactam CO). NMR δ: 7.18—6.45 (1H, broad s., NH), 3.68—3.30 (1H, m., C_{8a}–H). *Anal.* Calcd. for $C_9H_{15}ON$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.59; H, 9.87; N, 9.05.

***cis*-Decahydroquinoline (6)**——A mixture of 80 mg of *cis*-decahydroquinol-2-one (**5**), 200 mg of $LiAlH_4$ and 60 ml of dry ether was refluxed with stirring for 7 hr. After cooling, excess reagent was decomposed with wet ether. The ether layer was washed with 5% HCl, and the acidic aqueous layer was made alkaline with 28% NH_4OH and extracted with $CHCl_3$. The extract was washed with water, dried and evaporated to give 74 mg of pale yellow oily *cis*-decahydroquinoline (**6**). IR ν_{max} cm^{-1}: 2920 and 1450. The NMR spectrum of the base was identical with that of the base reported by Armarego.[13] The oily base was characterized as its hydrochloride, mp 222—224° (EtOH–AcOEt). The melting point of a sample was identical with that reported.[13] IR ν_{max} cm^{-1}: 2930, 1589, and 1450. *Anal.* Calcd. for $C_9H_{18}NCl$: C, 61.52; H, 10.33; N, 7.97. Found: C, 61.58; H, 10.33; N, 8.01.

N-Benzyl-*cis*-decahydroquinol-6-en-2-one (7)——To a solution of 500 mg of *cis*-octahydroquinol-2-one (**4**) in 50 ml of dry benzene was added 500 mg of 50% NaH. After the mixture was refluxed for 1 hr, 1.26 g of benzyl chloride was added and the mixture was refluxed for 4 hr. Excess NaH was decomposed with water under ice cooling and the mixture was extracted with ether. The ether extract was washed, dried, and evaporated. The residual oil in $CHCl_3$ was chromatographed over silica gel and eluted with the same solvent to give N-benzyl-*cis*-decahydroquinol-6-en-2-one (**7**) as a colorless oil (771 mg: 95% yield). IR ν_{max} cm^{-1}: 1623 (lactam CO). NMR δ: 7.29 (5H, s., aromatic protons), 5.45—5.62 (2H, m., C_6 and C_7 olefinic protons), 5.31 and 4.05 (each 1H, d., J=15 Hz, benzylic protons), 3.12—3.61 (1H, m., C_{8a}–H). Mass Spectrum m/e: 241 (M^+), 91 (base peak).

The Epoxy-lactam (8)——To a solution of 3.80 g of the N-benzyl compound (**7**) in 100 ml of CH_2Cl_2 was added 3.26 g (1.2 equivalents) of MCPBA, and the mixture was allowed to stand at room temperature for 20 hr. The mixture was poured into ice-water and extracted with CH_2Cl_2. The extract was washed with dil. NH_4OH, water, dried and evaporated to leave a crystalline solid. Recrystallization from acetone–ether (1: 5) gave 3.40 g of the epoxy-lactam (**8**) as colorless prisms, mp 98°. IR ν_{max} cm^{-1}: 1626 (CO). *Anal.* Calcd. for $C_{16}H_{19}O_2N$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.42; H, 7.48; N, 5.41.

The Bromohydrin (9)——To a solution of 300 mg of the epoxy-lactam (**8**) in 6 ml of $CHCl_3$ was added 1 ml of 48% HBr under vigorous stirring and the mixture was further stirred for 30 min. The reaction mixture was mixed with 10 ml of ice water and extracted three times with $CHCl_3$. The combined extract was dried and evaporated to leave a crystalline solid. Recrystallization from acetone–ether (1: 3) gave 328 mg of the bromohydrin (**9**) as colorless prisms, mp 134°. IR ν_{max} cm^{-1}: 3560, 3410 (OH), and 1627 (CO). *Anal.* Calcd. for $C_{16}H_{20}O_2NBr$: C, 56.81; H, 5.96; N, 4.14. Found: C, 56.82; H, 5.72; N, 4.06.

The Bromo-ketone (10)——To a solution of 304 mg of the bromohydrin (**9**) in 5 ml of acetone was added 1 ml of Jones' reagent under stirring at 0° and the mixture was stirred for 1 hr. The excess reagent was decomposed with MeOH and the solution was extracted with $CHCl_3$. The extract was washed, dried and evaporated to leave a crystalline solid. Recrystallization from acetone–ether (1: 3) gave 182 mg of the bromo-ketone (**10**) as colorless prisms, mp 144°. IR ν_{max} cm^{-1}: 1724 (α-bromo-ketone) and 1632 (lactam

CO). NMR δ: 7.28 (5H, s., aromatic protons), 5.37 and 3.90 (each 1H, d., $J=15$ Hz, benzylic protons), 4.70 (1H, q., $J_A=12$ Hz, $J_B=6$ Hz, C_6–H). *Anal.* Calcd. for $C_{16}H_{18}O_2NBr$: C, 57.15; H, 5.40; N, 4.17. Found: C, 57.06; H, 5.16; N, 4.02.

