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INDOLE ALKALOIDS FROM *ANTIRHEA PORTORICENSIS*

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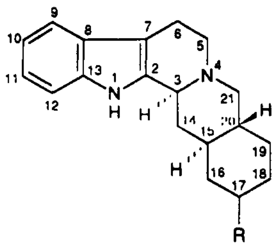
ABSTRACT.—Two new indole alkaloids, 20-*epi*-antirhine [**4**] and 19(*S*)-hydroxydihydrocorynantheol [**6**], have been isolated from *Antirhea portoricensis* (Rubiaceae), collected in the Caribbean. Structures have been established on the basis of spectral data. In addition, four known alkaloids have been isolated, namely, yohimbol [**1**], epi-yohimbol [**2**], antirhine [**3**] and iso-antirhine [**5**].

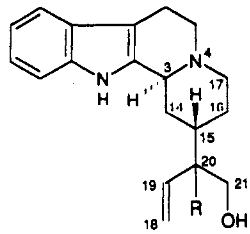
Antirhea portoricensis (Britton & Wilson) Standl. (Rubiaceae), formerly known as *Stenostomum portoricense* Britton & Wilson, is a small- or medium-sized endemic tree of Puerto Rico (1). As part of our continuing interest in Caribbean plants and the chemotaxonomy of West Indian Rubiaceae in particular (2), we report the isolation of two new indole alkaloids from this species.

From the peeled roots (450 g), alkaloids were extracted by the usual process (see Experimental) furnishing 1.2 g of a crude alkaloid mixture (AM). Purification of alkaloids was performed by means of cc and prep. tlc. Six alkaloids were isolated. They were, in order of elution from Si gel, yohimbol [**1**] (3-5) (1.2% of AM), epi-yohimbol [**2**] (3-5) (1.2%), antirhine [**3**] (6,7) (2.5%), 20-*epi*-antirhine [**4**] (1.8%), iso-antirhine [**5**] (8) (2.3%) and 19(S)-hydroxydihydrocorynantheol [**6**] (0.8%). Compounds **1**, **2**, **3** and **5** were identified through their spectral and physical properties (ir, uv, nmr, mass spectra, $[\alpha]^{25}$D). Alkaloids **4** and **6** are new. As the spectral data of compounds **1**, **2** and **5** are incompletely described in the literature, the complete assignments of their ^{1}H- and ^{13}C-nmr spectra are given in the Experimental section.

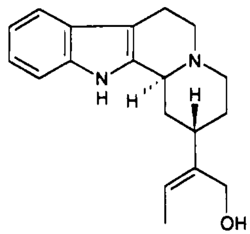
Alkaloid **4** was isolated as an amorphous compound $[\alpha]^{25}$D $+57°$ (c=0.5, $CHCl_3$). The eims showed a molecular ion at *m/z* 296, which was analyzed by hrms for $C_{19}H_{24}N_2O$ and exhibited the same fragmentation pattern as antirhine (6,7). Examination of the ^{1}H-nmr spectrum of **4** revealed the presence of a deshielded broad resonance at δ 4.04, which could be attributed to a proton (H-3) located at the ring junction of a cis-quinolizidine. The configuration of C-15 is assumed to be 15*S* as found in antirhine for biogenetic reasons. Coupling constant values of H-14 indicated that **4** and antirhine possess the same C-3 and C-15 configurations. The most significant differences with antirhine were observed for the H-21 and H-14 chemical shifts (see Experimental). Examination of the ^{13}C-nmr spectrum of **4** showed great similarity with that of **3**. Therefore, the structure 20-*epi*-antirhine was proposed for this novel alkaloid. Its formation pre-



1 R=α-OH
2 R=β-OH



3 R=β-H
4 R=α-H



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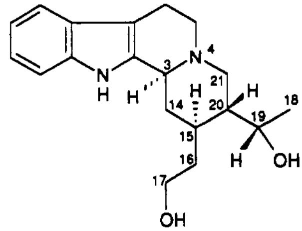

6

sumably resulted from a C-20 epimerization of the biogenetic aldehyde precursor.

