Synthesis of (±)-Depentylperhydrohistrionicotoxin

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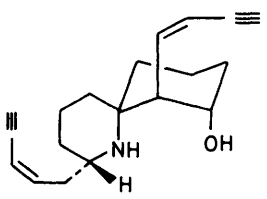
Palladium(0)-catalysed cyclisation of 3-acetoxy-1-(4-aminoalkyl)cyclohexenes provides convenient access to the 1-azaspiro[5.5]undecane ring system found in the histrionicotoxins. Hydroboration of the 7-butyl derivative (4; R^1 = Bu^n, R^2 = H) and oxidation of the purified borane adduct with trimethylamine oxide afforded *N*-benzyldepentylperhydrohistrionicotoxin, which was readily converted into (±)-depentylperhydrohistrionicotoxin by hydrogenolysis over palladium–carbon.

Histrionicotoxin (1) and a number of analogues were isolated [1] from the venom of the Colombian frog *Dendrobates histrionicus*. Both histrionicotoxin and its octahydro and perhydro derivatives show valuable neurophysiological properties connected with inhibition of the ion-transport mechanism of cholinergic receptors,[2] and similar properties have been found recently in the depentylperhydro compound (2).[3] Because of this and the scarcity of the natural material there has been widespread synthetic interest in this field. Several syntheses of (±)-perhydrohistrionicotoxin have been reported [4,5] and the octahydro [5] compound has also been made, but histrionicotoxin itself has not yet been synthesized.

In our approach [6] to compounds in this series we had it in mind to set up the ring system (4) by palladium-catalysed cyclisation of suitably substituted 3-acetoxy-1-(4-aminoalkyl)-cyclohexenes (3). Reaction of carbon nucleophiles with allylic acetates catalysed by Pd^0 complexes has been widely studied [7] and a few reactions leading to the formation of carbon–nitrogen bonds in bridged and fused-ring nitrogen heterocycles have been described,[8] but no example of the formation of a spiro ring system by this procedure had been reported when we took up this work. In the event we have found that Pd^0-catalysed cyclisation of precursors of type (3; R^2 = H) leads smoothly to the 1-azaspiro[5.5]undecane system found in the histrionicotoxins and we have used this reaction in a convenient and flexible synthesis of (±)-depentylperhydrohistrionicotoxin.

The required cyclohexenyl acetate (3; R^1 = Bu^n, R^2 = H) was readily prepared from 2-butylcyclohexane-1,3-dione. Reaction of the derived ethyl enol ether with the Normant Grignard reagent [9] prepared from 4-chlorobutanol or, better, with the Grignard reagent from the tetrahydropyranyl ether of 4-chlorobutanol, gave the cyclohexenone (5) in good yield. This was readily converted into compound (6) by reduction of the derived toluene-*p*-sulphonate with sodium borohydride in the presence of cerium(III) chloride,[10] and thence into the required amine (3; R^1 = Bu^n, R^2 = H) by acetylation and displacement of the tosyloxy group by reaction with benzylamine and catalytic sodium iodide in dimethyl sulphoxide (DMSO).

Cyclisation of (3; R^1 = Bu^n, R^2 = H) was effected with tetrakis(triphenylphosphine)palladium in boiling acetonitrile and gave the spirocycle (4; R^1 = Bu^n, R^2 = H) in 60% yield in the best case. The assigned structure for the cyclisation product is fully supported by its high-resolution mass spectrum and the ^{13}C and ^1H n.m.r. spectra. In particular the ^{13}C and ^1H spectra clearly show the presence of a vinylic $=C^-H$ group, thus eliminating the possible alternative structure (7). The spirocycle (4; R^1 = Bu^n, R^2 = H) has also been obtained recently by Pearson by a different route using organoiron chemistry; [11] the properties of our compound agree closely with those of his. † The Pd^0-catalysed cyclisation of the parent compound (3; R^1 = R^2 = H) to the spirocycle (4; R^1 = R^2 = H) was reported by Godleski and his colleagues [12] while the present work was in progress. We had also effected this cyclisation before taking up work with the butyl derivative (3; R^1 = Bu^n, R_2 = H), obtaining results very similar to theirs.



