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Rhombifoline and 5,6-Dehydrolupanine from *Anagyrus foetida* L.

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Rhombifoline and 5,6-dehydrolupanine were isolated for the first time from the leaves and stems of *A. foetida* L. indigenous to Saudi Arabia. In addition, five other alkaloids, previously identified in *A. foetidia* L., namely N-methylcytisine, sparteine, anagyrine, lupanine and cytisine, were isolated. The isolated alkaloids were characterized by UV, ^{1}H-NMR, ^{13}C-NMR and Mass spectral data. ^{13}C-NMR data of rhombifoline and 5,6-dehydrolupanine are reported for the first time.

Key words: *Anagyrus foetida* L., Leguminosae, Alkaloids, Rhombifoline, 5,6-Dehydrolupanine, Lupanine, Anagyrine, Sparteine, Cytisine and N-Methylcytisine

INTRODUCTION

Anagyrus foetida L. is a plant belonging to the tribe Podalyrieae, subfamily Lotoideae (Papillionoideae), family Leguminosae (Hutchinson, 1964). Such a tribe, together with the tribes Sophorae and Genistae represent the main contributors of quinolizidine alkaloids (Mears and Mabry, 1971). The leaves and bark of the plant are used in Saudi folk medicine for the treatment of flatulance, maldigestion and constipation (Ageel *et al.*, 1987).

Several alkaloids have been detected by TLC or paper electrophoresis (Ing, 1933) or isolated from *A. foetida* L. (Ing, 1935; Adzet *et al.*, 1970; Orjales Venero, 1971; Mears and Mabry, 1971; Viguera Lobo *et al.*, 1977). These include anagyrine and sparteine (Ing, 1933 & 1935; Adzet *et al.*, 1970; Orjales Venero, 1971), N-methylcytisine (Ing, 1935; Orjales Venero, 1971), cytisine (Ing, 1933; Adzet *et al.*, 1970; Orjales Venero, 1971; Mears and Mabry, 1971; Viguero Lobo *et al.*, 1977), retamine (Ing, 1933) and lupanine (Ing, 1935). Ing (1935) also reported a hydroxyanagyrine, which was not fully identified. Except for a study of the coumarins of *A. foetida* L. (El-Beih, 1984), no other reports could be traced in the literature on the saudi plant.

The present study deals with the isolation and identification of the alkaloids of Saudi *A. foetida* L.. Rhombifoline **1** and 5,6-dehydrolupanine **2** are reported in the genus *Anagyrus* for the first time, in addition to five previously reported alkaloids.

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MATERIALS AND METHODS

Plant Material

Leaves and stems of *A. foetida* L. were collected from wild plants growing in Saudi Arabia. They were dried in the shade and powdered.

Extraction

The powdered dried plant material (3 kg) was defatted with pet. ether (60-80℃). The defatted powder was then exhaustively extracted with MeOH (Soxhlet) and the methanolic extract was evaporated under reduced pressure at 40℃ to a semisolid residue (630 g). The residue was taken in $CHCl_3$ and extracted with 2% citric acid solution to exhaustion (tested for alkaloids). The combined citric acid extract was rendered alkaline (pH 8-9) with NH_4OH and extracted 3 times with $CHCl_3$. The combined $CHCl_3$ extract was evaporated under reduced pressure, to yield the crude total alkaloids (160 g).

Column Chromatography

The crude total alkaloids (25 g) were fractionated on a silica gel (600 g) column, using CH_2Cl_2 and CH_2Cl_2 containing increasing amounts of MeOH and finally with pure MeOH. Fractions were monitored by TLC (silica gel/EtOAc-Toluene-Diethylamine (7 : 2 : 1) or (13

: 4 : 3); 10% EtOH in $CHCl_3$, and 25% MeOH in Et_2O-H_2O-NH_4OH (100 : 4 : 3); similar fractions were combined (fractions I-VII).

