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Alkaloids of *Haloxylon salicornicum* (Moq.) Bunge ex Boiss. (Chenopodiaceae)

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Received November 16, 2004, accepted January 13, 2005

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Pharmazie 60: 949–952 (2005)

Haloxylon salicornicum is a desert plant that contains several alkaloids. From the aerial parts a new piperidyl alkaloid, haloxynine, was isolated and characterized on the basis of mass spectrometry, ^{1}H and ^{13}C NMR. A GLC/MS analysis revealed the presence of 17 additional known alkaloids of which piperidine, halosaline, anabasine, hordenine, *N*-methyltyramine, haloxine and aldotripiperideine had been previously reported in this genus. Among the 18 identified alkaloids, ten alkaloids were recorded for the first time from this plant and the genus *Haloxylon*. Haloxynine, halosaline, haloxine, anabasine, and smipine figure as major alkaloids with a relative abundance of more than 5% of total alkaloids. Some of these alkaloids are known be strong agonists at nicotinic acetylcholine receptors and it is thus likely that they serve as chemical defence compounds against insects and mammalian herbivores.

1. Introduction

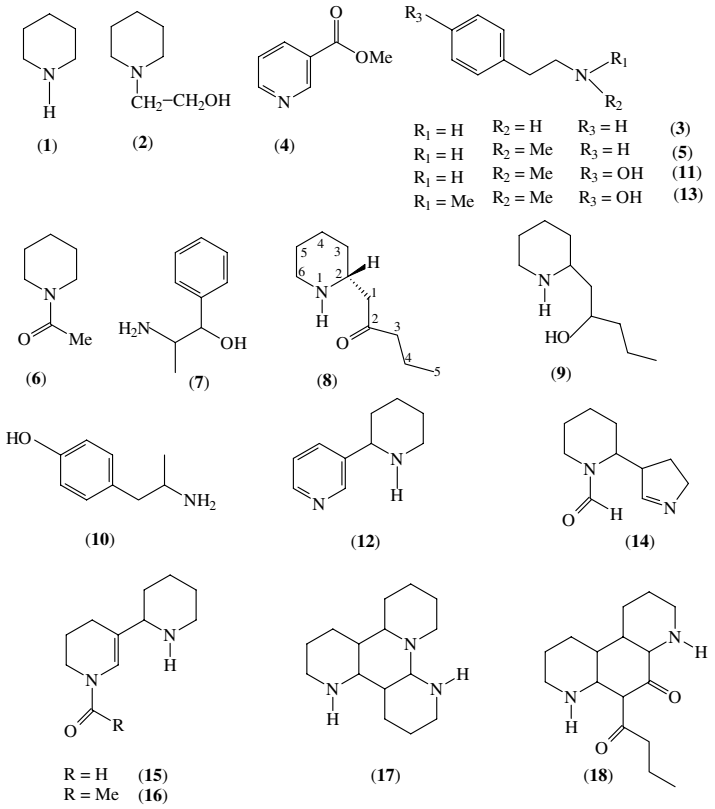
The genus *Haloxylon* (syn. *Hammada*, Chenopodiaceae) consists of approximately 25 species and is widely distributed throughout Irano-Turanian, Saharo-Arabian and E. Sudanian territories (Boulos 1999). In Egypt, the genus is represented by four species (Boulos 1999). *Haloxylon salicornicum* (Moq.) Bunge ex Boiss. (syn. *H. elegans*) is commonly found in sandy and stony deserts and wadis. The plant is locally known as Rimth (Täckholm 1974). It exhibits remarkable biological activities (Zohary 1981; Gouda et al. 1987; Shabana et al. 1990; Wasfi et al. 1995). So far, only a few alkaloid constituents of this species from Iraq (Michel et al. 1967), Saudi Arabia (Awaad 1990) and Egypt (Sandberg et al. 1960; Michel et al. 1967; Michel and Sandberg, 1968; Shehata 1985) have been reported. Recently, Gibbons et al. (2000) reported the isolation of a new pyranone derivative from this plant. Thus, in a continuation of our studies on the chemistry of some Chenopodiaceous plants (El-Shazly and Wink 2003; Ateya et al. 2004), the alkaloidal constituents of *H. salicornicum* have been investigated. In this paper, we report the isolation of a new piperidine alkaloid, haloxynine (**8**), which has not been isolated before. The structure of this new compound was established on the basis of MS, ^{1}H, ^{13}C NMR and HETCOR experiments. In addition, a GLC-mass spectroscopic study revealed the presence of 17 other piperidyl, di-piperidyl and phenylamine alkaloids. Most of these alkaloids are reported here for the first time from this plant and genus *Haloxylon*.

