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THE HOMOAPORPHINE ALKALOIDS OF *ANDROCYMBIUM PALAESTINUM*

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ABSTRACT.—*Androcymbium palaestinum* of Jordanian origin has yielded the new homoaporphines (+)-kreysigine [**2**], (+)-androcine [**3**], (+)-androcimine [**4**], (+)-androbine [**5**], (+)-nor-*O*-methylkreysigine [**6**], and (+)-norandrobine [**7**]. The latter two alkaloids are the first norhomoaporphines to be characterized. (+)-*O*-Methylkreysigine [**1**] exists preferentially in conformation **1a**. Hofmann degradation of (+)-androbine [**5**] methiodide provided androbinemethine [**9**], which is strongly dextrorotatory.

The genus *Androcymbium*, belonging to the plant family Liliaceae, counts some 35 species spread from the Mediterranean to South Africa (1). Only a few of these species have been chemically investigated, and these were found to possess 1-phenethyltetrahydroisoquinoline-derived alkaloids. *Androcymbium* species have been used in folk medicine for the treatment of a variety of illnesses (2).

Androcymbium palaestinum (Boiss.) Bak. is native to the Middle East and had not been previously investigated for its alkaloidal content. The bulbs of this plant were collected in Ghour Khanizirah, in the Wadi Araba, in southern Jordan, and subjected to cold EtOH extraction.

Extensive chromatography of the extracts furnished six new dextrorotatory homoaporphines, derived from the 1-phenethyltetrahydroisoquinoline system, together with two known homoaporphines, namely (+)-*O*-methylkreysigine [**1**] and (+)-szovitsamine [**8**].

Our first known homoaporphine, (+)-*O*-methylkreysigine [**1**], $C_{23}H_{29}NO_5$, was easily characterized (3,4). The detailed ^{1}H-nmr spectrum at 360 MHz for this species is now given for the first time around expression **1**. Assignments are based on decoupling as well as on nOe experiments (see Experimental). [(+)-*O*-Methylkreysigine has the C-6a *S* configuration rather than the *R* configuration as claimed in Yusupov *et al.* (3).]

The nmr spectral data actually furnished an insight into the conformation of the molecule. The coupling constants between H-6a and the two C-7 protons ($J_{6a,7\alpha} = 6.4$ Hz, $J_{6a,7\beta} = 11.0$ Hz) suggested a boat-like conformation for ring C, as depicted in expression **1a**. This conformation would minimize the steric compression between the methoxyl substituents at C-1 and at C-12. The close proximity of H-8α to the aromatic H-9, as suggested by expression **1a**, was also indicated by an enhancement of the H-9 signal (δ 6.56) upon irradiation of H-8α (δ 2.45). Ring B approximates a half-chair, and an enhancement of H-7β (δ 1.99) was noted upon irradiation of the pseudo-axial H-5β (δ 3.19) (see Experimental).

Our first new alkaloid, the monophenolic (+)-kreysigine [**2**], $C_{22}H_{27}NO_5$, had previously been characterized in the racemic (5) and levorotatory (6) forms. The nmr spectrum has been summarized around expression **2**. It will be noticed that the C-2 methoxyl signal (δ 3.92) has undergone a slight downfield shift by comparison with the value for the corresponding group in (+)-*O*-methylkreysigine [**1**] (δ 3.88).

Turning now to the second and third new alkaloids, (+)-androcine [**3**] and (+)-androcimine [**4**], these two structurally isomeric compounds showed molecular composi-

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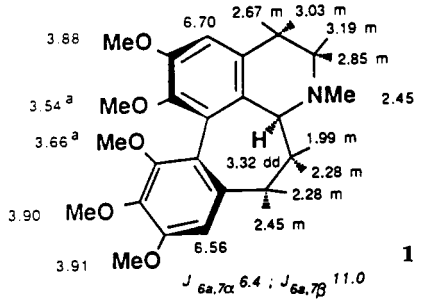
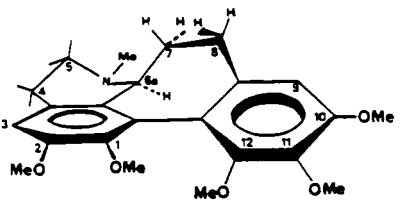
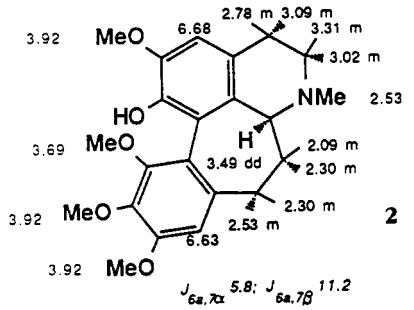