The α,β-Unsaturated Ketone (11)——To a solution of 4.03 g of the bromo-ketone (**10**) in 35 ml of dry DMF were added 5 g of LiBr and 5 g of Li_2CO_3 under stirring. The mixture was heated with stirring at 110° under nitrogen atmosphere for 3 hr. After cooling, the mixture was made acidic with 5% HCl and extracted with ether, and the organic layer was washed, dried and evaporated to give a reddish oil. The oil in $CHCl_3$ was chromatographed over a silica gel column (2.5×30 cm) and the column was eluted with the same solvent. Recrystallization of the residue from acetone–ether (1:4) afforded 1.310 g of the α,β-unsaturated ketone (**11**) as colorless prisms, mp 133—134°. IR ν_{max} cm^{-1}: 1680 (enone) and 1635 (lactam). NMR δ: 7.22 (5H, broad s., aromatic protons), 6.86 (1H, q,. $J_A=10$ Hz, $J_B=6$ Hz, C_5–H), 5.97 (1H, d., $J=10$ Hz, C_6–H), 5.33 and 3.94 (each 1H, d., $J=15$ Hz, benzylic protons), and 3.67—3.95 (1H, m., C_{8a}–H). *Anal.* Calcd. for $C_{16}H_{17}O_2N$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.15; H, 6.67; N, 5.43.

N-Benzyl-*cis*-decahydroquinol-2-one (13)——A solution of 90 mg of the compound (**7**) in 15 ml of MeOH was catalytically hydrogenated at room temperature and atmospheric pressure under the presence of 10% Pd–C catalyst. After the mixture had absorbed 7 ml of hydrogen, the catalyst was filtered off. The solvent of the filtrate was evaporated and the residue in ether was chromatographed over an alumina column (1×2 cm) and the column was eluted with the same solvent to give 95 mg of N-benzyl-*cis*-decahydroquinol-2-one (**13**) as a colorless oil. IR ν_{max} cm^{-1}: 1620 (lactam CO). NMR δ: 7.26 (5H, s., aromatic protons), 5.32 and 3.97 (each 1H, d., $J=15$ Hz, benzylic protons), 3.38—2.90 (1H, m., C_8—H). Mass Spectrum *m/e*: 243 (M^+), 200 and 91 (base peak).

N-Benzyl-*cis*-decahydroquinol-2,7-dione (12)——A solution of 100 mg of the enone (**11**) in 20 ml of MeOH was hydrogenated at room temperature and atmospheric pressure under the presence of 40 mg of 10% Pd–C catalyst. The hydrogen uptake (8 ml) ceased within 20 min. Work-up as usual manner afforded 105 mg of N-benzyl-*cis*-decahydroquinol-2,7-dione (**12**) as a colorless oil. IR ν_{max} cm^{-1}: 1710 (ketone) and 1630 (lactam CO). NMR δ 7.28 (5H, s., aromatic protons), 5.35 and 3.88 (each 1H, d., $J=15$ Hz, benzylic protons), 3.75—3.30 (1H, m., C_{8a}–H). Mass Spectrum *m/e*: 257 (M^+), 91 (base peak), 85 and 83.

N-Benzyl-*cis*-decahydroquinol-2-one (13)——A mixture of 77 mg of the dione (**12**), 5 ml of ethylene glycol, 180 mg of KOH and 0.4 ml of 85% hydrazine hydrate was heated at 150° for 20 hr. After cooling, the mixture was made acidic with 5% HCl and extracted with $CHCl_3$. The extract was washed, dried, and evaporated to leave 80 mg of a yellow oil. The oil in $CHCl_3$ was chromatographed on a silica gel column (1.5×15 cm) and elution of the column with the same solvent afforded 55 mg of N-benzyl-*cis*-decahydroquinol-2-one (**13**) as a colorless oil. This compound was identical with an authentic sample prepared from the compound (**7**).

N-Benzyl-5β-methyl-*cis*-decahydroquinol-2,7-dione (14)——To a stirred suspension of 1.52 g of cuprous iodide in 15 ml of dry ether at 0° was added 32 ml (15 mmoles) of methyllithium etherial solution. To the above solution was added dropwise a solution of 600 mg of the enone (**11**) in 40 ml of ether–tetrahydrofuran (1:1 mixture) at nitrogen atmosphere under stirring. The mixture was stirred for 1 hr and poured into 100 ml of ice-water. The solution was made acidic with 5% HCl and extracted with ether. The extract was washed, dried, and evaporated to give a yellow oil. The oil $CHCl_3$ was chromatographed over a silica gel column (1.5×15 cm) and the column was eluted with the same solvent to afford 544 mg (86% yield) of N-benzyl-5β-methyl-*cis*-decahydroquinol-2,7-dione (**14**) as a colorless oil. IR ν_{max} cm^{-1}: 1711 (ketone) and 1631 (lactam CO). NMR δ: 7.24 (5H, s., aromatic protons), 5.26 and 3.99 (each 1H, d., $J=15$ Hz, benzylic protons), 3.47—3.93 (1H, m., C_{8a}–H) and 0.92 (3H, d., $J=7$ Hz, C_5–Me). Mass Spectrum *m/e*: 271 (M^+), 214 and 91.

