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THE DIBENZOCYCLOHEPTYLAMINE ALKALOIDS

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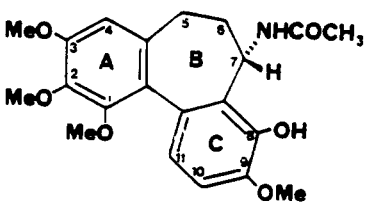
ABSTRACT.—*Androcymbium palaestinum* of Jordanian origin has yielded the new alkaloid (−)-androbiphenyline [**1**], which in $CDCl_3$ solution exists as conformers **1a** and **1b**. Two previously known and related alkaloids are K-3 [**3**] and K-4 [**4**] obtained from a *Colchicum* species. (−)-Androbiphenyline [**1**], K-3 [**3**], and K-4 [**4**] are the only known representatives of the dibenzocycloheptylamine class of alkaloids.

An investigation of *Androcymbium palaestinum* (Boiss.) Bak. (Liliaceae), native to Jordan, has yielded several homoaporphines (1). It has also provided the new tricyclic alkaloid (−)-androbiphenyline, $C_{21}H_{25}NO_6$, which has been assigned the *N*-acetyldibenzocycloheptylamine structure **1** and which is the subject of the present report.

The mass spectrum of (−)-androbiphenyline [**1**] showed molecular ion *m/z* 387 (44%) and base peak *m/z* 328 $[M - AcNH_2]^+$ (2). The presence of an amidic function was also indicated by the the ir spectrum, which included a strong band at 1666 cm^{-1}. The uv spectrum, λ max (MeOH) 261 and 293 nm (log ε 4.10, 3.88), was suggestive of a biphenyl system. Additionally, a bathochromic shift in base pointed to the phenolic character of the alkaloid.

The 360 MHz ^{1}H-nmr spectrum in $CDCl_3$ displayed equal duplication of all of the signals. This indicated the presence of two isomers, **1a** and **1b**, in solution in a 1:1 ratio. When the solution was heated, isomer **1b** became prevalent. The challenge was, therefore, not only to determine the structure of (−)-androbiphenyline but also to establish the conformations of the two isomers.



1

The alkaloid possesses four aromatic methoxyl substituents, a phenolic function, and an *N*-acetyl amide. Additionally, three aromatic protons were in evidence, of which two were in an ortho relationship, with $J_o = 8.4$ Hz, while the third appeared as a singlet.

Through the use of proton selective decouplings and nOe experiments, it was possible to identify and differentiate between the twin sets of signals. All nOe's were measured as differences and are reported as percentages of maximum possible values.

We will start with the interpretation of the spectrum of **1b** because this was easier to analyze. The critical coupling constants, $J_{6\alpha,7} = 0$ Hz and $J_{6\beta,7} = 7.4$ Hz, denote dihedral angles of approximately 82° and 30°, respectively. Furthermore, H-6β (δ 2.55) shows an nOe with H-7 (δ 5.88), while H-5α (δ 2.45) exhibits an nOe with the aromatic H-4 (δ 6.65), which in turn displays an nOe with MeO-3 (δ 3.93). NOe's also interrelated 9-OMe (δ 3.93 or 3.95), H-10 (δ 6.84), H-11 (δ 7.02), MeO-1 (δ 3.62), and 2-OMe (δ 3.92) (see Experimental).

The above data led to conformation expression **1b** for this isomer, in which ring B is boat-like. The phenolic function was placed at C-8 because this is the substituted aromatic site devoid of any nOe.