1

$J_{6a,7\alpha}$ 6.4 ; $J_{6a,7\beta}$ 11.0

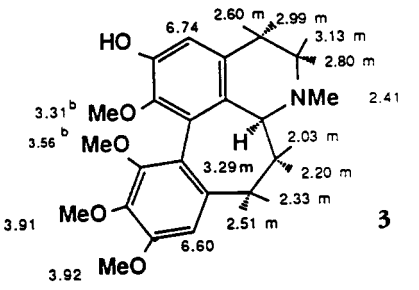


1a



2

$J_{6a,7\alpha}$ 5.8; $J_{6a,7\beta}$ 11.2



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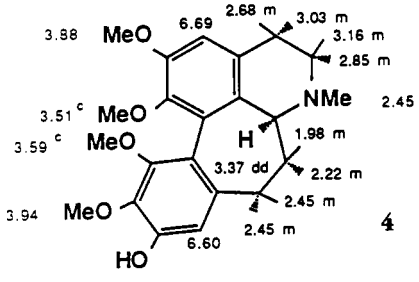

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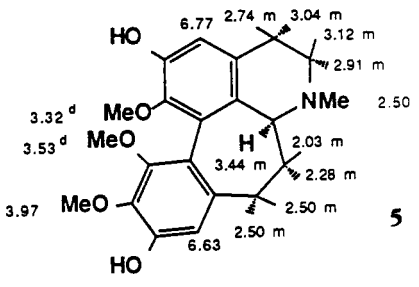
$J_{6a,7\alpha}$ 5.9; $J_{6a,7\beta}$ 10.3



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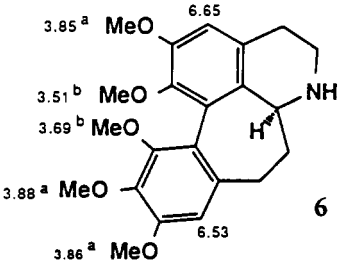

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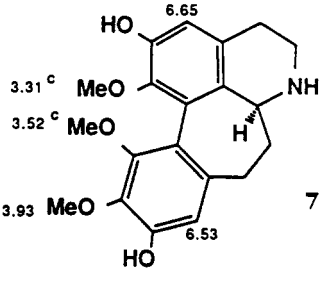

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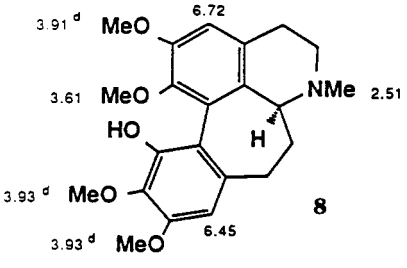

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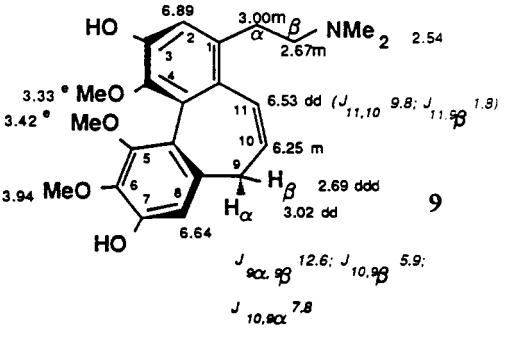

9

$J_{9\alpha,9\beta}$ 12.6; $J_{10,9\beta}$ 5.9;

$J_{10,9\alpha}$ 7.8

[a,b,c,d,e]Chemical shifts with identical superscripts are interchangeable.

tion $C_{22}H_{27}NO_5$. Their mass spectra were also quite close, with base peak *m/z* 354 $[M-31]^+$, corresponding to the loss of a methoxyl from the molecular ion. Such behavior is characteristic of homoaporphines with methoxyls at C-1 (7). CH_2N_2 *O*-methylation of **3** or **4** led to (+)-*O*-methylkreysigine [**1**].