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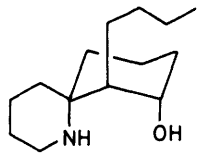

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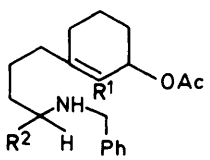

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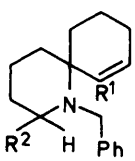

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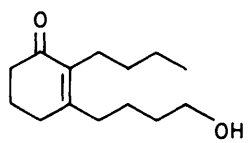

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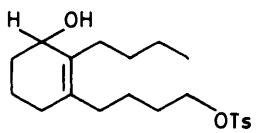
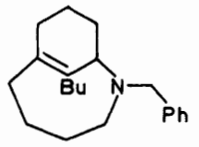


(6)

Conversion of compound (4; R^1 = Bu^n, R^2 = H) into depentylperhydrohistrionicotoxin requires anti-Markownikov hydration of the double bond. We sought to effect this by hydroboration and oxidation, in the expectation that the nitrogen would direct attack of the hydroborating agent to give the required *cis*-axial orientation of the hydroxy substituent.[13] Hydroboration was readily effected with diborane in tetrahydrofuran (THF), but oxidation of the resultant crude alkylborane with alkaline hydrogen peroxide [14] gave only poor yields of a mixture of alcohols and a considerable amount of unchanged alkylborane. Our attention was thus turned to oxidation with trimethylamine oxide.[15] Direct oxidation of the crude hydroboration product with trimethylamine oxide in boiling diglyme (diethylene glycol dimethyl ether) gave a complex mixture of products, but better results were obtained using borane adduct which had been purified by flash chromatography. This operation led to considerable loss of

† *Note added in proof.* An alternative synthesis of the spirocycle (4; R^1 = Bu^n, R^2 = H) has been reported recently by S. A. Godleski and D. J. Heacock (*J. Org. Chem.*, 1982, **47**, 4820) without physical data.



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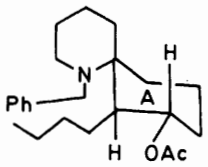

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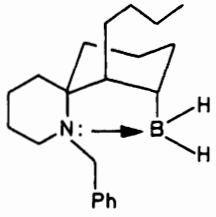

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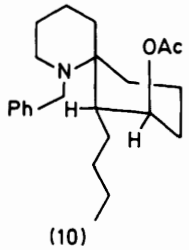

(10)

material but the recovered product (50%) was stable in air and appears from subsequent results to be largely in the form (9) which is presumably stabilised by the presence of the chelated five-membered ring. Oxidation of this material with trimethylamine oxide in boiling diglyme gave a mixture of alcohols (60%) whose acetates were readily separated by flash chromatography. The main component (90%) had ^{1}H and ^{13}C n.m.r. spectra and a high-resolution mass spectrum fully consistent with the desired acetate (8) in the conformation in which the benzyl-substituted nitrogen of the piperidine ring and the butyl and acetoxy substituents are all equatorial in ring A. In the 400 MHz ^{1}H n.m.r. spectrum the signal for the C*H*OAc proton appears as a triplet of doublets centred at δ 4.92, corresponding to coupling of an axial proton to two other axial protons (*J* 10.87 Hz) and to an equatorial proton (*J* 4.56 Hz). The ^{1}H spectrum of our acetate is very similar to that of an acetate obtained by Pearson [11] with greater difficulty after oxidation of the borane adduct with alkaline hydrogen peroxide and to which he assigned structure (8), and it also shows the very large non-equivalence of the benzylic protons which he notes. The minor acetate obtained from the chromatogram showed a narrower pattern for the C*H*OAc proton at δ 5.11 and a closer AB quartet for the benzylic methylene protons, in line with the *epi* structure (10).

