7,8-Dihydro-5(6*H*)Quinolones. Potential Intermediates for the Synthesis of Pumiliotoxic C

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An approach to Pumiliotoxin C (**1**) based on stereoselective hydrogenation of the regioselective condensation products of primary and tertiary vinylogous amides, 7,8-dihydro-5(6*H*)quinolones, is described. The 2-substituted quinolones fail to undergo complete saturation to the corresponding decahydroquinolines, stopping instead at the hexahydroquinoline oxidation state.

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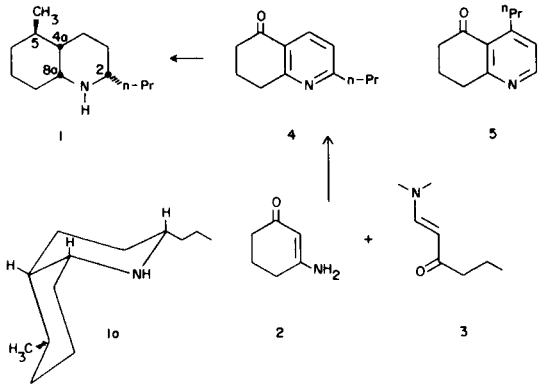
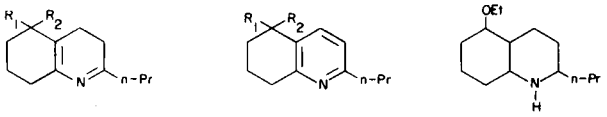
Several syntheses of Pumiliotoxin C (**1**), a neurotoxin isolated from the skin of the Panamanian tree frogs *Dendrobates pumilio* (1) and *D. Auratus* (2) have been reported (3-6). Most notable is the elegant enantioselective synthesis of Oppolzer which unequivocally established the 2*S* absolute configuration that had been incorrectly assigned by Witkop and co-workers on the basis of an x-ray analysis and enantioselective synthesis (3b).

Our approach to **1** was based on the regioselective reactivity of primary enaminoketones toward tertiary enaminoketones (7). It was expected that reaction of cyclohexanedione derivative **2** (8) with 3° enaminoketone **3** (9) would yield regioisomer **4** and not **5**. Properly controlled catalytic reduction of **4** should occur from a single face of the molecule, thus establishing in a single step the proper relative configuration at 3° carbons 2, 4a and 8a. Stereoselective methylation would then provide **1**. Functionalization of the C-4 carbonyl prior to hydrogenation would provide the wrong relative configuration at C-5. In such a case, it would be critical to introduce functionality which would allow for future isomerization at C-5 to the more conformationally stable equitorial position displayed by the natural product (**1a**).



Reaction of **2** with **3** in acetic acid at 85° gave an 85% yield of tetrahydroquinolone **4**, with no compound **5** detectable. It was decided to hydrogenate **4** prior to C-5 functionalization. Hydrogenation in acetic acid of the hydrochloride salt of **4** afforded hexahydroquinolol **6a**. At both atmospheric and 40 psi hydrogen pressures, reduction stopped after the uptake of two equivalents of hydrogen. Hydrogenation of the ketal tosylate **7a** gives ethoxy decahydroquinoline **8** as a complex mixture of stereoisomers.