The nmr spectra of (+)-androcine [**3**] and (+)-androcimine [**4**] each showed two upfield and two downfield methoxyl singlets, precluding conclusive identification of the positions of the phenolic functions at this stage. However, nmr nOe measurements allowed for a clear-cut differentiation. The C-10 methoxyl signal (δ 3.92) of (+)-androcine [**3**] showed strong reciprocating nOe's with H-9 (δ 6.60). On the other hand, for (+)-androcimine [**4**], it was the C-2 methoxyl (δ 3.88) that exhibited reciprocating nOe's with H-3 (δ 6.69). Irradiation of the H-4 signals (δ 2.68 and 3.03) also led to enhancement of H-3 (δ 6.69) (see Experimental). It follows that the phenolic function is at C-2 in (+)-androcine [**3**] and at C-10 in (+)-androcimine [**4**].

The diphenolic (+)-androbine [**5**] was the major alkaloid of the plant and could well be the biogenetic precursor for alkaloids **3** and **4**. The mass spectrum displayed molecular ion *m/z* 371 (22%) and base peak *m/z* 340 $[M-31]^+$ due mainly to loss of the C-1 methoxyl. CH_2N_2 *O*-methylation supplied (+)-*O*-methylkreysigine [**1**].

The detalied nmr spectrum of (+)-androbine has been indicated around expression **5**. The two relatively upfield methoxyl signals at δ 3.32 and 3.53 pointed to methoxyl substitution at C-1 and C-12 (8). Significantly, no nOe could be observed related to any of the methoxyl signals, so that the phenolic functions must be situated at C-2 and C-10.

An apparently constant feature of the nmr spectra of homoaporphines is that the H-3 absorption is always at lower field than that for H-9. To further confirm this assignment, a Hofmann degradation of (+)-androbine [**5**] methiodide was undertaken. One main product was obtained, which proved to be the homophenanthrene **9**, $C_{22}H_{27}NO_5$, which will be referred to as androbinemethine. The mass spectrum showed a small molecular ion *m/z* 385 (2%), while base peak *m/z* 58 represents the dimethyliminium cation. Decoupling and nOe experiments confirmed the nmr assignments as shown around expression **9**. Significantly, the H-3 singlet absorption in (+)-androbine [**5**], which was found at δ 6.77, has shifted further downfield to δ 6.89 in androbinemethine [**9**] because it is now part of a more highly conjugated system.

An interesting feature of androbinemethine [**9**] is its optical activity. The molecule shows a strong positive rotation, $[\alpha]_D$ +242° ($c = 0.21$, MeOH), even though it does not incorporate an asymmetric carbon. Rather, it is the permanent twist of the biphenyl system that imparts this activity, a reflection of the fact that the biphenyl system in all homoaporphines is non-planar. The specific rotation remained essentially unchanged after refluxing in MeOH for 15 min, indicating that the molecule cannot reach planarity or racemize even upon heating.

Our last two new homoaporphines, (+)-nor-*O*-methylkreysigine [**6**] and (+)-norandrobine [**7**] represent the first examples of norhomoaporphines obtained from a natural source. The uv, nmr, and mass spectra of **6** and **7** were close to those of (+)-*O*-methylkreysigine [**1**] and (+)-androbine [**5**], respectively. The main differences were the presence of mass spectral molecular ions that were 14 amu lower than for the corresponding species **1** and **5** and the absence of *N*-methyl singlets in the nmr spectra. Both **6** and **7** are minor alkaloids, so that insufficient amounts remained following their spectral characterization to allow for *N*-methylation to relate them chemically to **1** and **5**.

The second known homoaporphine we found in *A. palaestinum* is (+)-szovitsamine [**8**]. It is important to point out that its dextrorotatory character argues for the C-6a *S* configuration, rather than for the *R* configuration as previously indicated (9).

EXPERIMENTAL

PLANT COLLECTION, EXTRACTION, AND ALKALOID ISOLATION.—The bulbs of *A. palaestinum* (5.5 kg) were collected in February 1983. A voucher specimen was deposited in the Herbarium of the University of Jordan. The bulbs were dried, powdered, and extracted with cold EtOH. The concentrated extract was treated with 5% HCl, and the mixture was filtered. The filtrate was basified with NH_4OH and extracted with $CHCl_3$. Solvent evaporation afforded a dark residue (3 g) that was fractionated by cc over neutral alumina, using $CHCl_3$ gradually enriched with MeOH as eluent. Final purification was by tlc on Si gel glass plates using any of the following systems: $CHCl_3$-MeOH (90:10), $CHCl_3$-$(C_2H_5)_2NH$ (95:5), and $CHCl_3$-C_6H_6-$(C_2H_5)NH$ (40:50:10). Nmr spectra were obtained at 360 or 200 MHz, in $CDCl_3$ solution. Nmr nOe's were measured as differences, and are reported as percentages of maximum possible values.