Conversion of compound (8) into dependylperhydrohistrionicotoxin (2) confirmed the assigned structure. Hydrolysis with sodium hydroxide in warm methanol afforded the corresponding alcohol whose 400 MHz ^{1}H n.m.r. spectrum now showed a broad singlet for the C*H*OH proton possibly suggesting a conformational change leading to an equatorial disposition of this proton in contrast to that in the acetate. Hydrogenolysis of the alcohol over palladium–carbon led smoothly to dependylperhydrohistrionicotoxin (2). The structure is fully supported by its 400 MHz ^{1}H and ^{13}C n.m.r. spectra and the high-resolution mass spectrum. The ^{1}H n.m.r. spectrum agrees closely with that recently found by Pearson [11] and that reported by Witkop and his colleagues.[3] The signal due to the C*H*OH proton now appears as a narrow quartet at δ 3.87, indicating an equatorial disposition and suggesting that in the dependyl compound the hydroxy substituent is axial and hydrogen-bonded to the amino-group, as in histrionicotoxin.[1] Since the dependyl compound has already [16] been converted into perhydrohistrionicotoxin itself, the present work represents formally a synthesis of the latter compound.

Experimental

I.r. spectra were recorded on a Perkin-Elmer 398 spectrophotometer. Low-resolution mass spectra were obtained with a V.G. Micromass M.M.16F instrument; high-resolution spectra were determined at P.C.M.U. Harwell. N.m.r. spectra were recorded with a Jeol JNM-PS-100 instrument at 100 MHz for ^{1}H and 25 MHz for ^{13}C; 400 MHz spectra were recorded at Warwick University. Rapid (flash) chromatography [17] was carried out on silica gel (230—400 mesh, Merck type 60). Light petroleum refers to the fraction b.p. 40—60 °C unless otherwise stated.

2-Butylcyclohexane-1,3-dione.—A solution of methyl 5-oxodecanoate (33.6 g, 0.168 mol) in dry diethyl ether (1 dm^3) was added dropwise during 4 h to a stirred boiling solution of potassium t-butoxide (22.6 g, 0.2 mol) in t-butyl alcohol (75 cm^3) and diethyl ether (500 cm^3) under nitrogen. The solution was boiled for a further 1 h, cooled, and acidified with hydrochloric acid (2M; 125 cm^3). The product was recovered from the ether layer and crystallised from light petroleum (b.p. 60—80 °C)–diethyl ether as prisms (23.4 g, 83%), m.p. 115—117 °C (lit.,[18] 115—116 °C); $\nu_{max.}$ ($CHCl_3$) 3 555, 3 200, 2 950, 1 784, and 1 704 cm^{-1}; δ_H ($CDCl_3$) 0.88 (3 H, distorted t, Me), 1.1—1.7 (6 H, m, 3 × CH_2), 1.8—3.0 (6 H, m, CH_2CO and 2 × CH_2), and 7.30 (1 H, br s, enolic OH).

The dione (19.3 g) was converted into its ethyl enol ether by refluxing a solution in ethanol (100 cm^3) and dry benzene (300 cm^3) in the presence of toluene-*p*-sulphonic acid (0.5 g) under nitrogen for 24 h, with circulation of the refluxing solvent through a Soxhlet thimble containing 3 Å molecular sieve (50 g). The recovered product was distilled to give the enol ethyl ether as an oil (22.1 g, 98%), b.p. 84—86 °C/0.05 mmHg; $\nu_{max.}$ (film) 2 956, 2 926, 1 643, 1 610, 1 374, 1 231, and 1 139 cm^{-1}; δ_H ($CDCl_3$) 0.88 (3 H, t, *J* 6 Hz, Me), 1.1—1.6 (4 H, m, 2 × CH_2), 1.34 (3 H, t, *J* 6 Hz, Me), 1.7—2.3 (8 H, m, CH_2CO and 3 × CH_2), and 4.06 (2 H, q, *J* 6 Hz, CH_2O) (Found: M^+, 196.1466. Calc. for $C_{12}H_{20}O_2$: *M*, 196.1445).