6a R_1=H; R_2=OH

6b R_1=Me; R_2=OH

7a R_1=R_2=OEt • HOTS

7b R_1=OH; R_2=Me

7c R_1,R_2=$CHCO_2Et$

7d R_1=H; R_2=OH • HCl

7e R_1=CH_2CO_2Et; R_2=H

7f R_1,R_2=NOH

8

As a result, it was decided to functionalize **4** at C-5 prior to hydrogenation. Addition of methyllithium at -78° provides alcohol **7b**. Reduction from the methyl side of the molecule would provide the proper relation configuration at all 4 asymmetric centers C-2, 4a, 5 and 8a, whereas reduction from the alcohol face would provide the wrong relative configuration only at C-5. Compound **7b** failed to hydrogenate cleanly. Even at elevated pressures and temperatures, a mixture of **7b** and the hexahydroquinolol **6b** was isolated. High pressure (70 atmospheres) hydrogenation (12) of acrylate **7c**, prepared by reaction of **4** with the Na salt of triethyl phosphonoacetate (10), gave tetrahydroquinoline **7e**. Thus it would appear that hydrogenation of 2,5-disubstituted-5,6,7,8-tetrahydroquinolines, even at high pressures, stops after the uptake of only one equivalent of hydrogen with reduction only at C-3 and C-4, and that the electronic nature of the C-5 substituent does not significantly effect the reduction. Chemically, the carbonyl moiety of C-5 of quinolone **4** behaves in a normal manner, undergoing aldol (**10a**) condensation, aminoformylation (**10b**) and hydride reduction (**7d**), as well as ketal (**7a**) and oxime (**7f**) derivatization (10). That these systems (**4** or **7**) do not completely hydrogenate, even under high hydrogen pressures, with large catalyst to substrate ratios and at elevated temperatures was most discouraging.

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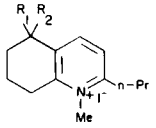
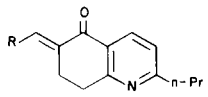


9a R_1, R_2=O

9b R_1=Me; R_2=OH



10a R=Ph

10b R=NMe_2

In general, hydride reduction of quinolines provides the more conformationally stable trans ring junction with significant mixtures of stereoisomers. Despite this, and because of our hydrogenation failures, the borohydride reductions of quaternary salts **9a** and **9b** were performed. As anticipated, both provided bad stereomixtures of octahydroquinolols, and this approach was quickly abandoned. No futher attempts at the hydrogenation of tetrahydroquinolines (**7**) or hexahydroquinolines (**6**) were made.

EXPERIMENTAL

The ir spectra were recorded on a Perkin Elmer Model 257 or 457 grating spectrophotometer and nmr spectra were recorded using either a Varian T-60 or EM-360 spectometer. ^{13}C nmr spectra were recorded using a Varian XLFT-100 spectrometer. Chemical shifts (δ) are recorded relative to TMS, coupling constants (J) are given in Hertz. Mass spectra were recorded using either an LKB 9000 or an AEI MS-30-D5-50 spectrometer. Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. In all workup procedures, the drying process involved swirling over magnesium sulfate and filtering prior to evaporation. The starting materials **2** (8) and **3** (9) were prepared by literature procedures.

7,8-Dihydro-2-*n*-propyl-5(6*H*)quinolone (**4**).

A mixture of 1-dimethylaminomethylene-2-pentanone (38 g., 0.27 mole) and vinylogous amide **2** (30 g., 0.27 mole) in glacial acetic acid (800 ml.) was heated at 85° for 10 hours and then evaporated *in vacuo* to remove the acetic acid. Water and ether were added, and the ether layer was separated, washed with dilute sodium bicarbonate, dried, filtered through silica gel (500 g.) and evaporated. Bulb-to-bulb distillation (120-128°/0.1 mm) of the residue afforded 43.2 g. (85%) of **4** as a clear liquid; nmr (deuteriochloroform): δ 0.98 (t, J = 6 Hz, 3H), 1.75 (m, 2H), 2.16 (m, 2H), 2.65 (t, J = 7 Hz, 2H), 2.79 (t, J = 7 Hz, 2H), 3.12 (t, J = 6 Hz, 3H), 7.11 (d, J = 8 Hz, 1H) and 8.14 (d, J = 8 Hz, 1H); ir (dichloromethane): 1675 and 1580 cm^{-1}.

Anal. Calcd. for $C_{12}H_{15}NO$: C, 76.1; H, 8.0; N, 7.4. Found: C, 75.9; H, 8.1; N, 7.8.

5-Hydroxy-2-*n*-propyl-3,4,5,6,7,8-tetrahydroquinoline (**6a**).