(+)-*O*-METHYLKREYSIGINE [**1**].—Compound **1** (8 mg): $[\alpha]_D$ +68° (c = 0.10, MeOH); cd (MeOH) $\Delta\epsilon$ (nm) −2.2 (254); uv λ max (MeOH) 220, 260, 289 sh nm (log ε 4.44, 3.95, 3.46); ir ν max ($CHCl_3$) 2920, 1700, 1590, 1455 cm^{-1}; eims *m/z* $[M]^+$ 399 (21), 384 (18), 368 (100). ^1H nmr nOe H-3 to 2-OMe, 4%; 2-OMe to H-3, 19%; H-9 to 10-OMe, 16%; 10-OMe to H-9, 15%; H-6 to NMe, 0.3%; NMe to H-6, 3%; H-5β to H-7β, 6%; H-5α to NMe, 7%; H-4β to H-3, 3%; H-4α to H-3, 15%; H-8α to H-9, 6%; H-7α to H-6, 4%. This material was spectrally (nmr, uv, ms) identical with (−)-*O*-methylkreysigine (3).

(+)-KREYSIGINE [**2**].—Compound **2** (28 mg): $[\alpha]_D$ +64° (c = 0.11, MeOH); cd (MeOH) $\Delta\epsilon$ (nm) −1.95 (254); uv λ max (MeOH) 216, 257, 287 sh nm (log ε 3.94, 3.49, 3.24); ir ν max ($CHCl_3$) 3520, 3000, 1595, 1460 cm^{-1}; eims *m/z* $[M]^+$ 385 (40), 368 (100), 354 (18). This material was spectrally (nmr, uv, ms) identical with (−) and with (±)-kreysigine (5).

(+)-ANDROCINE [**3**].—Compound **3** (77 mg): $[\alpha]_D$ +39° (c = 0.10, MeOH); cd (MeOH) $\Delta\epsilon$ (nm) −2.9 (254); uv λ max (MeOH) 217, 260, 292 sh nm (log ε 4.47, 3.99, 3.93); λ max (MeOH-OH^-) 313 nm (log ε 3.79); ir ν max ($CHCl_3$) 3520, 2920, 1590, 1460 cm^{-1}; eims *m/z* $[M]^+$ 385 (17), 370 (12), 354 (100). ^1H nmr nOe H-9 to 10-OMe, 10%; 10-OMe to H-9, 45%; H-6 to NMe, 26%; NMe to H-6, 35%; H-5β to H-7α, 20%; H-4α to H-3, 25%; H-4β to H-3, 31%. Hrms $[M]^+$ calcd for $C_{22}H_{27}NO_5$ *m/z* 385.1889, found 385.1878.

(+)-ANDROCIMINE [**4**].—Compound **4** (28 mg): $[\alpha]_D$ +51° (c = 0.11, MeOH); cd (MeOH) $\Delta\epsilon$ (nm) −0.79 (254); uv λ max (MeOH) 218, 260, 291 sh nm (log ε 4.47, 3.94, 3.60); uv λ max (MeOH-OH^-) 212, 262, 291 nm (log ε 4.47, 3.83, 3.82 nm); λ max ($CHCl_3$) 3520, 2930, 1590, 1460 cm^{-1}; eims *m/z* $[M]^+$ 385 (24), 370 (18), 354 (100). ^1H nmr nOe H-3 to 2-OMe, 27%; 2-OMe to H-3, 49%; H-6 to NMe, 34%; NMe to H-6, 34%; H-4α to H-3, 36%; H-4β to H-3, 31%; H-8 to H-9, 34%; H-5α to NMe, 14%. Hrms $[M]^+$ calcd for $C_{22}H_{27}NO_5$ *m/z* 385.1889, found 385.1895.