2. Investigations, results and discussion

2.1. Isolation and identification

Column chromatography of the alkaloidal extract of flowering *H. salicornicum* plants provided one major piperidyl alkaloid (**8**). Its structure was established by MS, ^{1}H and ^{13}C NMR analyses. The high resolution MS exhibited a molecular ion at m/z 169.1469 (calculated 169.1475 for $C_{10}H_{19}NO$). The CI$^+$ MS showed $M^+ + 1$, at 170 (100). EI-MS shows a base peak at m/z 84 ($M^+ - C_5H_9O$, piperidyl moiety) and other fragment ions at m/z 140, 126 and 98 corresponding to subsequent loss of C_2H_5, C_3H_7 and C_4H_7O radicals of the side chain. ^{13}C NMR spectra of this compound showed 10 carbon atoms, one methyl (δ_C 13.5), one methine (δ_C 52.9), one carbonyl (δ_C 207) and 7 methylenes. The identity of the piperidyl and pentanone moieties was substantiated from the ^{1}H NMR spectrum, a triplet at δ 0.83 ($J = 7.4$ Hz) was assigned to the terminal methyl of the side chain and the dq at δ 1.5 ($J = 1 \ldots 7.3$ Hz) for the adjacent methylene. However, the multiplet signals at δ 3.43 were assigned to H-2 proton in the piperidyl moiety. Complete analysis of the 500 MHz ^{1}H NMR spectrum was accomplished by ^{1}H and ^{13}C 2D-spectra. Both were in complete accordance with the structural assignments. Thus, according to the MS, ^{1}H and ^{13}H NMR data, alkaloid **8** was identified as 1-(2-piperidyl)-2-pentanone. This alkaloid has previously been prepared synthetically by Michel et al. (1967) and identified by IR spectrometry as 1-(2-piperidyl)-2-pentanone. However, to our knowledge, this is the first isolation of **8** from a natural source and it was named *haloxynine*.

Utilizing GLC-MS (EI and additionally CI), over 20 components were observed in the alkaloidal extract of *H. sali-*



cornicum, 18 of which could be identified (Table). Alkaloids were identified by capillary GLC by direct comparison (retention index, MS) with authentic alkaloids or by comparison of MS data with literature values. In the present study, the retention index of most of identified compounds is reported here for the first time. The identified alkaloids covered over 93% of all peaks observed in the chromatogram, with haloxynine (**8**) being the most abundant (42.4% of total alkaloids). Most of unidentified components (7% of total alkaloids) are present as traces with relative abundances of less than 0.1%. Only seven out of the eighteen identified alkaloids have previously been reported in literature, and eleven compounds are reported in this communication for the first time as constituents of *H. salicornicum*. On the other hand, we could not find any traces of nicotine, tyramine, oxedrine, and the quaternary bases choline and betaine, previously described by Sandberg et al. 1960; Michel et al. 1967; Michel and Sandberg, 1968; Shehata, 1985; Awaad 1990. However, two isomeric compounds expressed M^+ 265 (trace to 1% level) having RI at 2125 and 2140, with mass spectra that resembled those of aldotripiperideine (**17**). Probably, these alkaloids are aldotripiperideine derivatives containing hydroxyl groups. Further experiments are in progress to fully identify these alkaloids.