A mixture of quinolone **4** (1.89 g., 10 mmoles), concentrated hydrochloric acid (0.85 ml.) and platinum oxide (0.6 g.) in ethanol (50 ml.) was shaken under hydrogen (40 psi) for 48 hours. Filtration though silica gel and evaporation gave 1.85 g. of a yellow oil; nmr (deuteriochloroform): δ 0.90 (m, 3H), 1.42 (m, 4H), 1.88 (m, 4H), 3.25 (m, 1H) and 2.30 (m, 6H); ir (chloroform): 3460 and 1575 cm^{-1}.

Anal. Calcd. for $C_{12}H_{19}NO$: C, 74.6; H, 9.9; N, 7.3. Found: C, 74.5; H, 10.1; N, 7.0.

5,5-Diethoxy-2-*n*-propyl-5,6,7,8-tetrahydroquinoline tosylate (**7a**).

Evaporation *in vacuo* of a mixture of quinolone **4** (1.89 g., 10 mmoles) and *p*-toluenesulfonic acid hydrate (1.90 g., 10 mmoles) in triethyl orthoacetate (100 ml.), which had been heated at reflux for 72 hours, gave 4.17 g. (96%) of tosylate **7a**, b.p. 100-115°/0.15 mm; nmr (deuteriochloroform): δ 0.98 (t, J = 7 Hz, 3H), 1.24 (t, J = 7 Hz, 6H), 1.80-2.32 (m, 4H), 2.43 (s, 3H), 2.50-2.88 (m, 4H), 3.10 (t, J = 6 Hz, 2H), 4.19 (q, J = 7 Hz, 4H), 7.10 (d, J = 8 Hz, 1H), 7.52 (ABq, 4H), and 8.13 (d, J = 8 Hz, 1H).

Anal. Calcd. for $C_{25}H_{33}NO_5S$: C, 63.4; H, 7.6; N, 3.2. Found: C, 63.2; H, 7.8; N, 3.1.

5-Ethoxy-2-*n*-propyldecahydroquinoline (**8**).

A mixture of ketal **7a** (0.435 g., 1 mmole) and 10% palladium-charcoal (0.050 g.) in acetic acid (20 ml.) was stirred under an atmosphere of hydrogen until hydrogen uptake stopped. Filtration through celite and evaporation gave a dark oil, **8**, as a mixture of stereoisomers; nmr (deuteriochloroform): δ 0.99 (t, J = 7 Hz, 3H), 1.32 (t, J = 7 Hz, 3H), 1.70-2.10 (M, 10H), 2.44 (s, 3H), 2.50-3.10 (M, 6H), 4.10 (q, J = 7 Hz, 2H), 4.80 (broad s, 1H) and 7.53 (ABq, 4H).

5-Hydroxy-5-methyl-2-*n*-propyl-5,6,7,8-tetrahydroquinoline (**7b**).

To quinoline **4** (1.89 g., 10 mmoles) in ether (30 ml.) at -78°, under an atmosphere of nitrogen, was added methyllithium (6.0 ml. of a 1.7 *M* ether solution) and the resulting mixture was stirred at -78° for 3 hours, then quenched with water (5 ml.) and allowed to warm to ambient temperature. To the ether layer was added hydrazine (1 ml.) and ether (70 ml.). After a water wash, filtration through silica gel, evaporation of the ether and distillation of the residue (105-115°/0.1 mm) gave 1.56 g. (75%) of **7b**; nmr (deuteriochloroform): δ 0.98 (t, J = 7 Hz, 3H), 1.51 (s, 3H), 1.60-3.04 (m, 11H), 6.95 (d, J = 8 Hz, 1H) and 7.64 (d, J = 8 Hz, 1H); ir (chloroform): 3610 and 1580 cm^{-1}.

Anal. Calcd for $C_{13}H_{19}NO$: C, 76.0; H, 9.3; N, 6.8. Found: C, 75.7; H, 8.9; N, 7.0.