(+)-ANDROBINE [**5**].—Compound **5** (120 mg): $[\alpha]_D$ +39° (c = 0.12, MeOH); cd (MeOH) $\Delta\epsilon$ (nm) −2.5 (254); uv λ max (MeOH) 215, 262, 289 sh nm (log ε 4.44, 3.98, 3.65); λ max (MeOH-OH^-) 295, nm (log ε 3.95 nm); ir ν max ($CHCl_3$) 3520, 2930, 1590, 1460 cm^{-1}; eims *m/z* $[M]^+$ 371 (22), 356 (13), 340 (100); hreims found *m/z* 371.1722, calcd 371.1732. No nmr nOe could be observed involving any of the methoxyl signals.

(+)-NOR-*O*-METHYLKREYSIGINE [**6**].—Compound **6** (3 mg): $[\alpha]_D$ +27° (c = 0.07, MeOH); cd (MeOH) $\Delta\epsilon$ (nm) −1.8 (254); uv λ max (MeOH) 218, 259, 292 sh nm (log ε 4.37, 3.88, 3.38); ir ν max ($CHCl_3$) 3000, 1590, 1410; eims *m/z* $[M]^+$ 385 (33), 370 (25), 354 (100), 338 (14). Hrms $[M]^+$ calcd for $C_{22}H_{27}NO_5$ *m/z* 385.1889, found 385.1894.

(+)-NORANDROBINE [**7**].—Compound **7** (2 mg): $[\alpha]_D$ +20° (c = 0.10, MeOH); cd (MeOH) $\Delta\epsilon$ (nm) −1.5 (254); uv λ max (MeOH) 218, 258, 291 sh nm (log ε 3.89, 3.42, 3.10); λ max (MeOH-OH^-) 313 nm (log ε 3.40); ir ν max ($CHCl_3$) 3680, 3000, 1595, 1460 cm^{-1}; eims *m/z* $[M]^+$ 357 (27), 342 (26), 326 (100), 310 (23); hrms $[M]^+$ calcd for $C_{20}H_{23}NO_5$ *m/z* 357.1576, found 357.1559.

(+)-SZOVITSAMINE [**8**].—Compound **8** (5 mg): $[\alpha]_D$ +55° (c = 0.10, MeOH); cd (MeOH) $\Delta\epsilon$ (nm) −1.2 (254); uv λ max (MeOH) 218, 260, 286 sh nm (log ε 4.29, 3.78, 3.50); λ max (MeOH-OH^-) 290, 314 nm (log ε 3.37, 3.18); ir ν max ($CHCl_3$) 3500, 2950, 1590, 1455 cm^{-1}; eims *m/z* $[M]^+$ 385 (19), 370 (17), 354 (100), 338 (21).

GENERAL PROCEDURE FOR *O*-METHYLATION.—A solution of the homoaporphine (5 mg) in MeOH (2 ml) was treated with excess ethereal CH_2N_2 for 16 h. Evaporation and workup provided the corresponding *O*-methyl ether.

HOFMANN DEGRADATION OF ANDROBINE [**5**].—A mixture of **5** (25 mg), MeI (1 ml) and MeOH (4 ml) was warmed for 3 h. Excess solvent was evaporated to provide androbine methiodide. This product in EtOH (2 ml) was refluxed for 45 min with a solution prepared by dissolving Na (130 mg) in EtOH (3 ml). Workup led to **9** (16 mg, 64%).

(+)-ANDROBINEMETHINE [**9**].—Compound **9**: $[\alpha]_D$ +242° (c = 0.21, MeOH) (this value remained unchanged after the compound was placed in refluxing MeOH for 15 min); cd (MeOH) $\Delta\epsilon$ (nm) +3.4 (258); uv λ max (MeOH) 251, 285 sh nm (log ε 4.33, 3.72); uv λ max (MeOH-OH^-) 272, 301 sh nm (log ε 4.27, 4.00); ir ν max ($CHCl_3$) 3510, 2990, 1590, 1445 cm^{-1}; eims *m/z* $[M]^+$ 385 (2), 327 (0.4), 58 (100); hreims found *m/z* 385.1913, calcd 385.1889. ^{1}H nmr nOe H-11 to H-10, 62%; H-10 to H-11, 9%; H-8 to H-9α, 11%; H-9α to H-8, 48%; H-9α to H-9β, 34%; H-9α to H-10, 16%; H-α to H-2, 32%; H-2 to H-α, 30%.

ACKNOWLEDGMENTS

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