The other new alkaloid [**6**] was isolated in minor amounts $[\alpha]^{25}D$ $-3°$ (c=0.6, MeOH), displaying an $[M]^+$ at m/z 314 ($C_{19}H_{26}N_2O_2$ from hrms) and a uv spectrum (λ max 214 and 281 nm) characteristic of an indole chromophore. Its ir spectrum indicated the presence of an NH and/or OH group (3300 cm^{-1}). The ^{1}H-nmr spectrum exhibited four aromatic protons and nineteen aliphatic protons identified by 2D nmr experiments. The ^{1}H- and ^{13}C-nmr spectra showed α-OH ethyl side-chain signals (Me-18 δ_H 1.19, δ_C 16.91 and CH-19 δ_H 4.27, δ_C 66.92) and β-OH ethyl side-chain signals (CH_2-17OH δ_H 3.80, δ_C 60.27 and CH_2-16 δ_H 1.47 and 2.00, δ_C 36.16). The complete assignments were performed using homo- and heteronuclear 2D nmr experiments and were consistent with a dihydrocorynantheol skeleton. From these data, compound **6** was concluded to be 19-hydroxydihydrocorynantheol. Although no data exist for 19-hydroxycorynantheol derivatives, the *S* configuration of C-19 was deduced through comparison of the chemical shifts and coupling constants of compounds of analogous substitution in other series (9,10). 11-Methoxy-19-hydroxydihydrocorynantheol has already been obtained by rearrangement of tetraphylline (11), but this is the first report of such a structure from a natural source.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Optical rotations were determined on a Perkin-Elmer model 141 polarimeter. Spectra were recorded with the following instruments: uv, Perkin-Elmer Lambda 5; ir, Nicolet 205 Ft-ir spectrometer; ms, AEI MS50; ^{1}H nmr (300 MHz) and ^{13}C nmr (75.3 MHz) on a Bruker AC 300. Chemical shifts are given in ppm relative to TMS (δ=0); coupling constants (J) are given in Hz; abbreviations s, d, t, q, and m refer to singlet, doublet, triplet, quadruplet and multiplet, respectively; COSY spectra and ^{1}H-^{13}C HETCOR were performed with the use of the Bruker library of microprograms.

PLANT MATERIAL.—Root material of *Antirhea portoricensis* was collected in Maricao, 18 miles south east of Mayagüez, Puerto Rico, in May 1991. A voucher specimen (G. Caminero, R. García & D. Kolterman N° 432 M-22) is deposited at the Herbarium of the University of Puerto Rico in Mayagüez.

EXTRACTION AND ISOLATION.—Dried and ground peeled roots (450 g) were moistened with 13% NH_4OH and extracted exhaustively with CH_2Cl_2 using a Soxhlet apparatus. The organic solution was extracted with 10% HCl until a Mayer's test was negative. The acid layer was separated, made alkaline with 13% NH_4OH and extracted with CH_2Cl_2. The CH_2Cl_2 layers were washed with H_2O, dried (Na_2SO_4) and evaporated *in vacuo* to give 1.2 g of alkaloid mixture (AM) (yield 0.27 %). The crude AM was fractionated by flash cc over a Si gel column (63–200 μm) using CH_2Cl_2-MeOH-NH_4OH 25% (80:19.5:0.5) as eluent to afford 12 fractions (1-12). Fr. 1, fr. 3, fr. 6, fr. 8, fr. 10, and fr. 12 were further purified by tlc [Si gel; EtOAc-MeOH-H_2O (80:13:7) as solvent], with a 10-min preconditioning time using a Camag Twin Trough Chamber and concentrated NH_4OH) to afford products **1** to **6**.