2-Butyl-3-(4-hydroxybutyl)cyclohex-2-enone (5).—A solution of 2-butyl-3-ethoxycyclohex-2-enone (3.6 g) in dry THF (20 cm^3) was added dropwise during 30 min to a stirred cooled (−78 °C) solution of the Grignard reagent prepared [19] from 1-chloro-4-tetrahydropyranyloxybutane (4.95 g), magnesium (1.0 g), and 1,2-dibromoethane (0.1 cm^3) in THF (60 cm^3). The reaction mixture was allowed to warm to room temperature during 3 h and was then stirred for a further 12 h. The recovered product was purified by flash chromatography to give starting material (22% recovery) and the required *2-butyl-3-(4-tetrahydropyranyloxybutyl)cyclohex-2-enone* (3.92 g, 71%) as a pale yellow oil, b.p. 230 °C/0.03 mmHg (Kugelrohr); $\nu_{max.}$ (film) 2 930, 1 660, 1 616, 1 140, and 1 037 cm^{-1}; δ_H ($CDCl_3$) 0.9 (3 H, distorted t, Me), 1.1—2.5 (24 H, m, 12 × CH_2), 3.2—4.1 (4 H, m, 2 × CH_2O), and 4.58 (1 H, br s, OCHO); δ_C ($CDCl_3$) 199.1 (C=O), 158.4 (olefinic C), 135.8 (olefinic C), 98.9 (CH), 67.1, 62.4, 38.1, 34.7, 31.9, 30.8, 30.5, 29.9, 25.5, 24.9, 24.8, 23.0, 22.6, 19.7 (14 × CH_2), and 14.0 p.p.m. (CH_3) (Found: M^+, 308.2347. $C_{19}H_{32}O_3$ requires *M*, 308.2343).

Hydrolysis of the above tetrahydropyranyl derivative (12.1 g) was effected in stirred ethanol (100 cm^3) with pyridinium toluene-*p*-sulphonate [20] (1.0 g) at 60 °C for 5 h. The recovered *2-butyl-3-(4-hydroxybutyl)cyclohex-2-enone* (5) was a pale yellow oil (7.9 g), b.p. 180 °C/0.01 mmHg (Kugelrohr); $\nu_{max.}$ (film) 3 450, 2 930, 2 868, 1 654, 1 620, and 1 369 cm^{-1}; δ_H ($CDCl_3$) 0.82 (3 H, distorted t, Me) 1.0—2.0 (10 H, m, 5 × CH_2), 2.0—2.4 (8 H, m, 4 × CH_2), 3.01 (1 H, br s, OH, removed by D_2O exchange), and 3.58 (2 H, br t, CH_2O,

addition of D_2O gives t, J 7 Hz); δ_C ($CDCl_3$) 199.6 (C=O), 159.2 (olefinic C), 135.7 (olefinic C), 62.1, 38.0, 34.7, 32.7, 31.9, 30.5, 24.8, 24.3, 23.0, 22.6 (all CH_2), and 14.0 p.p.m. (CH_3) (Found: C, 74.8; H, 10.7%; M^+ 224. $C_{14}H_{24}O_2$ requires C, 74.96; H, 10.8%; M, 224). The *toluene*-p-*sulphonate* was obtained as an oil (91%) after purification by flash chromatography; δ_H ($CDCl_3$) 0.91 (3 H, distorted t, Me), 1.0—2.25 (18 H, m, 9 × CH_2), 2.38 (3 H, s, Me), 3.99 (2 H, t, J 7 Hz, CH_2OTs), 7.35 (2 H, d, J 8 Hz, ArH), and 7.78 (2 H, d, J 8 Hz ArH); δ_C ($CDCl_3$) 198.9 (C=O), 157.4 (olefinic C), 144.8 (q), 136.0 (olefinic C), 133.0 (q), 129.2 (2 × CH), 127.8 (2 × CH), 70.1, 38.1, 34.0, 31.9, 30.4, 28.9, 24.9, 23.8, 22.9, 22.5 (all CH_2), 21.6 (CH_3), and 14.0 p.p.m. (CH_3); m/z 378 (M^+) (Found: C, 66.6; H, 7.9. $C_{21}H_{30}O_4S$ requires C, 66.6; H, 8.0%).

