New Natural Dibenzocycloheptylamine Alkaloids: A Possible Catabolic Route for the Colchicine Alkaloids

Musa H. Abu Zarga, Salim S. Sabri, Taleb H. Al-Tel, Atta-ur-Rahman, Zahir Shah, and M. Feroz

J. Nat. Prod., **1991**, 54 (4), 936-940• DOI: 10.1021/np50076a002 • Publication Date (Web): 01 July 2004

Journal of Natural Products
Vol. 54, No. 4, pp. 936-940, Jul-Aug 1991

NEW NATURAL DIBENZOCYCLOHEPTYLAMINE ALKALOIDS: A POSSIBLE CATABOLIC ROUTE FOR THE COLCHICINE ALKALOIDS

MUSA H. ABU ZARGA,* SALIM S. SABRI,*

Chemistry Department, University of Jordan, Amman, Jordan

TALEB H. AL-TEL,

College of Science and Technology, Jerusalem, Israel

ATTA-UR-RAHMAN,* ZAHIR SHAH, and M. FEROZ

H.E.J. Research Institute of Chemistry, University of Karachi, Karachi 75270, Pakistan

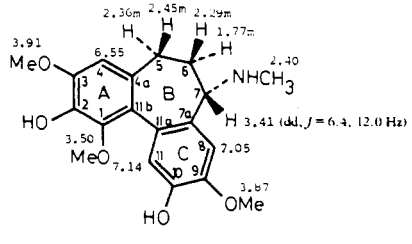
ABSTRACT.—*Colchicum decaisnei* of Jordanian origin has yielded three new alkaloids, (−)-jerusalemine [**1**], (−)-salimine [**2**], and (−)-suhailamine [**3**], besides the known alkaloid (−)-androbiphenyline.

Colchicum decaisnei Boiss. (Liliaceae) is native to the Middle East and has not been previously investigated for its alkaloidal content. The tubers of this plant were collected in Al-Salt near Amman, defatted, and subjected to cold MeOH extraction. Extensive chromatography of the extracts furnished three levorotatory dibenzocycloheptylamine alkaloids (1–3).

The eims of jerusalemine [**1**] showed the molecular ion peak at *m/z* 345 (80%). Hrms afforded the exact mass at *m/z* 345.1582 (calcd for $C_{19}H_{23}NO_5$, 345.1576). The base peak was present at *m/z* 314 ($C_{18}H_{18}O_5$, hrms 314.1227, calcd 314.1154) due to the facile loss of the methylamine residue.

The uv spectrum of **1** showed maxima at 212 and 267 nm typical for the dibenzocycloheptadiene chromophore (3,4). A broad absorption band at 3280 cm^{-1} and another band at 3515 cm^{-1} in the ir spectrum corresponded to the presence of NH and phenolic hydroxyl groups. The 400 MHz ^{1}H-nmr spectrum of **1** included three aromatic singlets, each integrating for one proton, indicating the absence of any neighboring protons in ortho or meta positions. Moreover, three 3H singlets were present for the three OMe protons at δ 3.91, 3.87, and 3.50. A sharp 3H singlet at δ 2.40 was due to the *N*-methyl protons.

In order to confirm the positions of these signals, a series of nOe experiments were performed. Irradiation of the aromatic singlet at δ 6.55 (H-4) produced an nOe enhancement for the singlet at δ 3.91 (3-OMe) and for the multiplet at δ 2.45 (H-5α). On the other hand, the 3-OMe (δ 3.91) showed reciprocating nOe with H-4 (δ 6.55). Irradiation of the upfield methoxyl group at δ 3.50 (1-OMe) did not show any enhancement of other methoxyl groups, indicating the presence of a hydroxyl group rather than a methoxyl group at C-2. The methoxyl singlet at δ 3.87 (9-OMe) showed mutual nOe interactions with the aromatic singlet at δ 7.05 (H-8). In view of the nOe interactions between H-7 and H-8 on the one hand, and between H-8 and the 9-OMe on the other



1

hand, as well as the lack of any coupling of H-8 and H-11 with any other proton, the second hydroxyl group was placed at C-10.