Piperidine, anabasine, aldotripiperideine, haloxine, halosaline and *N*-methyltyramine previously reported in this plant could be identified unambiguously by direct comparison of their mass spectra with published data (Sandberg et al. 1960; Michel et al. 1967; Michel and Sandberg 1968; Shehata 1985; Awaad 1990). Smipine and the dipiperidyl ammodendrine were identified by comparison of their mass spectra and retention indices (El-Shazly et al. 1996, 2000). The remaining eight alkaloids were identified as *N*-(2-hydroxyethyl) piperidine (**2**), phenethylamine (**3**), methylnicotinate (**4**), *N*-methylphenethylamine (**5**), *N*-acetylpiperidine (**6**), norephedrine (**7**), 4-(2-methylaminoethyl) phenol (**10**) and 3,4-dihydro-5-(2-piperidinyl)-1(2*H*)pyridine (**15**) on the bases of mass fragmentation, structure library (data system INCOS®) and biogenetic considerations.

Compounds **2** and **6** displayed parent ions at m/z M^+ 129 and 127, respectively. Alkaloid **6** with m/z 112 ($M^+ - CH_3$) and m/z 84 ($M^+ - CH_3CO$) was identified as *N*-acetylpiperidine and confirmed by comparison of its mass fragmentation with that reported in the literature (Lue et al. 1986, 1988). Also, mass fragmentation of **2** with m/z 98 ($M^+ - CH_2OH$) and m/z 84 ($M^+ - C_2H_5O$) as well as computer library search agree with the observed structure as *N*-(2-hydroxyethyl) piperidine; syn. 1-piperidine ethanol.

The MS of compound **3** (RI 1067) displayed M^+ at m/z 121 together with fragments at m/z 91, 77 and 65 that are characteristic for phenethylamine (Bogusz et al. 2000). The *N*-methyl substituation of **5** was deduced from the M^+ 135 (14 mass unit over **3**) and fragment ion m/z 91 and base peak at m/z 44 (C_2H_5NH). Thus, **5** has been identified as *N*-methylphenethylamine and confirmed by comparison with literature data (Soine et al. 1992). These phenethylamines were previously identified in *Alhagi pseudalhagi* (Ghosal et al. 1974) and *Hammillaria* species (Howe et al. 1977).

Methylnicotinate (**4**) and norephedrine (**7**) exhibited M^+ at m/z 137 and 151, respectively. Mass fragmentation as well as the data mining confirmed the identification of these compounds.

A compound tentatively identified as 4-(2-methylaminoethyl) phenol (**10**) was found to co-occur with *N*-methyltyramine (**11**). Both two alkaloids exhibited identical MS, but the former alkaloid possessed a shorter retention time in GLC-MS. This indicates that **10** is a steroisomer of **11**.

The alkaloid **15** with RI 1795 and molecular ion at m/z 194, showed close similarity to fragmentation pattern of ammodendrine suggested to be an ammodendrine deriva-

tive (El-Shazly et al. 1996, 2000). Yet, the mass difference between ammodendrine (**16**) (M^+, 208) and this alkaloid 194 ($M^+ -14$) indicates the presence of *N*-carboxaldehyde instead of the *N*-acetyl group in ammodendrine.
The presence of *N*-(2-hydroxyethyl) piperidine, phenethylamine, methylnicotinate, *N*-methylphenethylamine, *N*-acetylpiperidine, 4-(2-methylaminoethyl) phenol, smipine, 3,4-dihydro-5-(2-piperidinyl)-1(2*H*)pyridine and alkaloid **8** are reported in *H. salicornicum* and genus *Haloxylon* for the first time.

