A Synthesis of *dl*-Pumiliotoxin-C

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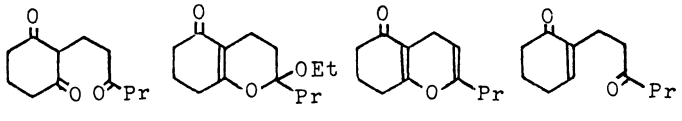
Synopsis. Reductive aminocyclization of trans-2-(3-oxohexyl)-3-methyl-1-cyclohexanone (**4**) with sodium cyanotrihydroborate and ammonium bromide gave *dl*-pumiliotoxin-C (**5**) and its stereochemical isomer (**6**) in a ratio of 48:52.

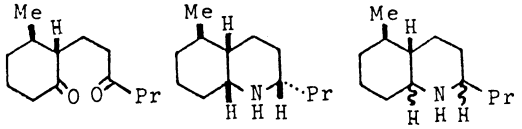
Recently, we have reported of reductive aminocyclization of 2,6-alkanediones with sodium cyanotrihydroborate and ammonium bromide to afford *cis*-6-alkyl-2-methylpiperidine as a sole product.[1]

This experimental fact stimulated us to synthesize **5**, a minor component of the frog Dendrobates pumilio,[2] although many chemists have already reported on its synthesis.[3–6]

This paper reports of experimental results and discussion of our synthesis of **5**.



1 **2** **2′** **3**



4 **5** **6**

Results and Discussion

For reductive aminocyclization, *trans*-2-(3-oxohexyl)-3-methyl-1-cyclohexanone (**4**) was prepared from 1,3-cyclohexanedione in 4 steps: In the first step, 1,3-cyclohexanedione was alkylated with 1-chloro-3-hexanone under alkaline conditions to afford 2-(3-oxohexyl)-1,3-cyclohexanedione (**1**) in 40% yield. **1** was refluxed in ethanol and benzene with a catalytic amount of *p*-toluenesulfonic acid to give 2-ethoxy-2-propyl-7,8-dihydro-5(6*H*)-chromanone (**2**) quantitatively. The structure of **2** was confirmed from the following two experimental facts: even when **2** was treated with an excess amount of lithium aluminum hydride, 2-(3-oxohexyl)-2-cyclohexen-1-one (**3**) as a sole product was given in 80% yield; **2** was easily converted to 2-propyl-5,6,7,8-tetrahydro-4*H*-chromen-5-one (**2′**) on distillation. The enone **3** was treated with lithium dimethylcuprate(**I**) in dry ether to give **4** in 90% yield. The stereochemical correlation between the methyl and 3-oxohexyl groups must be trans configuration. Thus **4** was treated with sodium cyanotrihydroborate and ammonium bromide in dry methanol at room temperature for 4 d and worked up to give a basic yellow oil in 88% crude yield. A GLC analysis showed that the basic oil consisted of two components in a ratio of 48:52 at R_t's 4.5 and 4.8 min, respectively. The first peak was identical with an authentic sample of **5** as revealed by the co-injection method. They were separated by means of preparative GLC using a glass column packed with 5% Silicone OV-1. Each of them was converted to its hydrochloride. The salt of the first peak component was identical with an authentic sample of *dl*-pumiliotoxin-C hydrochloride as revealed by comparison of their melting points and ^{13}C NMR spectra. The hydrochloride of the second one had the same chemical formula as the hydrochloride of **5** as a result of elemental analysis and melted at 246—250 °C. These facts suggest that the second one **6** seems to be a stereochemical isomer of **5**. But we could not determine its stereochemistry.

Experimental

All melting and boiling points are uncorrected. ^1H and ^{13}C NMR spectra were measured with a JEOL PS-100 and a JEOL FX-100, respectively, using tetramethylsilane as internal standard.

2-(3-Oxohexyl)-1,3-cyclohexanedione (1). Into 30 ml of aqueous solution of potassium hydroxide (8.4 g, 0.15 mol) was dissolved solid 1,3-cyclohexanedione (10.8 g, 0.15 mol). Then a solution of 1-chloro-3-hexanone (20.3 g, 0.15 mol) in methanol (75 ml) was added into it. The reaction mixture was stirred for 24 h at room temperature and then concentrated to one fifth volume. It was made alkaline with aqueous solution of potassium hydroxide and then extracted with ether several times. The aqueous layer was acidified with hydrochloric acid and then extracted with ether (30 ml×5). The ethereal extract was washed with brine and dried over anhydrous sodium sulfate. After removal of the solvent, the residue became crystalline, which was recrystallized from hexane to give **1** (7.5 g, 40% yield): mp 87—88 °C; IR (CCl_4) 3150, 1680, and 1600 cm^{-1}; UV (EtOH) 263 nm (1.5×10^4); MS 210 (M^+); ^1H NMR ($CDCl_3$) δ=0.93 (t, J=7 Hz, 3H), 1.42—2.20 (m, 5H), 2.20—2.60 (m, 8H), and 2.60—2.81 (m, 2H): Found C, 68.54; H, 8.63. Calcd for $C_{12}H_{18}O_3$: C, 68.56; H, 8.72.