N-Benzyl-5-methyl-*cis*-decahydroquinol-5-en-2,7-dione (15) and N-Benzyl-5β-methyldecahydroquinol-8-en-2,7-dione (16)——To a solution of 200 mg of the methyl-ketone (**14**) in 15 ml of $CHCl_3$ were added 118 mg of bromine and 2 drops of 48% HBr under stirring at 0°, and the mixture was stirred for 30 min. The solution was washed, dried and evaporated to leave 260 mg of a pale yellow oil. To a solution of 260 mg of the above oil in 4 ml of DMF were added 400 mg of LiBr and 400 mg of Li_2CO_3 under stirring. The mixture was heated at 120° for 3 hr under the nitrogen stream. After cooling, the mixture was made acidic with 5% HCl and extracted with $CHCl_3$. The extract was washed, dried and evaporated to afford 120 mg of an oily residue. The oily residue in $CHCl_3$ was chromatographed over a silica gel column (1.0×25 cm) and the column was eluted with the same solvent. Evaporation of $CHCl_3$ of the earlier eluate gave 58 mg of N-benzyl-5β-methyldecahydroquinol-8-en-2,7-dione (**16**) as a colorless oil. IR ν_{max} cm^{-1}: 1687 (α,β-unsatu-saturated ketone), 1646 (lactam CO) and 1583 (double bond). NMR δ: 7.37—7.00 (5H, m., aromatic protons), 5.54 (1H, m., C_8–H), 5.18 and 4.80 (each 1H, d., $J=15$ Hz, benzylic protons), 1.12 (3H, d., $J=6$ Hz, C_5–Me). Mass Spectrum *m/e*: 269 (M^+), 91, 85, and 83. Evaporation of the solvent of the middle fractions gave 10 mg of the starting material. Removal of $CHCl_3$ of the latter eluate afforded 25 mg of N-benzyl-5-methyl-*cis*-decahydroquinol-5-en-2,7-dione (**15**) as a colorless oil. IR ν_{max} cm^{-1}: 1655 (α,β-unsaturated ketone), and 1632 (lactam CO). NMR δ: 7.28 (5H, s., aromatic protons), 5.88 (1H, diffused s., C_6–H), 5.38 and 3.92 (each 1H, d., $J=15$ Hz, benzylic protons), 2.00 (3H, d., $J=1$ Hz, C_5–Me). Mass Spectrum *m/e*: 269 (M^+) and 91 (base peak).

N-Benzyl-5β-methyl-*cis*-decahydroquinol-2,7-dione (14), the Saturated Compound (18) and N-Benzyl-5β-methyl-*trans*-decahydroquinol-2,7-dione (19)——A solution of 58 mg of the dione (**16**) in 15 ml of MeOH was catalytically hydrogenated at atmospheric pressure over 100 mg of PtO_2 at room temperature. Work-up as usual manner afforded 48 mg of a colorless oil which in 5 ml of acetone was oxidized with Jones' reagent at 0° and the mixture was stirred for 1 hr. The solvent was removed under reduced pressure and the residue was extracted with $CHCl_3$. The extract was washed, dried and evaporated to give 40 mg of a yellow oil. The oil in $CHCl_3$ was chromatographed over a silica gel column (0.7×15 cm) and the column was eluted with the same solvent. Recrystallization of the earlier eluate from ether gave 5 mg of the saturated compound (**18**) as colorless prisms, mp 132°. IR ν_{max} cm^{-1}: 1713 (ketone) and 1628 (lactam CO). NMR δ: 1.10 (3H, d., J=5 Hz, C_5–Me). *Anal.* Calcd. for $C_{17}H_{27}O_2N$: C, 73.60; H, 9.81; N, 5.05. Found: C, 73.14; H, 9.50; N, 5.05. Mass Spectrum *m/e*: 277 (M^+). Removal of the solvent of the middle fractions gave 12 mg of N-benzyl-5β-methyl-*trans*-decahydroquinol-2,7-dione (**19**) as a colorless oil. IR ν_{max} cm^{-1}: 1713 (ketone), 1630 (lactam CO). NMR δ: 7.23 (5H, s., aromatic protons), 5.01 and 4.40 (each 1H, d., J=16 Hz, benzylic protons), 3.5—2.8 (1H, m., C_{8a}–H), 1.08 (3H, d., J=3.5 Hz, C_5–Me). Mass Spectrum *m/e*: 271 (M^+), 214, and 91 (base peak). Evaporation of $CHCl_3$ of the later eluate gave 3 mg of N-benzyl-5β-methyl-*cis*-decahydroquinol-2,7-dione (**14**) as a colorless oil. This compound was identical with the authentic methyl-ketone (**14**).