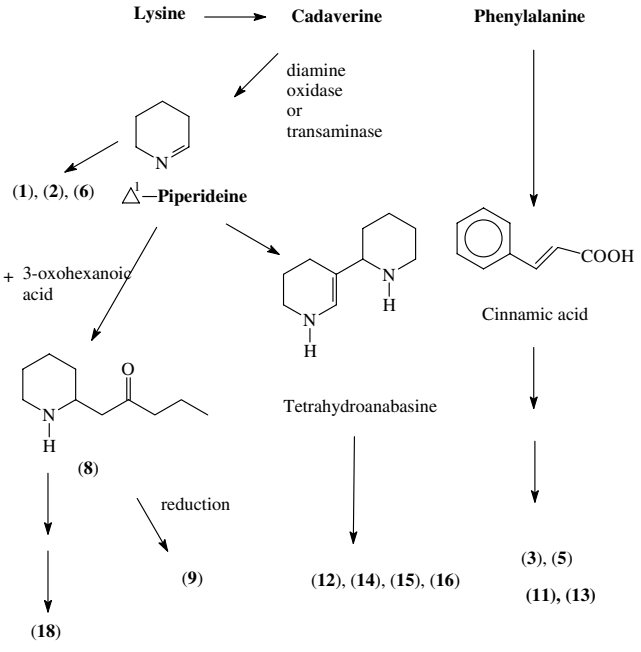
2.2. Biosynthetic implications

Isolation and characterization of haloxynine (**8**) supports the previous suggestion of **8** as intermediate in the biosynthesis of halosaline (**9**) and haloxine (**18**) in *H. salicornicum* (Liebisch and Schütte 1985). Halosaline is a lysine-derived alkaloid and assumed to be generated from the incorporation of Δ^1-piperideine with 3-oxohexanoic acid (Scheme). In the biosynthesis of haloxine (a bi-piperidyl alkaloid), the 3-oxohexanoic acid is preserved as an intact unit. Anabasine and related compounds resulted from the incorporation of Δ^1-piperideine with nicotinic acid. However, *N*-methyltyramine and derivatives resulted from phenylalanine (Schütte and Liebisch 1985).

2.3. Conclusions

H. salicornicum produces a set of simple alkaloids which have in common that their nitrogen is a quaternary ion under physiological conditions. Compounds with such a structure often interfere with acetylcholine and catecholamine receptors (for review: Wink and Schimmer 1989; Wink 2001).
Haloxynine and halosaline show structural similarities to *Conium* alkaloids, that are strong agonists at nicotinic acetylcholine receptors (nAChR) and responsible for the known toxicity of hemlock. For ammodendrine and anabasine nAChR agonist activities have already been reported (for review: Wink and Schimmer 1989; Wink 2001) and it is likely that the derivatives of these compounds show comparable activities. *N*-Methyltyramine and *N,N*-dimethyltyramine are known to stimulate dopamine receptors. Although the toxicology of *H. salicornicum* has not been determined in detail, we can assume that it appears to be a toxic plant that can deter herbivorous animals, such as insects and mammals. On Sinai, where the plant is abundant, we could not detect any predation, except from camels which appear to be able to tolerate this plant. It is thus likely that these alkaloids function as chemical defence mechanism for this desert plant.

Scheme



3. Experimental

3.1. Plant material

Flowering plants of *Haloxylon salicornicum* (Moq.) Bunge ex Boiss. (syn. *H. schweinfurthii* Asch., *Caroxylon salicornicum* Moq., *Hammada articulatum* (Cav.) Bunge, *H. elegans* (Bunge) Botsch., *H. salicornica* (Moq.) Iljin) were collected from the Sinai desert (Wadi feraan) in December 2001. Identity of the plant was confirmed by Dr. H. Abdel Baset, Ass. Professor of Plant Taxonomy, Faculty of Science, Zagazig University. A voucher specimen has been deposited at the Herbarium of the Department of Pharmacognosy, Faculty of Pharmacy, Zagazig University.