Yohimbol [**1**].—^{1}H Nmr ($CDCl_3$) δ 1.1–1.7 (m, H-16ax, H-14 ax, H-18ax, 2×H-19, H-20), 1.85 (m, H-15), 1.90 (m, H-16eq, H-18eq), 2.31 (dt, J=12.9 and 3.1 Hz, H-14eq), 2.35 (dd, J=11.5 and 7.1 Hz, H-21ax), 2.71–2.87 (m, H-5, H-6), 3.03 (dd, J=11.5 and 2.6 Hz, H-21eq), 3.09 (m, H-6), 3.25 (ddd, J=12.2, 7.0 and 2.3 Hz, H-5), 3.57 (br dd, J=11.4 and 1.7 Hz, H-3), 4.19 (m, H-17), 6.98 (td, J=7.2 and 1.1 Hz, H-10), 7.05 (td, J=7.2 and 1.1 Hz, H-11), 7.26 (dd, J=7.2 and 1.1 Hz, H-12), 7.38 (dd, J=7.2 and 1.1 Hz, H-9); ^{13}C nmr δ 22.2 (C-6), 25.1 (C-19), 33.1 (C-18), 36.0 (C-15), 36.8 (C-14), 39.8 (C-16), 42.2 (C-20), 54.3 (C-5), 62.2 (C-3), 62.3 (C-21), 67.1 (C-17), 107.5 (C-7), 112.0 (C-12), 118.6 (C-9), 119.9 (C-10), 122.1 (C-11), 128.3 (C-8), 135.2 (C-2), 138.1 (C-13).

epi-*Yohimbol* [**2**].—^{1}H Nmr ($CDCl_3$) δ 1.0–1.5 (m, H-14ax, H-15, H-16ax, H-18ax, H-19ax), 1.73 (dq, J=12.9 and 3.2 Hz, H-19eq), 2.07 (m, H-16eq, H-18eq), 2.15 (t, J=11.3 Hz, H-21ax), 2.27 (dt, J=12.6 and 2.8 Hz, H-14eq), 2.70–2.80 (m, H-5, H-6), 2.98 (dd, J=11.3 and 3.6 Hz, H-21eq), 3.05 (m, H-6), 3.17 (m, H-5), 3.32 (dd, J=11.1 and 2.8 Hz, H-3), 3.67 (tt, J=10.8 and 4.2 Hz, H-17), 7.08 (td, J=7.3 and 1.2 Hz, H-10), 7.14 (td, J=7.3 and 1.2 Hz, H-11), 7.38 (dd, J=7.3 and 1.2 Hz, H-12), 7.48 (dd, J=7.3 and 1.2 Hz, H-9); ^{13}C nmr δ 21.92 (C-6), 29.0 (C-19), 35.3 (C-18), 36.2 (C-14), 40.2 (C-15), 41.0 (C-20), 41.8 (C-16), 53.8 (C-5), 61.1 (C-3), 61.7 (C-21), 70.5 (C-17), 107.2 (C-7), 111.7 (C-12), 118.3 (C-9), 119.4 (C-10), 121.6 (C-11), 127.6 (C-8), 135.0 (C-2), 137.3 (C-13).

20-epi-*Antirhine* [**4**].—$[\alpha]^{25}$D +57° ($CHCl_3$, c=0.5); uv λ max (EtOH) 228 (log ε 4.38), 274 (3.78), 282 (3.81), 290 (3.68) nm; ir ν max ($CHCl_3$) 3400, 3250, 1445, 1320, 1205, 1110, cm^{-1}; eims m/z [M]$^+$ 296 (73), 295 (77), 265 (15), 225 (77), 223 (100), 197 (31), 184 (35), 169 (40), 156 (36); hrms m/z 296.1864 (calcd 296.1887 for $C_{19}H_{24}N_2O$); ^{1}H nmr ($CDCl_3$) δ 1.4–1.6 (m, H-15, 2×H-16), 1.71 (br t, J=11.2 Hz, H-14ax), 2.00 (br d, J=11.2 Hz, H-14eq), 2.16 (m, H-20), 2.45–2.60 (m, H-6, H-17), 2.68 (m, H-17), 2.90 (m, H-5, H-6), 3.10 (m, H-5), 3.38 (dd, J=10.8 and 7.5 Hz, H-21), 3.62 (dd, J=10.8 and 5.8 Hz, H-21), 4.03 (br s, H-3), 5.07 (dd, J=17.0 and 2.0 Hz, H-18), 5.16 (dd, J=10.3 and 2.0 Hz, H-18), 5.59 (ddd, J=17.0, 10.3, and 9.6 Hz, H-19), 7.00 (m, H-10, H-11), 7.25 (dd, J=7.2 and 1.2 Hz, H-12), 7.36 (dd, J=7.2 and 1.2 Hz, H-9), 8.42 (NH); ^{13}C nmr δ 16.5 (C-6), 28.7 (C-16), 31.1 (C-15), 31.3 (C-14), 47.2 (C-17), 49.4 (C-20), 51.8 (C-5), 54.1 (C-3), 63.2 (C-21), 107.9 (C-7), 110.8 (C-12), 117.9 (C-9), 118.6 (C-18), 119.3 (C-11), 121.3 (C-10), 127.5 (C-8), 133.3 (C-2), 135.8 (C-13), 138.1 (C-19).