Interestingly, H-7 resonated at δ 3.41 as a doublet of doublets with coupling constants 12.0 and 6.4 Hz, the larger coupling constant corresponding to a diaxial relationship with the C-6β proton. This larger coupling constant also reflects a boat conformation for ring B of jerusalemine [**1**], which is also in accord with the X-ray data recorded in the literature for the structurally related *N*-acetylcolchinol (5). The detailed ^{1}H-nmr data of (−)-jerusalemine [**1**] are indicated around expression **1**.

The GASPE spectrum of jerusalemine [**1**] indicated the presence of nineteen carbon atoms, of which there were three methoxyl, three aromatic methine, two methylene, and one *N*-methyl carbons. The ^{13}C-nmr assignments were determined with the help of an HMQC (6) experiment (see Experimental).

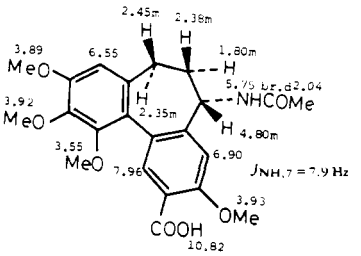
The second new alkaloid, (−)-salimine [**2**], showed a molecular ion peak in eims at *m/z* 415.1623 (100%) corresponding to the molecular formula, $C_{22}H_{25}NO_7$ (calcd 415.1631). Like (−)-jerusalemine [**1**], the 400 MHz ^{1}H-nmr spectrum of salimine [**2**] showed three aromatic singlets each integrating for one proton. Four aromatic methoxyls were also present, in addition to the acetyl methyl signal at δ 2.04. The most salient features of the ^{1}H-nmr spectrum of compound **2** were the lack of coupling of the aromatic protons and the presence of a downfield singlet at δ 10.82 for the carboxyl proton.

COSY-45 and nOe experiments were performed to confirm the structure. Weak interactions were seen in the COSY spectrum between H-4 and 3-OMe, between H-11 and 1-OMe, between H-8 and 9-OMe, between H-8 and H-7β, and between the C-5 and C-6 protons. The aromatic singlet at δ 6.55 (H-4) showed reciprocating nOe's with the methoxyl singlet at δ 3.89 (3-OMe). Similarly, irradiation at the sterically hindered methoxyl singlet at δ 3.55 (1-OMe) gave an nOe at the methoxyl singlet at δ 3.92 (2-OMe), as well as at H-11 (δ 7.96). Irradiation of the aromatic one-proton singlet at δ 6.90 (H-8) produced nOe enhancement of both the broad doublet centered at δ 5.75 (-NH) and of the multiplet at δ 4.80 (H-7β). The ^{1}H-nmr chemical shift data are summarized around expression **2**.

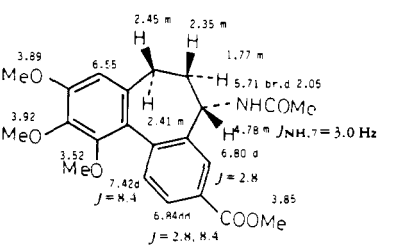
Again, as in **1**, ring B in **2** appeared to be mainly in a boat-like conformation, because nOe interactions were seen between H-4 and H-5α, on the one hand, as well as between H-8 and H-7 on the other hand. An nOe interaction was also seen between H-8 and the NH proton.

The ^{13}C-nmr data has been assigned using GASPE and HMQC experiments (Experimental).

The uv spectrum of the third alkaloid, (−)-suhailamine [**3**] along with ms and ^{1}H-nmr data indicated that it contains the dibenzocycloheptadiene skeleton. The eims showed a molecular ion peak at *m/z* 399.1680 (15%, calcd for $C_{22}H_{25}NO_6$, 399.1682) and the base peak at *m/z* 312.