N-Benzyl-5α-methyl-*cis*-decahydroquinol-2,7-dione (17)——A solution of 25 mg of the enone (**15**) in 5 ml of MeOH was hydrogenated at atmospheric pressure over 50 mg of 10% Pd–C catalyst. Work-up as usual gave 18 mg of N-benzyl-5α-methyl-*cis*-decahydroquinol-2,7-dione (**17**) as a colorless oil. IR ν_{max} cm^{-1}: 1709 (ketone) and 1629 (lactam CO). NMR δ: 7.26 (5H, s., aromatic protons), 5.35 and 3.86 (each 1H, d., J=15 Hz, benzylic protons), 1.03 (3H, d., J=5 Hz, C_5–Me). Mass Spectrum *m/e*: 271 (M^+), 214, 91 (base peak).

***trans*-3a,4,7,7a-Tetrahydro-1-indanone Oxime (25)**—— To a solution of 136 mg of *trans*-3a,4,7,7a-tetrahydro-1-indanone (**24**) in 10 ml of MeOH were added hydroxylamine hydrochloride (210 mg) and sodium acetate (250 mg) under stirring and the mixture was stirred at room temperature for 10 hr. The mixture was extracted with $CHCl_3$, and the extract was washed with 5% HCl, 5% NH_4OH, and water. The extract was dried and evaporated to leave a crystalline solid. Recrystallization from ether-petroleum ether (1: 2) gave 131 mg of *trans*-3a,4,7,7a-tetrahydro-1-indanone oxime (**25**) as colorless prisms, mp 121°. IR ν_{max} cm^{-1}: 3600 and 3320 (OH). *Anal.* Calcd. for $C_9H_{13}ON$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.39; H, 8.76; N, 9.23.

***trans*-Octahydroquinolone (26)**——To a solution of 1.0 g of the oxime (**25**) in 30 ml of dry pyridine was added 2.0 g of *p*-toluenesulfonyl chloride under stirring and the mixture was stirred at room temperature for 20 hr. The reaction mixture was poured into 5% HCl and extracted with $CHCl_3$. The extract was washed with water, dried, and evaporated to leave 880 mg of a colorless oil. Trituration of the oil with ether gave a crystalline mass which was recrystallized from acetone to give 775 mg of *trans*-octahydroquinolone (**26**) as colorless plates, mp 165—167°. IR ν_{max} cm^{-1}: 3450 (NH), 1665 (lactam CO). *Anal.* Calcd. for $C_9H_{13}ON$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.19; H, 8.76; N, 9.15.

***trans*-Decahydroquinol-2-one (27)**——A solution of 200 mg of *trans*-octahydroquinolone (**26**) in 20 ml of MeOH was hydrogenated at atmospheric pressure over 50 mg of 10% Pd–C catalyst at room temperature. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue in $CHCl_3$ was purified over an alumina column (0.8×2.0 cm) and the column was eluted with the same solvent. The crystalline residue was recrystallized from acetone to give 150 mg of *trans*-decahydroquinol-2-one (**27**) as colorless prisms, mp 154—156°. IR ν_{max} cm^{-1}: 3420 (NH) and 1655 (lactam CO). NMR δ: 7.4—6.8 (1H, broad s., NH), 3.2—2.6 (1H, m., C_{8a}–H). *Anal.* Calcd. for $C_9H_{15}ON$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.26; H, 10.01; N, 9.03.

***trans*-Decahydroquinoline (28)**——A mixture of 200 mg of *trans*-decahydroquinol-2-one (**27**), 60 ml of dry ether and 300 mg of $LiAlH_4$ was refluxed for 7 hr. After cooling, excess reagent was decomposed with water. The ether layer was washed with 5% HCl, and the acidic aqueous layer was made alkaline with 28% NH_4OH and extracted with $CHCl_3$. The extract was washed with water, dried and evaporated to give 152 mg of pale yellow oily *trans*-decahydroquinoline (**28**). The NMR spectrum of the base was identical with that reported by Armarego.[13] The oily base was characterized as its hydrochloride, mp 279—281°. The melting point of this sample was identical with that reported by Armarego.[13] *Anal.* Calcd. for $C_9H_{18}NCl$: C, 61.52; H, 10.33; N, 7.97. Found: C, 61.26; H, 10.59; N, 7.99.