3.2. Alkaloid extraction

Air-dried powdered aerial parts of *H. salicornicum* (1 kg) was extracted with 80% ethanol (3×5 l). The extract was concentrated under reduced pressure in a Rota Vapor and taken up in 300 ml 0.5 N HCl. The aqueous acidic solution was washed with CH_2CI_2 (2×500 ml), made alkaline with NH_4OH (pH 10), extracted with methylene chloride (5×500 ml), dried over anhydrous Na_2SO_4 and evaporated to obtain the total alkaloids (10.5 g). One mg of the resulting alkaloid extract was dissolved in methanol (1 ml) and subjected to analysis by capillary GLC and GLC-MS, results are recorded in the Table.

3.3. Isolation and analysis of compound 8

A part of this extract (8 g) was subjected to aluminum oxide (neutral, Brockmann Activity 1) column chromatography (75×3 cm, 500 g) packed with light petrol (40–60 °C) and gradient elution was made in increasing order with CH_2CI_2, and methanol containing 2.5% NH_4OH (25%) resulted in the isolation of one alkaloid (**8**) with R_f 0.61 [Si gel F_{254}, CH_2CI_2–MeOH–NH_4OH (25%), 80 : 20 : 1].
1-(2-Piperidyl)-2-pentanone (**8**); (haloxynine): eluted with 3% MeOH in CH_2Cl_2 obtained as a white needles (CH_2Cl_2–MeOH), M.P. 138–140 °C, IR (KBr) ν_{max} cm^{-1}, 3492 (N–H), 1714 (C=O), 1404 (C–N). High resolution EIMS m/z (rel. int.) [M^+] 169 (13), 140 (14), 126 (10), 98 (26), 84 (100), 71 (8), 56 (14), 42 (14). Positive mode CIMS $[M+H]^+$, 170 (100). ^{1}H NMR ($CDCI_3$, 500 MHz): pentanone moiety: δ 2.88 (1 H, dd, J = 8.7, 17.9 Hz, H-1 β), 3.17 (1 H, dd, J = 4.2, 17.9 Hz, H-1 β), 2.81 (1 H, dt, J = 3.1, 12.5 Hz, H-3 α), 3.41 (1 H, m, H-3 β), 1.53 (2 H, dq, J = 1.4, 7.3 Hz, H-4), 0.83 (3 H, t, J = 7.4, H-5); piperidyl moiety: δ 3.43 (1 H, m, H-2), 1.63 (1 H, dq, J = 3, 12 Hz, H-3 α), 1.89 (1 H, dq, J = 3, 12 Hz, H-3 β), 1.78 (1 H, dt, J = 2.1, 15 Hz, H-4 α), 1.89 (1 H, dq, J = 3, 12 Hz, H-4 β), 1.46 (1 H, td, J = 2.9, 13 Hz, H-5 α), 1.78 (1 H, dt, J = 2.1, 15 Hz, H-5 β), 2.35 (2 H, q, J = 7.3, H-6). ^{13}C NMR ($CDCI_3$, 125 MHz): pentanone moiety: δ 45.0 (t, C-1), 207 (s, C-2), 44.9 (t, C-3), 16.9 (t, C-4), 13.5 (q, C-5); piperidyl moiety: δ 52.9 (d, C-2), 28.2 (t, C-3), 22.0 (t, C-4), 22.1 (t, C-5), 45.1 (t, C-6).

3.4. Capillary GLC and GLC-MS analyses

Capillary GLC: A Carlo Erba ICU 600 gas chromatograph was used equipped with FID and a Spectra Physics Integrator. Column: DB1; 15 m (0.317 mm inner diameter). Conditions: carrier gas He (2 ml/min.); detector temp. 300 °C; injector temp. 250 °C; oven temp. program: initial temp. 70 °C, 2 min isothermal, 70–300 °C with 6 °C/min to 300 °C, then 10 min isothermal. Retention indices (RI) were calculated using co-chromatographed standard hydrocarbons (C10–C28).
GLC-MS Analysis: A Carlo Erba Mega 5160 gas chromatograph equipped with a fused silica column (DB1, 30 m) was employed. The capillary column was directly coupled to a quadruple mass spectrometer (Finnigan MAT 4515). Conditions: injector 250 °C; temp. program 70–300 °C, 6 °C/min; split ratio 1 : 20; carrier gas He 0.5 bar. EI-mass spectra were recorded at 70 eV.