2



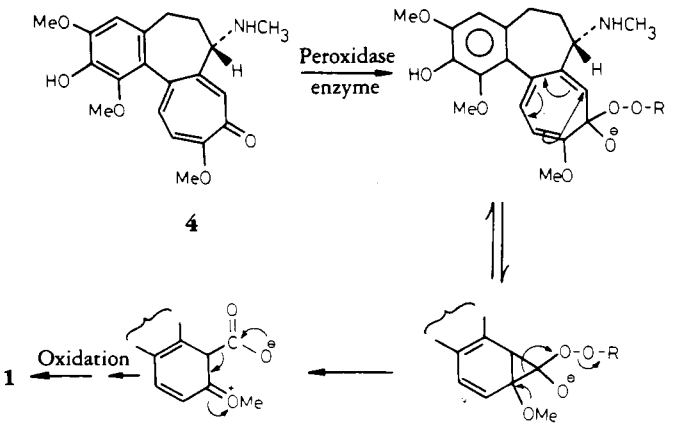
3

The ^{1}H-nmr spectrum of (−)-suhailamine [**3**] (400 MHz, $CDCl_3$) showed the presence of four aromatic protons and four methoxyl singlets (3 × OMe, 1 × COOMe) in addition to the acetyl methyl group at δ 2.05. The ^{1}H-nmr spectrum contained a downfield doublet at δ 7.42 for H-11 (J = 8.4 Hz) and a doublet of doublets at δ 6.84 for H-10 ($J_{10,11}$ = 8.4 Hz, $J_{10,8}$ = 2.8 Hz). Another doublet appeared at δ 6.80 for H-8 ($J_{8,10}$ = 2.8 Hz). The mol wt of suhailamine [**3**] is 16 mu less than that of salimine [**2**]. Moreover, the downfield proton at δ 10.82 for the carboxyl proton characterized in the spectrum of **2** is absent in the spectrum of suhailamine [**3**]. Extensive spectral studies (COSY-45, nOe, GASPE, and HMQC) resulted in unambiguous assignment of the ^{1}H-nmr data, which are presented around structure **3**.

In order to confirm the positions of the methoxyls and the aromatic protons, a series of ^{1}H-nmr nOe experiments were performed. The methoxyl singlet at δ 3.89 (3-OMe) produced reciprocating nOe with the aromatic singlet at δ 6.55 (H-4), which in turn showed nOe of the multiplet centered at δ 2.45 (H-5α). On the other hand, irradiation of the methoxyl singlet at δ 3.92 (2-OMe) affected the nOe of the upfield methoxyl at δ 3.52 (1-OMe). Interestingly, irradiation of the aromatic doublet centered at δ 6.80 (J = 2.8, H-8) resulted in an nOe of both the multiplet centered at δ 4.78 (H-7) and of the methoxyl at δ 3.85 (-COOMe). The latter in turn gave an nOe of the doublet of doublets at δ 6.84 (H-10). Furthermore, irradiation of the downfield ortho coupled proton at δ 7.42 (H-11) produced an nOe of the doublet of doublets at δ 6.84 (H-10). This resulted in the assignment of the carbomethoxy group at C-9. It is notable that H-11 appeared at δ 7.42 in **3** with a *meta*-disposed CO_2Me group, while H-11 in **2**, which has the COOH group in an ortho position, is present further downfield (δ 7.96) as expected. The downfield shift of this proton in **1**, **2**, and **3** is probably due to its location in the paramagnetic zone of ring A.

The ^{13}C-nmr spectrum (GASPE) of compound **3** was assigned with the help of HMQC data (see Experimental). The negative optical rotation of **1**, **2**, and **3** established that they have the same 7*S* configuration as other structurally related colchicine-type compounds (4).

With the characterization of (−)-jerusalemine [**1**], (−)-salimine [**2**], and (−)-suhailamine [**3**], it is possible to delineate the outlines of possible catabolic routes to the colchicine-type alkaloids (1). For (−)-jerusalemine [**1**], the presence of a peroxidase enzyme system in the plant may facilitate the decarbonylation of the tropolone ring of (−)-2-demethyldemecolcine [**4**], with accompanying oxidation resulting ultimately in the formation of (−)-jerusalemine [**1**] as shown in Scheme 1 (7).