N-Benzyl-*trans*-decahydroquinol-6-en-2-one (29)——A mixture of 300 mg of *trans*-octahydroquinolone (**26**), 40 ml of dry toluene and 300 mg of sodium hydride was heated under reflux for 4 hr. To the mixture was added 756 mg of benzyl chloride and the mixture was refluxed for 5 hr. After cooling, excess sodium hydride was decomposed with water, and the solution was made acidic with 5% HCl. The solution was extracted with ether and the extract was dried and evaporated to leave colorless oil. The oil in $CHCl_3$ was chromatographed over a silica acid column (1.5×15 cm) and the column was eluted with the same solvent. Trituration of the eluate with ether gave a crystalline solid. Recrystallization from ether–*n*-hexane (1: 1) gave 360 mg of N-benzyl-*trans*-decahydroquinol-6-en-2- one (**29**) as colorless prisms, mp 81°. IR ν_{max} cm^{-1}:

1625 (lactam CO). NMR δ: 7.19 (5H, s., aromatic protons), 5.55 (2H, m., olefinic protons), 5.18 and 4.25 (each 1H, d., $J=15$ Hz, benzylic protons), 3.38—2.78 (1H, m., C_{8a}–H). *Anal.* Calcd. for $C_{16}H_{19}ON$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.84; H, 8.07; N, 5.70. Mass Spectrum *m/e*: 241 (M^+), 187 and 91 (base peak).

The Epoxy-lactam, (30) and (31)——To a solution of 723 mg of N-benzyl-*trans*-decahydroquinol-6-en-2-one (**29**) in 20 ml of CH_2Cl_2 was added 620 mg of MCPBA, and the mixture was allowed to stand at room temperature for 20 hr. The mixture was poured into ice-water and extracted with CH_2Cl_2. The extract was washed with dil. NH_4OH, water, dried and evaporated to leave a pale yellow oil (1.22 g). From NMR spectral inspection, the oil was found to be a mixture (1: 1) of two kinds of epoxides. Separation of the mixture by preparative TLC Silica gel GF_{254}, developed by acetone–$CHCl_3$ (1: 20)] afforded two oily epoxides. One of them with higher *Rf* value was found to be the epoxy–lactam (**30**), IR ν_{max} cm^{-1}: 1629 (lactam) CO. NMR δ: 7.27 (5H, broad s., aromatic protons), 5.22 and 4.18 (each 1H, d., $J=16$ Hz, benzylic protons). Mass Spectrum *m/e*: 257 (M^+), 91 (base peak). The other epoxide with lower *Rf* value was the epoxy–lactam (**31**). IR ν_{max} cm^{-1}: 1628 (lactam CO). NMR δ: 7.25 (5H, broad s., aromatic protons), 4.88 and 4.47 (each 1H, d., $J=16$ Hz, benzylic protons). Mass Spectrum *m/e*: 257 (M^+) and 91 (base peak).

The Bromohydrin (32)——To a solution of 90 mg of the epoxy–lactam (**31**) in 5 ml of $CHCl_3$ was added 1 ml of 48% HBr under vigorous stirring and the mixture was stirred at room temperature for 30 min. The mixture was extracted with $CHCl_3$ and the extract was dried and evaporated to leave 139 mg of a pale yellow oil. Trituration of this oil with ether gave a crystalline solid, which was recrystallized from acetone–ether (1: 4) to give 92 mg of the bromohydrin (**32**) as colorless prisms, mp 175°. IR ν_{max} cm^{-1}: 3550, 3350 (OH) and 1622 (lactam CO). NMR (in pyridine-d_5) δ: 7.35 (5H, m., aromatic protons), 4.85 (2H, broad s., benzylic protons), and 3.8—3.3 (1H, m., C_{8a}–H). Mass Spectrum *m/e*: 339, 337 (M^+), 91, 85 and 83.

N-Benzyl-6-bromo-*trans*-decahydroquinol-2,7-dione (33)——To a solution of 1.450 g of the bromohydrin (**32**) in a mixture of 50 ml of acetone–AcOH (4: 1) was added 7 ml of Jones' reagent under stirring at 0° and the mixture was stirred for 1 hr. The excess reagent was decomposed with MeOH and the solution was extracted with $CHCl_3$. The extract was washed, dried and evaporated to leave 1.930 g of a crystalline solid. Recrystallization of the solid from acetone–ether (1: 3) gave 910 mg of N-benzyl-6-bromo-*trans*-decahydroquinol-2,7-dione (**33**) as colorless prisms, mp 166—167°. IR ν_{max} cm^{-1}: 1716 (α-bromo-ketone) and 1635 (lactam CO). NMR δ: 7.26 (5H, s., aromatic protons), 5.06 and 4.84 (each 1H, d., $J=16$ Hz, benzylic protons), and 4.79 (1H, t., $J=3$ Hz, C_6–H). *Anal.* Calcd. for $C_{16}H_{18}O_2NBr$: C, 57.15; H, 5.40; N, 4.17. Found: C, 57.27; H, 5.12; N, 4.02.