2-*Butyl*-3-(4-p-*tolylsulphonyloxybutyl*)*cyclohex*-2-*en*-1-*ol* (6). —Sodium borohydride (2.26 g) was added portionwise during 30 min to a rapidly stirred solution of the foregoing toluene-*p*-sulphonate (7.5 g) and cerium(III) chloride hexahydrate [10] in methanol (53 cm³), whilst the temperature of the reaction mixture was kept <35 °C. Towards the end of the reaction a white precipitate formed and further methanol (70 cm³) was added to allow easy stirring. After the addition was complete the mixture was stirred for a further 15 min. The recovered product [7.6 g; $\nu_{max.}$ (film) 3 540, 3 400, 3 028, 2 922, 2 858, 1 600, 1 360, 1 191, and 1 178 cm⁻¹ (Found: $M + NH_4^+$, 398.2574. $C_{21}H_{36}NO_4S$ requires m/z, 398.2365)] was unstable, even at −10 °C, and was converted directly into the acetate by reaction with acetic anhydride (3.8 cm³) and 4-dimethylaminopyridine [21] (4.9 g) in dichloromethane (75 cm³) at 0 °C; the temperature rose to 25 °C during 3 h. Purification by flash chromatography and elution with ethyl acetate–light petroleum (1 : 4) afforded the *acetate* as an oil (8.02 g), $\nu_{max.}$ (film) 3 050, 2 962, 2 860, 1 722, 1 600, 1 360, 1 288, 1 189, and 1 173 cm⁻¹; δ_H ($CDCl_3$) 0.95 (3 H, distorted t, Me), 1.2—2.2 (18 H, m, 9 × CH_2), 2.12 (3 H, s, OCOMe), 2.58 (3 H, s, Ar*Me*), 4.22 (2 H, t, J 6 Hz, CH_2OTs), 5.59 (1 H, br s, C*H*OAc), 7.77 (2 H, d, J 8 Hz, ArH), and 8.22 (2 H, d, J 8 Hz, ArH); δ_C ($CDCl_3$) 171.0 (C=O), 144.7 (q), 137.2 (olefinic C), 133.3 (q), 129.8 (2 × CH), 129.5 (olefinic C), 127.9 (2 × CH), 70.4 (CH_2), 70.0 (CH), 32.5, 31.2, 29.6, 29.2, 29.1, 29.0, 24.1, 22.9 (all CH_2), 21.6 (CH_3), 21.4 (CH_3), 18.4 (CH_2), and 14.0 p.p.m. (CH_3); m/z 362 (M − HOAc) (Found: C, 65.2; H, 8.4. $C_{23}H_{34}O_5S$ requires C, 65.4; H, 8.1%).