SCHEME 1. Proposed catabolic pathway for the formation of **1** from **4**.

On the other hand, (−)-salimine [**2**] and (−)-suhailamine [**3**] may arise from (−)-colchicine by enzymatic peroxidation of ring C followed by hydroxylation and methylation (7).

EXPERIMENTAL

PLANT COLLECTION, EXTRACTION, AND ALKALOID ISOLATION.—The dried tubers were collected during the flowering period in November 1988 near Al-Salt 20 km northwest of Amman. The plant was identified by Dr. Dawud El-Isawi, Department of Biological Sciences, Faculty of Science, University of Jordan, Amman, Jordan. A voucher specimen has been deposited in the University Herbarium. The powdered material (tubers, 15 kg) was extracted with petroleum ether and then with cold MeOH. The solvent was evaporated, and the residual material was partitioned between $CHCl_3$-H_2O (1:1). The H_2O layer was extracted with *n*-BuOH. The *n*-BuOH was evaporated, and the residual material was kept for further investigation. The $CHCl_3$ layer was evaporated and the residue was dissolved in 10% H_2O/MeOH and extracted with hexane. The aqueous MeOH-soluble material (200 g) was fractionated on a Si gel column packed in $CHCl_3$. The polarity was gradually increased by addition of MeOH until pure MeOH was used. Further purification of the compounds was achieved by cc, followed by preparative tlc on Si gel, using $CHCl_3$-EtOAc-Et_2NH (8:1:1). The purity of the substances was checked by repeating the tlc in the following solvent systems: (A) EtOAc-MeOH (7.5:2.5), (B) C_6H_6-$CHCl_3$-Et_2NH (8:1:1), and (C) EtOAc-iPrOH (6:4).

The ^{13}C-nmr spectra ($CDCl_3$, 75.43 MHz) of compounds **1–3** were homogeneous and only showed resonances appropriate for the indicated structures.

The ^{1}H-nmr spectra were recorded in $CDCl_3$ at either 300 or 400 MHz. Chemical shifts are in δ scale, and coupling constants are in Hz. Values with identical superscripts are interchangeable.

(−)-JERUSALEMINE [**1**].—Yield 50 mg; amorphous; R_f in solvent system A 0.46, in B 0.20, in C 0.26; $[\alpha]_D$ −35° (c = 0.17, MeOH); uv (MeOH) λ max 212, 267, 290 nm; ir ($CHCl_3$) ν max 3200–3520, 1610 cm^{-1}; eims *m/z* 345 (78), 314 (100), 299 (40), 288 (18), 271 (10), 255 (9), 243 (7); hrms 345.1582 ($C_{19}H_{23}NO_5$, calcd 345.1576), 314.1227 ($C_{18}H_{18}O_5$, calcd 314.1218), 283.0959 ($C_{17}H_{15}O_4$, calcd 283.0970).

Significant nmr nOe's for **1** are: 9-OMe to H-8, 65%; 3-OMe to H-4, 44%; H-4 to 3-OMe, 65%; H-4 to H-5α, 25%; H-8 to 9-OMe, 60%. ^{13}C nmr δ 145.25* (C-1), 146.51 (C-2), 144.31 (C-3), 107.30 (C-4), 137.41 (C-4a), 30.71 (C-5), 40.18 (C-6), 59.56 (C-7), 132.42 (C-7a), 113.06 (C-8), 126.56 (C-9), 131.27 (C-10), 110.06 (C-11), 124.65 (C-11a), 145.40* (C-11b), 34.52 (NMe), 60.18 (1-OMe), 56.25 (3-OMe), 56.25 (9-OMe).