Ethyl (2-*n*-Propyl-5,6,7,8-tetrahydroquinolin)-Δ^{5},α-acrylate (**7c**).

To a suspension of 50% sodium hydride (0.48 g., 10 mmoles) in toluene (100 ml.) at ambient temperature was added dropwise triethylphosphonoacetate (2 ml.) and, after the solution cleared a solution of quinolone **4** (1.89 g., 10 mmoles) in toluene (5 ml.). The resulting mixture was heated at 80° for 2 hours and then for 8 hours at 65°. After cooling water was added and the product extracted with ether. The combined ether extracts were washed with water, dried, evaporated and the residue distilled (100-110°/0.1 mm) to give 0.85 g. (44%) of **7c** as a yellow oil; nmr (deuteriochloroform): δ 0.95 (t, J = 7 Hz, 3H), 1.23 (m, 3H), 1.45-2.05 (m, 4H), 2.35-3.30 (m, 6H), 4.14 (m, 2H), 6.57-8.10 (m, 3H); ir (chloroform): 1705, 1625 and 1595 cm^{-1}.

Anal. Calcd. for $C_{16}H_{23}NO_2$: C, 73.5; H, 8.8; N, 5.4. Found: C, 73.1; H, 8.7; N, 5.0.

5-Hydroxy-2-*n*-propyl-5,6,7,8-tetrahydroquinoline (**7d**).

To a solution of quinolone **4** (1.89 g., 10 mmoles) in wet ethanol (25 ml.) was added portionwise sodium borohydride (0.42 g. 11 mmoles) and the resulting mixture was stirred at ambient temperature for several hours, poured into water and extracted thoroughly with ether. The ether extracts were washed with brine, dried and evaporated to give 1.62 g. (85%) of quinolol **7d** as a yellow oil; nmr (deuteriochloroform): δ 0.94 (t, J = 7 Hz, 3H), 1.50-2.05 (m, 6H), 2.40-2.95 (m, 4H), 4.21 (broad s, 1H), 4.71 (m, 1H), 6.92 (d, J = 8 Hz, 1H) and 7.67 (d, J = 8 Hz, 1H); ir (chloroform): 3605, 1600 and 1580 cm^{-1}.

Ethyl (2-*n*-Propyl-5,6,7,8-tetrahydroquinolyl)-5-acetate (**7e**).

Exposure of a mixture of acrylate **7c** (1.31 g., 5 mmoles) and 5% rhodium on alumina (0.26 g.) in ethanol 100 ml. at 80° to hydrogen at 70 atmosphere pressure for 24 hours gave, after removal of the catalyst by filtration and evaporation of the solvent 1.31 g. of **7e** as an analytically pure yellow oil; nmr (deuteriochloroform): δ 0.95 (t, J = 7 Hz, 3H), 1.21 (t, J = 6 Hz, 3H), 1.50-3.00 (m, 13H), 4.19 (q, J = 6 Hz, 2H), 6.92 (d, J = 8 Hz, 1H) and 7.36 (d, J = 8 Hz, 1H); ir 1715 and 1580 cm^{-1}.

Anal Calcd. for $C_{16}H_{25}NO_2$: C, 73.0; H, 9.5; N, 5.3. Found: C, 72.6; H, 9.9; N, 4.9.

7,8-Dihydro-2-*n*-propyl-5(6*H*)quinolone Oxime (**7f**).

A mixture of quinolone **4** (3.8 g., 20 mmoles), sodium acetate (2.5 g.), and hydroxylamine hydrochloride (2.0 g.) in absolute ethanol (50 ml.) was heated at reflux for 8 hours, cooled, filtered and evaporated. Recrystallization of the residue from ethanol gave 2.5 g. (61%) of **7f** as a white

powder, m.p. 182-182.5°; nmr (deuteriochloroform): δ 0.97 (t, J = 8 Hz, 3H), 1.56-2.08 (m, 4H), 2.67-3.06 (m, 6H), 7.02 (d, J = 8 Hz, 1H), 8.16 (d, J = 8 Hz, 1H) and 9.80 (broad s, 1H); ir (chloroform): 3600, 3100-3300 and 1600 cm^{-1}.