3-*Acetoxy*-1-(4-*benzylaminobutyl*)-2-*butylcyclohex*-1-*ene* (3; R^1 = Bu^n, R^2 = H).—A solution of the above 3-acetoxy-2-butyl-1-(4-*p*-tolylsulphonyloxybutyl)cyclohex-1-ene (8.6 g) in dry DMSO (40 cm³) was added dropwise to a stirred solution of benzylamine (6.56 g) and sodium iodide (50 mg) in DMSO (10 cm³) under nitrogen. The mixture was kept overnight and was then poured into saturated brine and extracted with diethyl ether. The recovered product was chromatographed on aluminia (500 g; Brockmann grade I); elution with ethyl acetate–light petroleum (3 : 7) gave the *benzylamino compound* as an oil (6.3 g), $\nu_{max.}$ ($CHCl_3$) 3 350, 3 040, 3 028, 2 860, 1 715, 1 600, and 1 245 cm⁻¹; δ_H ($CDCl_3$) 0.82 (3 H, distorted t, Me), 1.0—2.0 (18 H, m, 9 × CH_2), 2.01 (3 H, s, Me), 2.59 (2 H, t, J 7 Hz, CH_2CH_2N), 3.70 (2 H, s, $PhCH_2N$), 5.22 (1 H, br s, C*H*OAc), and 7.21 (5 H, s, ArH); δ_C ($CDCl_3$) 171.0 (C=O), 140.2 (q), 138.0 (olefinic C), 128.9 (olefinic C), 128.4 (2 × CH), 128.1 (2 × CH), 126.9 (CH), 70.1 (CH), 54.1, 49.3, 33.2, 31.3, 30.2, 29.6, 29.3, 29.2, 26.1, 22.9 (all CH_2), 21.4 (CH_3), 18.4 (CH_2), and 14.0 p.p.m. (CH_3) [Found: (M^+ − HOAc) 297.2444 (23%). $C_{21}H_{31}N$ requires 297.2431. Found: C, 77.3; H, 9.8; N, 3.9. $C_{23}H_{35}NO_2$ requires C, 77.3; H, 9.9; N, 3.9%].

Further elution of the column afforded a small amount (0.75 g) of another product which appeared to be the *N,N*-disubstituted benzylamine.

1-*Benzyl*-7-*butyl*-1-*azaspiro*[5.5]*undec*-7-*ene* (4; R^1 = Bu^n, R^2 = H).—A suspension of 3-acetoxy-1-(4-benzylaminobutyl)-2-butylcyclohex-1-ene (320 mg), freshly distilled, dry triethylamine (0.25 cm³), and tetrakis(triphenylphosphine)-palladium(0) (90 mg) in acetonitrile (8 cm³) was heated under reflux under argon for 72 h. The cooled reaction mixture was diluted with diethyl ether and filtered through a pad of Celite. The recovered product was purified by flash chromatography (eluant methyl acetate) to yield the cyclised product followed by starting material (55 mg, 17% recovery). The cyclised product was taken up in diethyl ether and extracted into dilute hydrochloric acid. The recovered 1-*benzyl*-7-*butyl*-1-*azaspiro*-[5.5]*undec*-7-*ene*, b.p. 155 °C/0.01 mmHg, was an oil (159 mg, 60%), $\nu_{max.}$ ($CHCl_3$) 3 058, 2 990, 2 922, 2 859, 1 598, 1 089, 1 068, and 1 021 cm⁻¹; δ_H ($CDCl_3$; 400 MHz), 0.85 (3 H, t, J 7.1 Hz, Me), 1.24—2.53 (20 H, m, 10 × CH_2), 3.12 and 3.76 (each 1 H, d, J 14.7 Hz, PhC*H*H), 5.58 (1 H, br t, J 7.6 Hz, olefinic H), 7.18 (1 H, t, J 7.6 Hz, ArH), 7.28 (2 H, t, J 7.3 Hz, ArH), and 7.35 (2 H, d, J 7.6 Hz, ArH); δ_C ($CDCl_3$) 144.2 (q), 141.2 (q), 128.0 (2 × CH), 127.8 (2 × CH), 126.1 (CH), 124.0 (CH), 59.8 (q), 55.1, 45.2, 33.2, 31.8, 28.2, 26.3, 25.7, 23.1, 21.8, 20.3 (all CH_2), and 14.2 p.p.m. (CH_3) (Found: M^+, 297.2452. $C_{21}H_{31}N$ requires M, 297.2456).

Several subsequent reactions were carried out on a gramme scale (up to 5 g), affording yields of the spiro compound in the range 45—55%.