(−)-SALIMINE [**2**].—Yield 15 mg; amorphous; R_f in solvent system A 0.78, in B 0.25, in C 0.88; $[\alpha]_D$ −17 (c = 0.11, MeOH); uv (MeOH) λ max 319, 270, 221, 205 nm; ir ($CHCl_3$) ν max 3290, 1670, 1600 cm^{-1}; eims *m/z* 415 (100), 383 (20), 368 (22), 356 (68), 340 (62), 313 (43), 293 (10), 253 (12), 225 (15); hrms 415.1623 (calcd 415.1631).

Significant nmr nOe's for **2** are: 1-OMe to H-11, 25%; 3-OMe to H-4, 36%; 9-OMe to H-8, 9%; NH to H-8, 9%; NH to H-8, 18%; NH to acetyl methyl, 9%; H-4 to 3-OMe, 25%; H-4 to H-5α, 15%; H-8 to NH, 15%; H-8 to acetyl methyl 6%; H-11 to 1-OMe, 14%. ^{13}C nmr δ 108.00 (C-4), 29.70 (C-5), 39.08 (C-6), 49.60 C-7), 111.48 (C-8), 131.72 (C-11), 23.27 (Ac), 61.18 (1-OMe), 61.18 (2-OMe), 56.24 (3-OMe), 52.2 (9-OMe).

(−)-SUHAILAMINE [**3**].—Yield 7 mg; amorphous; R_f in solvent system A 0.80, in B 0.52, in C 0.88; $[\alpha]_D$ −22 (c = 0.13, MeOH); uv (MeOH) λ max 275 sh, 261.6, 207.6 nm; ir ($CHCl_3$) ν max 3320, 1610, 1590 cm^{-1}; eims *m/z* 399 (10), 371 (80), 340 (22), 312 (100), 297 (50), 281 (42), 254 (20); hrms 399.1660 (calcd 399.1682).

Significant nmr nOe's for **3** are: COOMe to H-10, 34%; COOMe to H-8, 34%; 3-OMe to H-4, 50%; 2-OMe to 1-OMe, 43%; H-7 to acetyl methyl, 35%; H-7 to H-6β, 45% NH to H-8, 36%; NH to MeCO, 21%; H-4 to 3-OMe, 47%; H-4 to H-5α, 47%; H-8 to COOMe, 43%; H-8 to -NH, 30%; H-10 to COOMe, 65%; H-10 to H-11, 40%; H-11 to H-10, 45%; ^{13}C nmr δ 108.03 (C-4), 29.70 (C-5), 39.76 (C-6), 49.40 (C-7), 109.20 (C-8), 110.78 (C-10), 131.42 (C-11), 23.31 (Ac), 60.92 (1-OMe), 61.21 (2-OMe), 56.26 (3-OMe), 55.26 (COOMe).

ACKNOWLEDGMENTS

The authors are grateful to ISESCO, Rabat (Morocco) for providing financial assistance for this project.

LITERATURE CITED

1. T.H. Al-Tel, M.H. Abu Zarga, S.S. Sabri, A.J. Freyer, and M. Shamma, *J. Nat. Prod.*, **53**, 623 (1990).
2. E. Tojo, M.H. Abu Zarga, A.J. Freyer, and M. Shamma, *J. Nat. Prod.*, **52**, 1163 (1989).
3. A.J. Freyer, M.H. Abu Zarga, S. Firdous, H. Guinaudeau, and M. Shamma, *J. Nat. Prod.*, **50**, 684 (1987).
4. J. Hrbek Jr., L. Hruban, V. Šimánek, F. Šantavý, G. Snatzke, and S.S. Yemul, *Collect. Czech. Chem. Commun.*, **47**, 2258 (1982).
5. T.N. Margulis and L. Lessinger, *Biochem. Biophys. Res. Commun.*, **83**, 472 (1978).
6. Atta-ur-Rahman, "One- and Two-dimensional NMR Spectroscopy," Elsevier, Amsterdam, 1989, p. 406.
7. Maria A. Iorio, *Heterocycles*, **22**, 2207 (1984).

Received 30 August 1990