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HIRSUTINE: A NEW ALKALOID FROM *COCCULUS HIRSUTUS*

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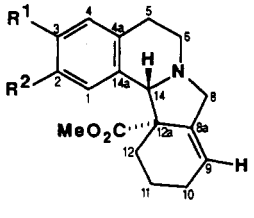
ABSTRACT.—A new alkaloid, hirsutine, was isolated from *Cocculus hirsutus*. Its structure has been assigned as **1** on the basis of chemical and spectral studies.

Plants of the Indian subcontinent are a continuing source of fascinating natural products. *Cocculus hirsutus* (L.) Diels (Menispermaceae), locally known as "jamti-ki-bel," is a climbing shrub commonly found in southeastern Pakistan. Its various parts are known for their medicinal properties in the indigenous systems of medicine (1–3). Earlier investigations of various parts of this plant led to the isolation of trilobine, coclaurine, magnoflorine, and sitosterol (4–6). As a result of continuing investigations, we have isolated hirsutine, a new isoquinoline alkaloid, to which structure **1** has been assigned on the basis of chemical and spectral studies.

RESULTS AND DISCUSSION

The pure alkaloid, hirsutine [**1**], was isolated as a gum from the whole plant of *C. hirsutus* as described in the Experimental section. Its uv spectrum showed absorptions at 220, 240, and 302 nm. The ir spectrum indicated the presence of an OH group at 3500 and the presence of an ester carbonyl at 1720 cm^{-1}. The hrms indicated the molecular ion peak at *m/z* 329.1613 (calcd 329.1627), consistent with the molecular formula $C_{19}H_{23}NO_4$, indicating nine double-bond equivalents in the molecule. Other prominent peaks were found at *m/z* 298, 285, 271, 226, and 208. The base peak at *m/z* 271 corresponded to the loss of the 58 mu carbomethoxy group from *m/z* 329 and suggested the attachment of the methyl ester to a quaternary carbon (7). The molecular ion was confirmed by fabms (8).



1 R^1=OH, R^2=OMe
2 R^1=R^2=OMe

The ^{1}H-nmr spectrum of **1** showed a singlet at δ 3.23, corresponding to the carbomethoxy group, which is shifted upfield due to the shielding influence of the aromatic nucleus (9,10). The H-8α and H-8β protons resonated at δ 3.15 and 3.9, respectively, while the H-14 proton appeared as a singlet at δ 4.02. The C-9 olefinic proton resonated at δ 5.91 as a broad singlet. The presence of two singlets at δ 6.68 and 7.60 in the aromatic region revealed that the substitutions must be at the C-2 and C-3 positions. The methoxy group showed a peak at δ 3.87.

The *O*-methyl derivative **2**, derived from **1** by methylation with CH_2N_2, was identified by comparison of ir, ms, and R_f values with those of deoxyjamtin-*N*-oxide as an authentic sample (11).

The presence of a phenolic hydroxyl group in **1** was suggested when the compound was treated with D_2O; therefore, the eims was recorded again. The molecular ion peak $[M]^+$ was found to be shifted by 1 mu to *m/z* 330 due to the one exchangeable hydrogen (OH group) in the molecule (12).

The preceding data of **1** closely resembled those of jamtine-*N*-oxide, which bears methoxy groups at C-2 and C-3. The two compounds, however, differed widely in their respective optical rotations. Their ir spectra showed common features, but they could not be superimposed. In the ^{13}C-nmr spectrum, the chemical shifts of the nucleus carbon atoms showed close agreement with those of the published spectrum of jamtine-*N*-oxide but indicated the absence of one methoxy group and an upfield shift of C-6, C-8, and C-14. This suggested the absence of a quaternary nitrogen as in jamtine-*N*-oxide and the presence of a tertiary nitrogen. Compound **1** has, therefore, the same basic skeleton and stereochemistry as jamtine-*N*-oxide and differs only in the substituents at C-2 and C-3 as well as in the absence of a quaternary nitrogen. The positions of the aromatic methoxy and aromatic hydroxy group were determined at C-2 and C-3, respectively, on the basis of the nOe enhancement spectroscopy (NOESY) spectrum. The ester group showed strong cross peaks with the signals at δ 6.68 for H-1 and at δ 3.88 for the methoxy proton. This suggested that the methoxy group at δ 3.88 is present on C-2, while the phenolic hydroxy group is present on C-3.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Uv spectra were recorded on a Shimadzu UV-240 spectrophotometer, and ir spectra were recorded on JASCO A-302 spectrophotometer. Hrms were recorded on a Finnigan MAT-312 mass spectrometer connected to a PDP 11/34 (DEC) computer system. The ^{1}H-nmr spectra were recorded at 300 MHz on a Bruker AM-300 spectrometer with TMS as the internal reference. The ^{13}C-nmr spectra were recorded at 75 MHz on the same instrument. The optical rotation was recorded on a polartronic Universal Australian Standard K-157 digital polarimeter. Tlc experiments were performed on Si gel (GF-254, 0.2 mm) plates (E. Merck).

PLANT MATERIAL.—The whole plant material was collected from the Karachi region and was identified by Dr. S.I. Ali, Head of the Department of Botany, University of Karachi. A voucher specimen [no. 14-12-66 (KUH)] has been deposited at the Herbarium of the Department of Botany, University of Karachi.

EXTRACTION AND ISOLATION.—The plant material was chopped into small pieces and extracted exhaustively with EtOH. The EtOH extract was evaporared under reduced pressure, and the residue was partitioned between EtOAc and H_2O. The aqueous layer was basified with NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ layer was evaporated, dried with anhydrous Na_2SO_4 (74 gm), and subjected to cc. The fraction obtained with hexane-Me_2CO (1.8:0.7) was subjected to preparative tlc on Si gel (GF-254) precoated plates with $CHCl_3$-MeOH (9.5:05) as the solvent system. This afforded the pure alkaloid hirsutine [**1**], R_f 0.3 (8 mg), $[\alpha]^{25}D$ +178 ($CHCl_3$), which gave a characteristic brown color reaction with Dragendorff's reagent. Uv (MeOH) λ max 220, 240, 302 nm; ir ($CHCl_3$) ν max cm^{-1} 3500 (OH) and 1720 (ester carbonyl); eims *m/z* (rel. int. %) 329 (3), 298 (20), 285 (6), 271 (100), 226 (9), 208 (17); ^{1}H nmr ($CDCl_3$, 300 MHz) δ 1.93 (1H, m, H-11), 2.37 (1H, m, H-11), 2.51 (1H, m, H-12), 2.66 (1H, m, H-10), 3.15 (1H, d, $J_{8\alpha,8\beta}$ = 10.1 Hz, H-8α), 3.22 (3H, s, -C-OMe), 3.88 (3H, s, OMe), 3.9 (1H, d, $J_{8\beta,8\alpha}$ = 10.1 Hz, H-8β), 4.02 (1H, s, H-14), 5.91 (1H, bs, H-9), 6.68 (1H, s, H-1), 7.60 (1H, s, H-4); ^{13}C nmr ($CDCl_3$, 75 MHz) 111.08 (C-1), 157.62 (C-2), 156.36 (C-3), 124.51 (C-4), 135.68 (C-4a), 29.93 (C-5), 52.46 (C-6), 59.88 (C-8), 135.22 (C-8a), 132.39 (C-9), 24.01 (C-10), 27.49 (C-11), 28.30 (C-12), 79.31 (C-12a), 64.11 (C-14), 133.81 (C-14a), 57.17 (2-OMe), 53.09 (Ac-Me), 172.82 (Ac-Me).

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