3.5. General

Melting point was determined on a SMP2 melting point apparatus STUART SCIENTIFIC and is uncorrected. IR was recorded in Gensis II

Table: Alkaloid composition and mass spectral data of eighteen alkaloids from *Haloxylon salicornicum* separated by capillary GLC

Alkaloid	RI**	Area (%)	M^+ and other characteristic ions (relative abundance in %)
1 Piperidine	1015	0.10	85(100), 56(18), 42(28), 44(27)
2 N-(2-Hydroxyethyl) piperidine*	1035	0.29	129(4), 98(100), 84(5), 70(7), 55(10)
3 Phenethylamine*	1067	tr.	121(4), 91(100), 77(25), 65(40)
4 Methylnicotinate*	1102	0.13	137(61), 106(100), 78(70), 51(30)
5 N-Methylphenethylamine*	1120	1.64	135(3), 91(10), 77(4), 65(5), 44(100)
6 N-Acetylpiperidine*	1153	tr.	127(100), 112(20), 99(10), 84(98), 70(33), 57(40), 56(35), 43(63)
7 Norephedrine*	1290	4.31	151(05), 77(10), 91(3), 44(100)
8 Haloxynine*	1309	42.37	169(8), 140(8), 126(5), 98(20), 84(100), 71(7), 56(15), 43(18)
9 Halosaline	1363	23.70	171(2), 142(0.5), 128(6), 110(0.5), 98(3), 84(100), 56(10), 43(5)
10 4-[2-Methylamino ethyl]-phenol*	1420	2.10	151(5), 107(9), 91(1), 77(6), 44(100)
11 N-Methyltyramine	1426	2.10	151(4), 107(10), 91(2), 77(6), 44(100)
12 Anabasine	1432	5.41	162(40), 161(26), 133(50), 119(40), 106(43), 105(60), 92(18), 84(100), 80(20), 65(8), 58(7), 51(8)
13 Hordenine (syn. *N*,*N*-dimethyltyramine)	1438	0.43	165(1), 121(0.9), 107(1), 91(2), 77(3), 58(100)
14 Smipine*	1578	4.78	180(3), 151(17), 135(6), 109(100), 96(70), 84(10), 67(5), 56(9)
15 3,4-Dihydro-5-(2-piperidinyl)-1(2*H*) pyridine carboxaldehyde*	1795	0.17	194(90), 177(20), 165(100), 151(26), 137(65), 123(48), 110(20) 109(47), 102(20), 94(40), 84(35), 80(30), 67(15), 54(16)
16 Ammodendrine*	1865	tr	208(100), 191(25), 179(58), 165(70), 152(30), 137(45), 123(61), 120(75), 110(80), 109(35) 94(47), 81(20), 72(32), 51(28), 44(71)
17 Aldotripiperideine	2023	0.15	249(25), 248(45), 191(75), 165(30), 137(9), 110(15), 96(16), 84(80), 83(100), 86(16), 55(16)
18 Haloxine	2260	5.33	278(4), 249(1), 235(3), 207(100), 193(3), 165(9), 150(9), 124(8), 96(5), 84(28), 68(3), 55(5)

* New for *Haloxylon salicornicum*, tr. = traces
** RI = Kovat's retention indices were calculated relative to *n*-alkanes on a BD1 column under condition listed in the Experimental section

FTIR spectrophotometer. High resolution EIMS was recorded at 70 eV by direct inlet in JMS (Japan). Positive mode CI was performed in 1-butane. NMR measurements: ^1H and ^{13}C NMR spectra were recorded with AC 500 Bruker instrument in $CDCI_3$, at 500 and 125 MHz, respectively. Identification and assignments were aided by DEPT and 2D COSY experiments.

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