Reaction of 1-*Benzyl*-7-*butyl*-1-*azaspiro*[5.5]*undec*-7-*ene with Diborane.—Isolation of borane adduct.* A solution of diborane in THF (1M; 14 cm³) was added to a stirred solution of 1-benzyl-7-butyl-1-azaspiro[5.5]undec-7-ene (2.06 g) in THF (10 cm³) at 0 °C under argon. The reaction mixture was allowed to warm to room temperature and was then heated under reflux for 30 min. The cooled solution was poured into ice–water, basified with aqueous sodium carbonate (1M; 20 cm³), and extracted with dichloromethane. Flash chromatography of the recovered product, using dichloromethane as eluant, led to an exothermic reaction on the column and only part of the borane adduct (1.1 g, 52%) was recovered. This adduct was found to be stable in air for prolonged periods; $\nu_{max.}$ ($CHCl_3$) 2 946, 2 878, 2 330 (B–H stretch), 1 465, 1 261, 1 109, and 908 cm⁻¹; δ_H ($CDCl_3$) 0.95 (3 H, distorted t, Me), 1.1—3.2 (24 H, m, 10 × CH_2, 2 × CH, and 1 × BH_2), 3.83 and 4.38 (each 1 H, d, J 12.0 Hz, PhC*H*HN), and 7.2—7.9 (5 H, m, ArH) (Found: M^+, 311.2790 and 310.2720. $C_{21}H_{34}{}^{11}BN$ requires 311.2784, $C_{21}H_{34}{}^{10}BN$ requires 310.2821).

Oxidation of Purified Borane Adduct.—O-*Acetyl*-N-*benzyl-depentylperhydrohistrionicotoxin* (8). A stirred solution of the above chromatographed borane adduct (524 mg) and trimethylamine *N*-oxide dihydrate (562 mg) in diglyme (8 cm³) was refluxed under nitrogen for 18 h. The cooled solution was diluted with dichloromethane (50 cm³), washed (brine), dried, and evaporated under reduced pressure. The residual oil was purified by flash chromatography; elution with diethyl ether–light petroleum (1 : 1) gave a mixture of *N*-benzyldepentylperhydrohistrionicotoxin and its C-8 epimer (300 mg, 56%) followed by unchanged alkylborane (131 mg, 25% recovery).

The alcohols (300 mg), without separation, were converted into their acetates with acetic anhydride (0.18 cm³) and 4-dimethylaminopyridine (230 mg) in dichloromethane (6 cm³). Flash chromatography of the mixture of acetates and elution with ethyl acetate–light petroleum (1 : 40) gave O-*acetyl*-N-

benzyldepentylperhydrohistrionicotoxin (8) as a waxy solid (290 mg, 86%), m.p. 40—42 °C; $\nu_{max.}$ ($CHCl_3$) 2 936, 2 860, 1 720, 1 605, and 1 255 cm^{-1}; δ_H ($CDCl_3$; 400 MHz) 0.78 (3 H, t, *J* 7.3 Hz, Me), 0.9—2.5 (21 H, m, 10 × CH_2, and C*H*Bu), 2.02 (3 H, s, $COCH_3$), 3.04 and 4.14 (each 1 H, d, *J* 14.3 Hz, PhC*H*H), 4.92 (1 H, t of d, *J* 10.9 and 4.5 Hz, C*H*OAc), and 7.19—7.33 (5 H, m, ArH); δ_C ($CDCl_3$) 170.5 (C=O), 141.2 (q), 128.0 (2 × CH), 127.6 (2 × CH), 126.2 (CH), 76.9 (CH), 60.3 (q), 52.1 (benzylic CH_2), 48.2 (CH), 46.6, 33.7, 32.5, 26.9, 26.4, 26.1, 23.5, 22.9 (8 × CH_2), 21.4 (Me), 19.7 (2 × CH_2), and 13.9 (Me) (Found: M^+, 357.2672. $C_{23}H_{35}NO_2$ requires *M*, 357.2668).