The α,β-Unsaturated Ketone, (34) and (35)——To a solution of 910 mg of the bromo-ketone (**33**) in 8 ml of DMF were added 1.5 g of LiBr and 1.5 g of Li_2CO_3 under stirring. The mixture was heated with stirring at 120° under nitrogen atmosphere for 3 hr. After cooling, the mixture was made acidic with 5% HCl and extracted with ether. The extract was washed, dried and evaporated to leave a yellow oil. The oil in $CHCl_3$ was chromatographed over a silica gel column (2.3 × 17 cm) and the column was eluted with the same solvent. Evaporation of the solvent of the earlier eluate gave 18 mg of the α,β-unsaturated ketone (**35**) as a colorless oil. IR ν_{max} cm^{-1}: 1691 (α,β-unsaturated ketone), 1644 (lactam CO) and 1583 (double bond). NMR δ: 7.25 (5H, s., aromatic protons), 5.56 (1H, d., $J=1.5$ Hz, C_8–H), 5.20 and 4.82 (each 1H, d., $J=16$ Hz, benzylic protons). Mass Spectrum *m/e*: 255 (M^+) and 91 (base peak). Removal of the solvent of the later eluate gave 162 mg of the α,β-unsaturated ketone (**34**) as a colorless oil. IR ν_{max} cm^{-1}: 1678 (α,β-unsaturated ketone) and 1640 (lactam CO). NMR δ: 7.25 (5H, s., aromatic protons), 6.80 (1H, q., $J_A=10$ Hz, $J_B=2$ Hz, C_5–H), 6.01 (1H, q., $J_A=10$ Hz, $J_B=3$ Hz, C_6–H) and 5.07 and 4.04 (each 1H, d., $J=16$ Hz, benzylic protons). Mass Spectrum *m/e*: 255 (M^+) and 91 (base peak).

N-Benzyl-5α-methyl-*trans*-decahydroquinol-2,7-dione (36)——To a stirred suspension of 510 mg of CuI in 15 ml of dry ether at 0° was added 13 ml (6.5 mmoles) of methyllithium etherial solution. To the above solution was added dropwise a solution of 122 mg of the α,β-unsaturated ketone (**34**) in a mixture of 2 ml of tetrahydrofuran and 15 ml of ether at nitrogen atmosphere under stirring. The mixture was stirred for 1 hr and poured into 100 ml of ice-water. The solution was made acidic with 5% HCl and extracted with ether. The extract was washed, dried and evaporated to leave a pale yellow oil. The oil was purified by preparative TLC [Silica gel GF_{254}, developed by acetone–$CHCl_3$ (1: 20)] to yield 86 mg of oily N-benzyl-5α-methyl-*trans*-decahydroquinol-2,7-dione (**36**). IR ν_{max} cm^{-1}: 1712 (ketonic CO) and 1633 (lactam CO). NMR δ: 7.25 (5H, s., aromatic protons), 4.09 and 4.43 (each 1H, d., $J=16$ Hz, benzylic protons), 3.8—3.1 (1H, m., C_8—H) and 0.81 (3H, d., $J=7$ Hz, C_5–Me). Mass Spectrum *m/e*: 271 (M^+), 214 and 91 (base peak).

N-Benzyl-5β-methyl-*cis*-decahydroquinol-2,7-dione Monothioacetal (37)——To a solution of 160 mg of the methyl–ketone (**14**) in 15 ml of $CHCl_3$ were added 0.2 ml of ethanedithiol and 10 drops of BF_3–ether. The mixture was allowed to stand at room temperature for 5 hr and the mixture was washed with 5% sodium bicarbonate solution and water. The solvent was evaporated to leave 190 mg of oily colorless N-benzyl-5β-methyl-*cis*-decahydroquinol-2,7-dione monothioacetal (**37**). IR ν_{max} cm^{-1}: 1626 (lactam CO). NMR δ: 7.26 (5H, s., aromatic protons), 5.33 and 4.11 (each 1H, d., $J=15$ Hz, benzylic protons), 3.37—3.76 (1H, m., C_{8a}–H), 3.27 (4H, s., thioacetal four protons) and 1.06 (3H, d., $J=7$ Hz, C_5–Me). Without further purification, the thioacetal (**37**) was used for the next step.