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OMe 3.93
OMe 3.92
OMe 3.62
1.58 CH3CONH 5.22 br.d
5.88 dd H
2.15 m Hα
2.45 m Hα
2.25 m Hβ
2.35 m Hβ
7.02 d
6.84 d
5.99 HO
3.93 or 3.95 MeO
1b
4.95 m H
NHCOCH3 1.97
7.74 br.d
2.40 m Hβ
2.45 m Hβ
2.25 m Hα
1.95 m Hα
OH 6.08
OMe 3.93 or 3.95
6.85 d
7.01 d
3.90 MeO
3.92 MeO
3.58 MeO
1a
NHCOCH3
COCH3
RO
OMe
MeO
3 R=Me
4 R=H
OMe 3.93
OMe 3.92
OMe 3.62
1.57 CH3CONH
5.57 dd H
2.15 m Hα
2.43 m Hα
2.45 m Hβ
2.47 m Hβ
7.35 d
6.96 d
2.41 CH3COO
3.87 MeO
2

The H-6α and H-6β vicinal coupling constants with H-7 could not be as accurately measured in the case of isomer **1a** due to peak overlap. However, $J_{6\alpha,7}$ was approximately 9 Hz, and $J_{6\beta,7}$ was about 4 Hz, denoting dihedral angles of around 175° and 45°, respectively, as required by conformation **1a**. Additionally, a strong nOe could be observed between H-6β (δ 2.40) and H-7 (δ 4.95), whereas no nOe was noted between H-6α (δ 1.95) and H-7.

Another indication of the conformations of isomers **1a** and **1b** was derived from the chemical shifts for H-7. In species **1b**, H-7 lies almost in the same plane as ring C and is therefore deshielded, appearing downfield at δ 5.88. Such is not the case with conformation **1a**, in which H-7 is not significantly influenced by rings A or B and appears upfield at δ 4.95.

Geometrical isomerism is, of course, possible around the amidic nitrogen, but because no nOe's could be observed involving the acetyl methyl group it was not possible to specifically define this isomerism. It will be noted, however, that the methyl group in question falls at δ 1.97 in **1a** and further upfield at δ 1.58 in **1b**.

The ^{13}C-nmr spectrum of (−)-androbiphenyline [**1**] also showed twin peaks, reflecting the presence of the two conformers. Through the use of ^{13}C-^{1}H correlations, it was possible to make some specific assignments. In particular, C-6, C-7, C-10, and C-11 for isomer **1a** were found at δ 38.1, 49.7, 109.0, and 122.0. The corresponding values for **1b** were 39.4, 43.1, 108.4, and 122.5. The *N*-acetyl methyl carbon was at δ 23.7 for **1a** and at 23.2 for **1b**.

Acetylation of (−)-androbiphenyline [**1**] with Ac_2O in pyridine furnished acetate ester **2**, $C_{23}H_{27}NO_7$, whose ^{1}H-nmr spectrum showed that it existed in only one preferred conformation. The values for the *N*-acetyl methyl (δ 1.57) and NH (δ 5.22) suggested that this molecule existed in a conformation closely related to that for **1b**. Additionally, the coupling constants for **2**, $J_{6\alpha,7}=0$ Hz, $J_{6\beta,7}=7.7$ Hz, and $J_{NH,7}=9.1$ Hz, were very close to those for **1b**. As expected, H-11 (δ 7.35) in ester **2**, which lies para to the acetate function, was shifted much more downfield than H-10, which is meta to the acetate and is in evidence at δ 6.96.

Molecular models for **1a** and **1b** show that steric crowding is less severe around the C-8 phenol in conformation **1b**, so that acetylation of the phenolic function results in preference for a conformation similar to that of **1b**. Also, and as pointed out earlier, an increase in temperature favors **1b** over **1a**.

Basic hydrolysis of acetate **2** regenerated (−)-androbiphenyline [**1**] which again existed in $CDCl_3$ solution as two conformers, as indicated by the nmr spectrum.

The negative specific rotation of alkaloid **1** and its cd spectrum with a trough at 255 nm are indicative of the *S* absolute configuration (3). This is the same chirality that prevails in the colchicinoid-type alkaloids which are also present in *A. palaestinum*.

Two other *N*-acetylated dibenzocycloheptylamine alkaloids are known from the literature (4). These have been labeled K-3 and K-4 and assigned structures **3** and **4**. They originated from *Colchicum kesselringii* Rgl. (Liliaceae) native to Central Asia. No optical measurements were carried out at the time, and no statement was made concerning their absolute configuration.

