COCSULINE-N-2-OXIDE, A NEW ALKALOID FROM COCCULUS HIRSUTUS DC.

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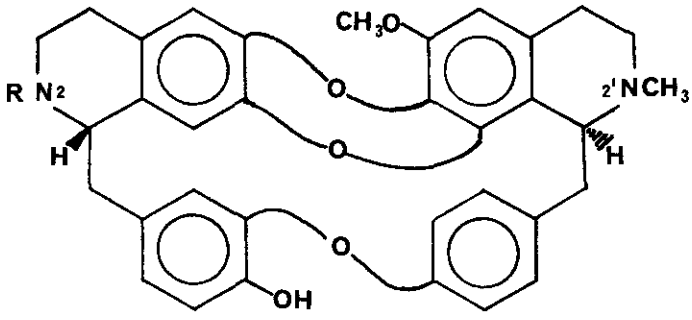
Abstract - Chromatography of an ethanol extract of Cocculus hirsutus DC. (Menispermaceae) over silicic acid afforded a new bisbenzylisoquinoline alkaloid, cocsuline-N-2-oxide (1). The alkaloid was characterized by a consideration of its physicochemical data and conversion to cocsuline (2).

Cocculus hirsutus DC. (Menispermaceae), commonly known as Jai-jamni in India,[1] has been used in folk medicine as a tonic and diuretic.[2] Extracts of this plant have been found to possess hypotensive, cardiotonic, anticonvulsive and central sedative activities.[3] Constituents previously reported in this plant include; magnoflorine,[4,5] coclaurine,[5,6] trilobine[5,6] and isotrilobine.[5] An ethanolic extract of Cocculus hirsutus stems and roots (15 kg) was submitted to an acid-base partition procedure. Subsequent silicic acid column and preparative thin-layer chromatography afforded cocsuline-N-2-oxide (1) (18 mg) as an amorphous residue from MeOH; mp 182-187°; $[\alpha]_D^{25}$ + 125° (c 0.5, MeOH); uv λ_{max}^{MeOH} nm (log ε) 272(3.36), 282(sh)(3.76) and 303(sh) (3.24); uv $\lambda_{max}^{MeOH + 0.1N\ NaOH}$ 285(3.48) and 300(3.45); ir ν_{max}^{KBr} cm^{-1} 3400 (br) 1590, 1508, 1450, 1440, 1385, 1280, 1220 and 1115. The ^{1}H-nmr spectrum (60 MHz, $CDCl_3$-CD_3OD, δ in ppm) indicated the presence of one N-methyl group at 2.60 (3H,s), one N-methyl group at 2.85 (3H,s), one aromatic methoxy group at 3.87 (3H,s) and a complex multiplet of ten aromatic protons (6.25-7.70). The mass spectrum showed a M^+ at m/z 578 (2%) for $C_{35}H_{34}N_2O_6$ with other significant fragment ions at m/z 557(3%), 562(7)(M^+-O), 561(8), 350(21), 349(19), 336(15), 335(2), 334(7),

and 175(100). A consideration of the spectral data suggested that 1 was one of the two possible N-oxides of cocsuline (2).

Treatment of 1 (15 mg) with sulfurous acid (6%)(2 ml) gave a reduction product (cocsuline) (2) (9mg). The product was identical (uv, ir, ^{1}H-nmr, ms, $[\alpha]_D$) to an authentic sample of cocsuline (2) available in our laboratory. The ^{1}H-nmr spectrum (60MHz, $CDCl_3$ δ in ppm) of cocsuline (2) showed the presence of two N-methyl groups at 2.38 (3H,s) and 2.56 (3H,s), one aromatic methoxy group at 3.90 (3H,s) and a complex multiplet of ten aromatic protons (6.18-7.80). The shift in position of the signal at 2.85 (3H,s) in the N-oxide (1) to 2.38 (3H,s) in the reduced product (2) indicates that the N-oxide was present at the N-2 of cocsuline. Therefore, 1 is cocsuline-N-2-oxide.



1 $R = CH_3$; $\rightarrow O$

2 $R = CH_3$

Thin-layer chromatography of the original extract indicated the presence of cocsuline-N-2-oxide (1) [Rf 0.42 $CHCl_3$:MeOH:NH_4OH (85:15:0.2)]. In addition, the N-oxide was not formed by exposing cocsuline (2)(3 mg) in chloroform solution (20 ml) to silicic acid (5 gm) for two weeks thus indicating that cocsuline-N-2-oxide (1) was not an artifact of the isolation procedure.

It is interesting to note that the specific rotation of each bisbenzylisoquinoline N-oxide isolated to date[7,8] shows a lower magnitude (of the same sign) than the corresponding parent alkaloid.

This is the first report of the isolation of a dibenzodioxinbiphenyletherbisbenzylisoquinoline N-oxide and the first N-oxide isolated from a member of the genus Cocculus.

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