The Compound (38) and the Debenzylated Compound (39)——To a solution of 160 mg of the thioacetal (**37**) in 40 ml of ethanol was added 5 g of Raney W-2 nickel and the mixture was refluxed for 8 hr. After cooling, the catalyst was filtered off, and the filtrate was concentrated under reduced pressure. The residue in $CHCl_3$ was chromatographed on a silica gel column (1.0×10 cm) and the column was eluted with the same solvent. Evaporation of the solvent of the earlier eluate gave 97 mg of the compound (**38**) as a colorless oil. IR ν_{max} cm^{-1}: 1621 (lactam CO). NMR δ: 7.24 (5H, s., aromatic protons), 5.29 and 4.04 (each 1H, d., J=15 Hz, benzylic protons) and 3.18—3.56 (1H, m., C_{8a}–H). Removal of the solvent of the later eluate yielded 4 mg of the debenzylated compound (**39**) which was recrystallized from ether to give 3 mg of the debenzylated compound (**39**) as colorless plates. IR ν_{max} cm^{-1}: 3440, 3340, 3250 (NH) and 1650 (lactam CO). NMR δ: 6.10—6.62 (1H, broad s., NH), 3.63 (1H, m., C_8—H) and 0.92 (3H, d., J=6 Hz, C_5–Me). *Anal.* Calcd. for $C_{10}H_{17}ON$: C, 71.81; H, 10.25; N, 8.38. Found: C, 71.63; H, 10.16; N, 8.33.

5β-Methyl-*cis*-decahydroquinol-2-one (39)——To a mixture of 40 ml of liquid ammonia, 1.0 g of the compound (**38**) and 4 ml of dry ether was added 50 mg of metallic sodium at −33° under stirring. Stirring was continued for further 30 min at −33° and then, 1 g of am monium chloride was added to the solution. Evaporation of ammonia left the residue which was made acidic with 5% HCl. The acidic solution was extracted with $CHCl_3$ and the extract was washed, dried and evaporated to leave 870 mg of a yellow oil. Trituration of the oil with ether gave a crystalline solid which was recrystallized from ether to yield 460 mg of 5β-methyl-*cis*-decahydroquinol-2-one (**39**) as colorless plates, mp 152°. This compound was found to be identical with an authentic sample prepared from the thioacetal (**37**) with Raney W-2 nickel reduction.

The Thio-lactam (40)——To a solution of 50 mg of the debenzylated compound (**39**) in 20 ml of dry benzene was added 30 mg of phosphorous pentasulfide and the mixture was heated under reflux for 2 hr. After cooling, the solvent was evaporated and the residue was extracted with $CHCl_3$. The extract was washed, dried and evaporated to give 90 mg of the oily product. Trituration of the oil with ether gave a crystalline solid which was recrystallized from acetone–ether (1: 3) to give 43 mg of the thio-lactam (**40**) as colorless pillars, mp 130°. IR ν_{max} cm^{-1}: 3360, 3170 (NH). NMR δ: 8.92—8.32 (1H, broad s., NH), 3.62 (1H, m., C_{8a}–H), and 0.92 (3H, d., J=4.5 Hz, C_5–Me). *Anal.* Calcd. for $C_{10}H_{17}NS$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.60; H, 9.52; N, 7.54.

The Thiazole Derivative (41)——To a solution of 100 mg of the thio-lactam (**40**) in 5 ml of freshly distilled CH_2Cl_2 over P_2O_5 was added 75 mg of bromoacetone at room temperature under stirring and the mixture was stirred further for 1 hr. The solvent was removed under reduced pressure and the residue was recrystallized from ether to give 153 mg of the thiazole derivative (**41**) as colorless prisms, mp 252°. IR ν_{max} cm^{-1}: 3050 (OH) and 1605 (C=N). NMR δ: 1.88 (3H, s., HO–C–Me) and 1.15 (3H, d., J=7 Hz, C_5–Me). *Anal.* Calcd. for $C_{13}H_{22}ONSBr$: C, 48.74; H, 6.93; N, 4.38. Found: C, 48.74; H, 6.66; N, 4.45.

The Vinylogous Amide (42)——A solution of 153 mg of the thiazole derivative (**41**) in 100 ml of CH_2Cl_2 was washed with 5% sodium bicarbonate solution, and the organic layer was dried and evaporated to leave a yellow oil. To a solution of the oil in 10 ml of dry benzene were added 700 mg of triphenylphosphine, 15 mg of KOBu(t) and 1 ml of HOBu(t). The mixture was stirred at 60° under nitrogen atmosphere for 5 hr. After removal of the solvent, the residue was extracted with CH_2Cl_2, and the extract was dried and evaporated to leave a colorless oil. The oil in $CHCl_3$ was chromatographed over a silica gel column (0.8×16 cm) and the column was eluted with the same solvent to give 70 mg of the vinylogous amide (**42**) as a colorless oil. IR ν_{max} cm^{-1}: 3300 (NH), 1603 and 1558 (vinylogous amide). NMR δ: 11.00 (1H, broad s., NH), 4.88 (1H, diffused s., olefinic proton), 3.55 (1H, m., C_{8a}–H), 1.97 (3H, s., –CO–Me), 0.91 (3H, d., J=5 Hz, C_5–Me). Mass Spectrum m/e: 207 (M^+), 192, 164 and 136 (base peak).

