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(2S,5S)-2,5-DIBENZYL-1,4-DIMETHYLPIPERAZINE, A NOVEL ALKALOID FROM ZANTHOXYLUM ARBORESCENS

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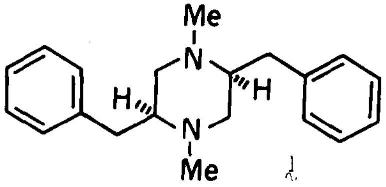
Abstract: The isolation and structure determination of (2S,5S)-2,5-dibenzyl-1,4-dimethylpiperazine (**1**), a new alkaloid biogenetically related to L-phenylalanine diketopiperazine, is described.

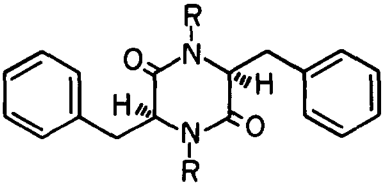
Dreyer investigated[1] the alkaloid content of seed husks from Zanthoxylum arborescens Rose, a Mexican member of the citrus family (Rutaceae), and found two new quinazolones. We have been investigating the leaves, bark, and wood of this species and have found a number of alkaloids. The structure of one of these is described here.

Dried, ground leaves were extracted with hexane and then with MeOH. The residue from the MeOH extraction was dissolved in dil. aq. H_2SO_4. This solution was extracted with $CHCl_3$, made basic to pH 9 (NH_4OH) and extracted again with $CHCl_3$. The last extract was dried and evaporated to leave a crude alkaloid fraction which was purified by flash chromatography[2] on Si gel (EtOAc/EtOH/NH_4OH 35:5:1) and Al_2O_3 plc ($CHCl_3$/MeOH 50:1) to yield a white solid: mp 116-120°;$[\alpha]_D^{23}$ = + 96° (c 0.11, EtOH); Si gel tlc R_f 0.32 (EtOAc); UVλ_{max}^{EtOH} (nm) 253, 222; ^1H NMR ($CDCl_3$, 360 MHz) δ 2.29(dd, J = 3 Hz, J = 13 Hz, 1H), 2.38(s, 3H), 2.53(dd, J = 6 Hz, J = 13 Hz, 1H), 2.65(m, 1H), 2.79(dd, J = 8 Hz, J = 11 Hz, 1H), 3.00(dd, J = 3 Hz, J = 11 Hz, 1H), 7.18-7.32(m, 5H); ^{13}C NMR ($CDCl_3$) δ 33.09(t), 42.67(q), 55.28(t), 62.64(d), 125.81(d), 128.20(d), 129.20(d), 139.76(s); electron impact MS (m/e, %) 203(100), 160(6), 117(6), 111(10), 91(14), 83(10), 78(7), 71(8), 70(78), 57(10), 43(10), 42(21), 41(6), 40(13); high resolution MS (m/e) calcd. for $C_{13}H_{16}N_2$ 203.1548 (obs. 203.1589), calcd. for C_4H_8N 70.0657(obs. 70.0679); chemical ionization MS (NH_3) (m/e, %) 295(100); IR (thin film, cm^{-1}) 2940, 2785, 1490, 1450, 1157, 735, 695.

Although the unknown alkaloid gave an electron impact mass spectrum with only two major peaks: m/e 203 ($C_{13}H_{19}N_2$ by high resolution) and m/e 70 (C_4H_8N by high resolution), the chemical ionization mass spectrum showed that 203 was not the molecular ion, but rather m/e 294. This indicated a molecular formula of $C_{20}H_{26}N_2$ for the unknown. The ^1H NMR spectrum indicated 13 rather than 26 protons, while the ^{13}C NMR spectrum showed 8 resonances. Two of these were probably the result of two identical carbons each, which would mean that we were seeing half the required number of carbon resonances. These data indicated a high degree of symmetry or magnetic equivalence among the various carbons and hydrogens. The NMR spectra were best interpreted as resulting from a monosubstituted benzene with three additional carbons and an N-CH_3 group making up a $C_6H_5CH_2CH(NCH_3)CH_2$ array. If two of these units were joined, the result would be structure **1** or the corresponding trans-isomer. The trans-isomer has a center of symmetry and would not exhibit optical rotation, while the cis-isomer **1** would be optically active, as was the unknown alkaloid. The correctness of structure **1** for the unknown was established by total synthesis.



1



2 R = H
3 R = CH_3

The L-phenylalanine cyclic dipeptide **2** was prepared in 70% yield from t-BOC-L-phenylalanine and L-phenylalanine methyl ester hydrochloride according to the procedure of Nitecki:[3] mp 302-304°C (lit.[3] mp 308-310°C). This was N-methylated to **3** with NaH and MeI in DMF in 77% yield as described by Radding and Goodman:[4] mp 147-150°C (lit.[4] mp 150-151°C).

3 (0.26 mmol) was dissolved in 10 mL THF and 0.77 mmol $LiAlH_4$ was added. The mixture was kept at reflux for 12 hours and then poured into 30 mL water. The aqueous layer was extracted with $CHCl_3$ and the combined $CHCl_3$ solutions were washed with water, 10% $NaHCO_3$ solution, and saturated NaCl solution. The $CHCl_3$ was evaporated in vacuo and the residue purified by silica gel plc (EtOAc) and recrystallized from EtOAc to yield 0.162 mmol of the crystalline solid **1**: mp 123.0-124.5°C; silica gel tlc R_f 0.32 (EtOAc); $[\alpha]_D^{23} = +118°$ (c 0.054, EtOH). ^1H and ^{13}C NMR, IR and mass spectra were identical with those for isolated **1**. Anal. Calcd. for $C_{20}H_{26}N_2$: C, 81.59; H, 8.90; N, 9.51. Obs. C, 81.63; H, 8.85; N, 9.52.

As far as we are aware, **1** is the first simple piperazine alkaloid reported from higher plants. Complex diketopiperazines are known as microbial products and some have also been found in lichens and sponges. A simple N-methylated (but not reduced) diketopiperazine derived from trichloroleucine has been reported[5] from the sponge Dysidea herbacea or its blue-algal symbiont.

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