Iso-antirhine [**5**].—^{1}H Nmr ($CDCl_3$) δ 1.44 (m, H-16), 1.46 (d, J=6.8 Hz, H-18), 1.81 (qd, J=12.3 and 3.8 Hz, H-16ax), 2.07 (br d, J=12.3 Hz, H-14eq), 2.22 (td, J=12.3 and 4.9 Hz, H-14ax), 2.33 (tt, J=12.3 and 3.1 Hz, H-15ax), 2.48 (br dd, J=15.7 and 4.3 Hz, H-6), 2.67 (dt, J=11.2, and 3.8 Hz, H-17eq), 2.80 (ddd, J=12.3, 11.2, and 2.6 Hz, H-17ax), 2.93 (dddd, J=15.7, 13.1, 6.2, and 2.1 Hz, H-6), 3.13 (m, 2×H-5), 4.03 (AB system, 2×H-21, J=12.4 Hz), 4.40 (br s, H-3), 5.48 (q, J=6.8 Hz, H-19), 7.03 (td, J=7.2 and 1.2 Hz, H-10), 7.08 (td, J=7.2 and 1.2 Hz, H-11), 7.27 (dd, J=7.2 and 1.2 Hz, H-12), 7.41 (dd, J=7.2 and 1.2 Hz, H-9).

19(S)-Hydroxydihydrocorynantheol [**6**].—$[\alpha]^{25}$D −3.0° ($CDCl_3$, c=0.6); uv λ max (EtOH) 214 (log ε 4.70), 226 (4.41), 281 (3.80), 290 (3.72) nm; ir ν max (KBr) 3450, 3250, 1450, 1330, 1210, 1035 cm^{-1}; eims m/z [M]$^+$ 314 (90), 313 (100), 269 (34), 267 (20), 241 (15), 223 (15), 184 (46), 170 (21); hrms m/z 314.1982 (calcd 314.1996 for $C_{19}H_{26}N_2O_2$); ^{1}H nmr (MeOH) δ 1.19 (d, J=6.7 Hz, Me-18), 1.37 (dt, J=12.9 and 12.0 Hz, H-14ax), 1.47 (m, H-16), 1.69 (m, H-15), 1.94 (tdd, J=11.4, 4.1, and 3.7 Hz, H-20), 2.00 (m, H-16), 2.41 (t, J=11.4 Hz, H-21ax), 2.57 (ddd, J=12.9, 3.6, and 2.9 Hz, H-14eq), 2.80 (m, H-5, H-6), 3.07 (m, H-6), 3.23 (m, H-5), 3.31 (dd, J=11.4 and 3.7 Hz, H-21eq), 3.35 (dd, J=12.0 and 2.9 Hz, H-3), 3.80 (m, 2×H-17), 4.27 (qd, J=6.7 and 4.1 Hz, H-19), 7.06 (td, J=7.5 and 1.0 Hz, H-10), 7.13 (td, J=7.5 and 1.0 Hz, H-11), 7.38 (dd, J=7.5 and 1.0 Hz, H-12), 7.47 (dd, J=7.3 and 1.0 Hz, H-9); ^{13}C nmr δ 16.9 (C-18), 22.3 (C-6), 35.6 (C-14), 35.8 (C-15), 36.2 (C-16), 47.6 (C-20), 54.6 (C-5), 55.5 (C-21), 60.3 (C-17), 61.8 (C-3), 66.9 (C-19), 107.7 (C-7), 112.0 (C-12), 118.6 (C-9), 119.8 (C-10), 122.0 (C-11), 128.3 (C-8), 135.4 (C-2), 138.1 (C-13).

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