It is likely that (−)-androbiphenyline [**1**] and alkaloids K-3 and K-4 are derived biogenetically from (−)-colchicine or one of its close analogues. It is presently unclear why K-3 and K-4 incorporate a carbomethoxy substituent on ring C, whereas (−)-androbiphenyline [**1**] bears a hydroxyl and a methoxyl on that ring. It should be pointed out in conclusion that the in vitro contraction of the tropolonic ring of (−)-colchicine using H_2O_2 has been achieved (5).

Known alkaloids that we also found in *A. palaestinum* are the colchinoids (−)-demecolcine and (−)-3-demethylcolchiceine, and the homomorphinandienone (−)-collutine (6).

EXPERIMENTAL

PLANT COLLECTION AND ALKALOID EXTRACTION.—Collection and extraction were as described in Tojo *et al.* (1). A specimen of the plant was deposited in the herbarium of the Department of Biological Sciences, University of Jordan. The following amounts of alkaloids were obtained, starting with 5.5 kg of bulbs of *A. palaestinum*: (−)-androbiphenyline [**1**], 20 mg; (−)-demecolcine, 4 mg; (−)-3-demethylcolchiceine, 4 mg; (−)-collutine, 8 mg. The latter three compounds, being known alkaloids, were identified by spectral comparisons.

(−)-ANDROBIPHENYLINE [**1**].—Amorphous; $[\alpha]_D$ −48° (c = 0.10, MeOH); cd $\Delta\epsilon$ (nm) (MeOH) −0.54 (255); uv λ max (MeOH-OH^-) 249, 261, 298, 313 nm (log ε 4.11, 4.00, 3.76, 3.64); ir ν max ($CHCl_3$) 3520, 3430, 2996, 1666, 1590 cm^{-1}; eims *m/z* 387 (44), 328 (100), 313 (30), 297 (12); hreims found *m/z* 387.1654, calcd for $C_{21}H_{25}NO_6$, 387.1682. ^1H nmr nOe for **1a** 1-OMe to H-11, 18%; 1-OMe to 2-OMe, 18%; 3-OMe to H-4, 32%; H-4 to 3-OMe, 18%; H-5β to H-4, 18%; H-6β to H-7, 18%; 9-OMe to H-10, 62%. ^1H nmr nOe for **1b** 1-OMe to H-11, 18%; 1-OMe to 2-OMe, 18%; 3-OMe to H-4, 18%; H-4 to 3-OMe, 9%; H-5α to H-4, 12%; H-6β to H-7, 12%; 9-OMe to H-10, 62%. ^{13}C nmr 169.0, 168.1 (CO); 152.7, 152.5, 151.1, 150.9, 145.7, 145.4, 142.2, 142.1, 141.4, 141.1, 136.0, 135.0, 129.0, 127.6, 126.0, 125.3, 124.8, 123.1 (C-1, C-1a, C-2, C-3, C-4a, C-7a, C-8, C-9, C-11a); 122.4, 122.0 (C-11); 109.0, 108.4 (C-10), 108.0, 107.9 (C-4); 61.0, 60.4 (1-OMe), 61.2, 61.1, 60.4, 56.1, 56.0, 55.9 (2-OMe, 3, 9); 49.8, 43.1 (C-7); 39.4, 38.1 (C-6); 31.1, 31.0 (C-5), 23.7, 23.2 (C-16).

O-ACETYLANDROBIPHENYLINE [**2**].—Obtained from **1** by treatment with Ac_2O in pyridine at room temperature: amorphous, uv λ max (MeOH) 260, 289 nm (log ε 4.09, 3.89); ir ν max ($CHCl_3$) 3420, 3000, 1780, 1675, 1480 cm^{-1}; eims *m/z* $[M]^+$ 429 (15), 387 (28), 361 (12), 328 (100). Saponification of this compound with KOH in MeOH regenerated **1**.

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