Anal. Calcd. for $C_{12}H_{16}N_2O$: C, 70.6; H, 7.9; N, 13.7. Found: C, 70.2; H, 7.8; N, 13.4.

6-Benzylidene-2-*n*-propyl-7,8-dihydro-5(6*H*)quinolone (**10a**).

A mixture of quinolone **4** (1.89 g., 10 mmoles), benzaldehyde (1.06 g., 10 mmoles), 15% potassium *t*-butoxide in *t*-butyl alcohol (4 ml.) and *t*-butyl alcohol (12 ml.) was stirred under nitrogen at ambient temperature for 18 hours. After neutralization with acetic acid, water and ether were added, the ether layer was removed, washed well with brine and sodium bicarbonate, dried and evaporated. Bulb-to-bulb distillation (180-210°/0.06 mm) of the residue gave 1.50 g. (54%) of **10a** as a clear oil; nmr (deuteriochloroform): δ 0.98 (t, J = 7 Hz, 3H), 1.77 (m, 2H), 2.80 (m, 4H), 3.13 (s, 2H), 7.15 (d, J = 8 Hz, 1H), 7.35 (s, 5H), 7.84 (s, 1H) and 8.30 (d, J = 8 Hz, 1H); ir (chloroform): 1680 and 1600 cm^{-1}.

Anal. Calcd. for $C_{19}H_{19}NO$: C, 82.3; H, 6.9; N, 5.1. Found: C, 82.7; H, 7.1; N, 4.9.

6-(Dimethylaminomethylene)-2-*n*-propyl-7,8-dihydro-5(6*H*)quinolone (**10b**).

Quinolone **4** (1.89 g., 10 mmoles) and methoxybis(dimethylamino)methane (11) (25 ml.) were heated at 100° for 12 hours. Evaporation *in vacuo* and recrystallization of the residue from chloroform gave 2.18 g. (89%) of **10b**, m.p. 100-103°; nmr (deuteriochloroform): δ 0.97 (t, J = 7 Hz, 3H), 1.72 (m, 2H), 2.70 (m, 4H), 3.00 (s, 2H), 3.14 (s, 6H), 7.07 (d, J = 8 Hz, 1H), 7.68 (s, 1H), and 8.07 (d, J = 8 Hz, 1H); ir (chloroform): 1655 and 1590 cm^{-1}.

Anal. Calcd. for $C_{15}H_{20}N_2O$: C, 73.7; H, 8.3; N, 11.5. Found: C, 73.9; H, 8.1; N, 11.4.

7,8-Dihydro-1-methyl-2-*n*-propyl-5(6*H*)oxoquinolinium Iodide (**9a**).

A solution of quinolone **4** (1.89 g., 10 mmoles) and methyl iodide (5 ml.) in acetonitrile (20 ml.) was heated at reflux for 8 hours or until no **4** remained. Evaporation of the solvent and trituration with ether gave 3.10 g., (93%) of **9a** as a white amorphous solid.

Anal. Calcd. for $C_{13}H_{18}INO$: C, 47.1; H, 5.5; N, 4.2; I, 38.3. Found: C, 47.0; H, 5.4; N, 4.5.

5,6,7,8-Tetrahydro-5-hydroxy-5-methyl-2-*n*-propylquinolinium Iodide (**9b**).

Treatment of quinolol **7b** with methyl iodide in a similiar manner gave 3.05 g. (88%) of **9b** as an amorphous white solid.

Anal. Calcd. for $C_{14}N_{22}INO$: C, 48.4; H, 6.4; N, 4.0; I, 36.5. Found: C, 48.2; H, 6.6; N, 4.0.

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