2-Ethoxy-2-propyl-7,8-dihydro-5(6H)-chromanone (2). A mixture of **1** (4 g, 19 mmol), a catalytic amount of *p*-toluenesulfonic acid, ethanol (60 ml), and benzene (180 ml) was slowly refluxed in a Dean-Stark apparatus to remove deposited water azeotropically. It was washed with 10% aque-

ous solution of sodium hydroxide three times and with brine, and dried over anhydrous sodium sulfate. After removal of the solvent, the residue obtained was used for the next step without further purification. When it was distilled under reduced pressure, it decomposed to 2-propyl-5,6,7,8-tetrahydro-4*H*-chromen-5-one (**2'**): Crude yield 4.5 g, quantitative; IR (neat) 1700, 1650, 1620, 1380, 1220, 1180, and 1130 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.95 (t, J=7 Hz, 3H), 1.10 (t, J=7.5 Hz, 3H), 1.2—1.7 (m, 4H), 1.7—2.1 (m, 4H0, 2.25 (t, J=7 Hz, 6H), and 3.45 (q, J=7.5 Hz, 2H).

2-Propyl-5,6,7,8-tetrahydro-4H-chromen-5-one (2'). ^1H NMR ($CDCl_3$) δ=0.93 (t, J=7 Hz, 3H), 1.50 (sex, J=7 Hz, 2H), 1.90 (t, J=7 Hz, 2H), 2.88 (t, J=7 Hz, 4H), and 4.70 (t, J=4.5 Hz, 1H).

2-(3-*Oxohexyl*)-2-*cyclohexen*-1-*one* (**3**). To a stirred suspension of lithium aluminum hydride (0.83 g, 0.02 mol) in dry ether (50 ml) was added dropwise a solution of **2** (2.38 g, 0.01 mol) in dry ether (50 ml). The mixture was stirred for 3 h at room temperature and then treated carefully with water. The white solid formed was filtered through Celite and washed successively with ether. The filtrate was washed with brine. After removal of the solvent, the residue was distilled under reduced pressure to give **3** (15.6 g, 80% yield): bp 81—90 °C (0.01 mmHg) (1 mmHg=133.322 Pa); IR (neat) 1700, 1660, 1610, 1440, 1410, 1370, 1250, 1170, 1130, 1100, 1080, 1000, and 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ= 0.9 (t, J=7.5 Hz, 3H), 1.55 (t, J=4.5 Hz, 2H), 2.00 (m, 2H), 2.15—2.60 (m, 1H), and 6.70 (t, J=4.5 Hz, 1H); MS 119 (M^+). Found: C, 74.19; H, 9.14. Calcd for $C_{12}H_{18}O_2$: C, 73.76; H, 9.35.

2-(3-Oxohexyl)-3-methyl-1-cyclohexanone (4). To a suspension of copper(I) iodide (5.73 g, 0.03 mol) in dry ether (100 ml) was added an ethereal solution of methyllithium (0.06 mol) at −15 °C in an argon atmosphere. When the mixture became transparent, a solution of **3** (3.88 g, 0.02 mol) in dry ether (60 ml) was added at −15 °C. The reaction mixture was stirred for 30 min and then treated with aqueous solution of ammonium chloride. The ethereal layer was washed with brine and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was distilled under reduced pressure to give **4** (3.8 g, 91% yield): bp 85—89 °C (0.03 mmHg); IR (neat) 1720, 1700, 1450, 1400, 1370, 1130, and 1040 cm^{-1}. ^1H NMR ($CDCl_3$) δ=9.25 (t, 7.5 Hz, 3H), 1.33 (d, J=7.5 Hz, 3H), 1.20—2.00 (m, 9H), and 2.20—2.70 (m, 7H). Found: C, 74.04; H, 10.53. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54.

Reductive Aminocyclization of 4 to dl-*Pumiliotoxin-C (5) and its Stereochemical Isomer (6).* To a suspension of **4** (2.38 g, 0.023 mol) and ammonium bromide (2.22 g, 0.023 mol) in dry methanol (30 ml) was added all at once sodium cyanotrihydroborate (0.71 g, 0.012 mol). The reaction mixture was stirred at room temperature for 4 d. Then it was acidified with conc. hydrochloric acid (pH 3) and stirred for additional 30 min. After evaporation of solvent from the reaction mixture under reduced pressure, the residue was washed with ether several times and then dissolved in water. The aqueous solution was extracted with ether by using an eternal extactor. The extracted ethereal solution was dried over anhydrous sodium sulfate and condensed to give a yellow oil (crude 2.93 g, 88% yield), which was offered for preparative GLC.

Preparative GLC of the Basic Yellow Oil. The GLC was carried out with a AEROGRAPH Model 920 (glass column, 5 mm×3 M, packed with 5% Silicone OV-1 on 80—100 mesh Chomosorb W, oven temp, 145 °C; injection temp, 160 °C). Two peaks appeared at R_t's 4.5 and 4.8 min in a ratio of 48:52, respectively. The first peak was identical with an authentic sample of **5**. The preparative GLC was carried out under the same conditions. The first component was converted to its hydrochloride in a usual manner: mp 230 °C [lit,[6] 232 °C]; ^{13}C NMR ($CDCl_3$) δ=13.19, 19.83, 20.63, 23.19, 25.29, 27.28, 29.15, 34.18, 34.69, 58.04, and 60.10. The second component also was converted to its hydrochloride, which was recrystallized from ethyl acetate and isopropyl alcohol (5:1): mp 246—250 °C (white needle); ^{13}C NMR ($CDCl_3$) δ=13.33, 18.28, 24.09, 25.29, 28.02, 29.89, 34.92, 36.56, 44.42, 58.12, and 61.70; Found: C, 67.26; H, 11.38, N, 5.94. Calcd for $C_{13}H_{26}ClN$: C, 67.39; H, 11.23; N, 6.05.

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