Further elution afforded the *epi*-acetate (10) (46 mg, 13%), $\nu_{max.}$ ($CHCl_3$) 2 938, 2 860, 1 720, 1 605, and 1 255 cm^{-1}; δ_H ($CDCl_3$; 100 MHz) 0.90 (3 H, distorted t, Me), 1.0—2.5 (21 H, m, 10 × CH_2 and C*H*Bu), 2.02 (3 H, s, CH_3CO), and 3.47 and 3.79 (each 1 H, d, *J* 15.5 Hz, PhC*H*H), 5.11 (1 H, m, C*H*OAc), and 7.26 (5 H, m, ArH) (Found: M^+, 357.2667).

N-*Benzyldepentylperhydrohistrionicotoxin*.—A mixture of *O*-acetyl-*N*-benzyldepentylperhydrohistrionicotoxin (8) (255 mg) and sodium hydroxide solution (1M in 50% aqueous methanol; 7 cm^3) was boiled for 2 h. The cooled solution was diluted with water and extracted with diethyl ether. Flash chromatography of the recovered product with diethyl ether–light petroleum (1 : 1) gave N-*benzyldepentylperhydrohistrionicotoxin* as an oil (204 mg), $\nu_{max.}$ ($CHCl_3$) 3 300, 2 940, 1 605, and 1 468 cm^{-1}; δ_H ($CDCl_3$; 400 MHz) 0.92 (3 H, t, *J* 7.5 Hz, Me), 1.1—3.2 (21 H, 10 × CH_2 and C*H*Bu), 3.66 and 4.07 (each 1 H, d, *J* 12.5 Hz, PhC*H*H), 4.00 (1 H, m, sharpens on D_2O exchange, C*H*OH), 7.2—7.4 (5 H, m, ArH), and 7.97 (1 H, d, *J* 9 Hz, exchanged with D_2O, OH); δ_C ($CDCl_3$) 139.0 (q), 128.6 (4 × CH), 127.0 (CH), 69.8 (CH), 59.6 (q), 48.8 (CH_2), 41.4 (CH_2), 38.2 (CH), 31.6, 30.4, 28.6, 28.2, 27.3, 23.1, 19.7, 17.9, 15.4 (9 × CH_2), and 14.0 p.p.m. (Me) (Found: M^+, 315.2559. $C_{21}H_{33}NO$ requires *M*, 315.2562).

(±)-*Depentylperhydrohistrionicotoxin* (2).—A solution of *N*-benzyldepentylperhydrohistrionicotoxin (160 mg) in ethanol was shaken with 5% palladium–charcoal catalyst (50 mg) in hydrogen for 4 h. The recovered oil was chromatographed on neutral alumina (40 g, Brockmann grade 1); elution with dichloromethane–methanol (9 : 1) gave (±)-depentylperhydrohistrionicotoxin (2) as an oil (98 mg). H.p.l.c. analysis [3] on a 10μ Sperisorb column (25 cm × 3 mm i.d.) and elution with a mixture of n-hexane (95%), propan-2-ol (4.9%), and triethylamine (0.1%) at a flow rate of 2 cm^3 min^{-1}, revealed a single peak (R_t 5.75 min); $\nu_{max.}$ ($CHCl_3$) 3 660, 3 160, 2 938, 1 463, and 970 cm^{-1}; δ_H ($CDCl_3$; 400 MHz) 0.90 (3 H, t, *J* 7 Hz, Me), 1.0—2.0 (21 H, 9 × CH_2, C*H*Bu, OH, and NH; changes with D_2O); 2.78 and 2.92 (each 1 H, m, C*H*HN), and 3.87 (1 H, dd, C*H*OH); δ_C ($CDCl_3$; 400 MHz) 69.9 (CH), 54.6 (q), 41.9 (CH), 40.2, 37.2, 33.3, 30.4, 28.0, 27.2 (×2), 22.9, 19.4, 15.1 (10 × CH_2), and 13.9 p.p.m. (Me) (Found: M^+, 225.2098. Calc. for $C_{14}H_{27}NO$: *M*, 225.2093).

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