The β-Amino-ketone (44)——A solution of 58 mg of the vinylogous amide (**42**) in 7 ml of AcOH was catalytically hydrogenated at atmospheric pressure over 120 mg of PtO_2 at room temperature for 4 hr. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue was made alkaline with ammonia and extracted with CH_2Cl_2. The extract was dried and evaporated to give 83 mg of a yellow oil. The oil in ether was chromatographed over an alumina column and the column was eluted with the same solvent to give 55 mg of the pale yellow oily amino–alcohol (**43**) which showed two spots on silica gel TLC. To a solution of 55 mg of the oily amino–alcohol (**43**) in 5 ml of acetone was added 0.2 ml of Jones' reagent at 0° under stirring and the solution was stirred for 1 hr. The excess reagent was decomposed with MeOH and the solvent was evaporated under reduced pressure. The residue was made alkaline with aq. ammonia and extracted with CH_2Cl_2. The extract was washed, dried and evaporated to give 40 mg of a yellow oil which was purified by preparative TLC [Silica gel GF_{254}, developed by MeOH–$CHCl_3$ (1: 6)] to give 20 mg of the β-amino–ketone (**44**) as a colorless oil. IR ν_{max} cm^{-1}: 3300 (NH) and 1704 (CO). NMR δ: 2.77—3.22 (2H, m., C_2–H and C_{8a}–H; overlapped), 2.13 (3H, s., COMe), and 0.83 (3H, d., J=6.5 Hz, C_5–Me). Mass Spectrum m/e: 209 (M^+). 166, 152 and 136. The oily β-amino–ketone (**44**) was characterized as its hydrochloride. Recrystallization from MeOH gave the β-amino–ketone (**44**) hydrochloride as colorless needles, mp 193°. *Anal.* Calcd. for $C_{13}H_{24}ONCl$: C, 63.48; H, 9.84; N, 5.70. Found: C, 62.99; H, 9.87; N, 5.48.

The Thioacetal (45)——To a solution of 20 mg of the β-amino–ketone (**44**) in 3 ml of $CHCl_3$ were added 75 mg of ethanedithiol and 4 drops of BF_3–ether, and the mixture was stirred at room temperature for 40 hr.

To the solution was added 20 ml of $CHCl_3$ and the solution was washed with 5% NH_4OH, dried and evaporated to leave 38 mg of a colorless oil. The oil was purified by preparative TLC [Silica gel GF_{254}, developed by MeOH–$CHCl_3$ (15: 85)] to give 20 mg of the thioacetal (**45**) as a colorless oil. The oil was characterized as its hydrochloride. Recrystallization of the hydrochloride from $CHCl_3$–AcOEt (1: 4) gave the thioacetal (**45**) hydrochloride as colorless needles, mp 119—120°. IR ν_{max} cm^{-1}: 2995 and 1588. NMR δ: 3.40 (4H, diffused s., thioacetal four protons), 1.83 (3H, s., Me–C–S–), 0.90 (3H, d., J=6.5 Hz, C_5–HMe). Mass Spectrum *m/e*: 285 (M^+), 242, 226 and 152 (base peak). *Anal.* Calcd. for $C_{15}H_{28}NS_2Cl \cdot 1/4H_2O$: C, 55.18; H, 8.80; N, 4.29. Found: C, 55.04; H, 8.86; N, 4.16.

***dl*-Pumiliotoxin C (46)**——To a solution of 375 mg of the thioacetal (**45**) hydrochloride in 40 ml of MeOH was added 6 g of Raney W–2 nickel and the mixture was refluxed under stirring for 7 hr. After cooling, the catalyst was filtered off, and the filtrate was made acidic with 5% HCl. The solvent of the filtrate was removed under reduced pressure at room temperature and the residue in $CHCl_3$ was chromatographed over a silica gel column (0.8×3 cm) and the column was eluted with the same solvent. The soluent of the eluate was evaporated and the residue was recrystallized from EtOH–AcOEt (1: 3) to give 152 mg of *dl*-pumiliotoxin C (**46**) hydrochloride as colorless needles, mp 232° (in a sealed capillary tube). IR ν_{max} cm^{-1}: 3200—3600 (NH), 1590, 1470, 1465, 1460, 1455 and 950. IR ν_{max}^{KBr} cm^{-1}: 3200—3600 (NH), 1582, 1465, 1420, 962 and 942. NMR (in $CDCl_3$, 100 MHz) δ: 2.97 (1H, broad s., $W_{1/2}$=15 Hz, C_2–H), 0.92 (3H, t., J=6 Hz, $-CH_2$–Me) and 0.89 (3H, d., J=6 Hz, C_5–Me). The NMR spectrum of the synthetic *dl*-pumiliotoxin C hydrochloride was identical with that of natural pumiliotoxin C reported by Witkop, *et al.*[4] Mass Spectrum *m/e*: 195 (M^+), 194 and 152 (base peak). *Anal.* Calcd. for $C_{13}H_{26}NCl$: C, 67.36; H, 11.31; N, 6.04. Found: C, 67.07; H, 11.57; N, 5.98.

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