Isolation of Individual Alkaloids

Fraction II [0.37 g, eluted with 2% MeOH/CH_2Cl_2], was flash chromatographed on a silica gel column (20 ×2.8 cm); elution was with CH_2Cl_2 containing increasing amounts of MeOH (0-5%), collecting 6 ml fractions. Rhombifoline (43 mg) was obtained in fractions, 32-48.

Fraction III [8.9 g eluted with 3% MeOH/CH_2Cl_2] contained primarily anagyrine and N-methylcytisine. A weight of 285 mg of this fraction, was applied to a silica gel chromatotron plate (2 mm), using EtOAc-toluene-diethylamine (14 : 5 : 1) as the solvent system (200 ml), collecting 4 ml fractions. Anagyrine (150 mg) was isolated in fractions 15-21 and N-methylcytisine (65 mg) in fractions 26-40.

Fraction IV (2.55 gm, eluted with 5% MeOH in CH_2Cl_2), contained 5,6-dehydrolupanine, lupanine and N-methylcytisine. A weight of 600 mg was applied to a silica gel chromatotron plate (4 mm) and eluted with EtOAc-toluene-diethylamine (60 : 37 : 3) as the initial eluent (400 ml), followed by EtOAc-toluene-diethylamine (70 : 20 : 1) as a second eluent (100 ml) and collecting 10 ml fractions. Fractions 6-11 yielded 5,6-dehydrolupanine (15.6 mg), while fractions 23-31 yielded lupanine (43 mg) and fractions 60-80, yielded an additional amount of N-methylcytisine (62 mg).

Fraction V (2.07 g, eluted with 10% MeOH in CH_2Cl_2) contained mainly cytisine. This was dissolved in the minimum volume of $CHCl_3$ and filtered to yield 1.5 g of $CHCl_3$-soluble fraction. This was chromatographed on a silica gel column (20×4 cm), using Et_2O-MeOH-H_2O-NH_4OH (85 : 15 : 4 : 3) as the eluent, collecting 10 ml fractions. Cytisine (30 mg) was obtained in fractions 14-18.

Fraction VII (3.3 g, eluted with 50% MeOH in CH_2Cl_2) contained sparteine. An aliquot (1.7 g) was flash-chromatographed on a silica gel column (20×4 cm) using EtOAc as the eluent and collecting 10 ml fractions; sparteine (760 mg) was obtained in fractions 41-101.

(−)-Rhombifoline 1

A yellowish oil, $[\alpha]_D^{25} = -232.4°$ (c=2.13, EtOH), UV λ_{MeOH} nm (ε): 232 (0.183×10^4), 306 (0.188×10^4); IR $\nu\,cm^{-1}$: 3080, 2940, 2790, 2760, 2705 (sh), 1650, 1560; ^{1}H-NMR (200 MHz, $CDCl_3$, δ): 7.27 (1H, dd, j=8.8, 7.1 Hz, H-4), 6.45 (1H, dd, j=8.8, 1.2 Hz, H-3), 6.02 (1H, dd, j=7.1, 1.2 Hz; H-5), 5.8 (1H, m, H-16), 4.9 (2H, m, H-17), 4.01 (1H, d, j=14.2 Hz, H-10_e) and 3.86 (1H, dd, j=14.2, 6.2 Hz, H-10_a); ^{13}C-NMR (Table I); MS (EI) m/z: M^+ 244 (4%), 203 (73%), 160 (13%), 146 (11%), 98 (13%) and 58 (100%).

Table I. ^{13}C-NMR chemical Shift of Certain *A. foetida* L. Alkaloids (in $CDCl_3$, δ)[a]

	5,6-Dehydrolupanine 2	Rhombifoline 1	N-Methylcytisine 7	Cytisine 6
2	170.9(s)	163.6(s)	163.5(s)	163.0(s)
3	31.8(t)	116.4(d)	116.6(d)	116.7(d)
4	22.8(t)	138.7(d)	138.5(d)	138.8(d)
5	102.4(d)	104.6(d)	104.5(d)	105.1(d)
6	142.9(s)	151.6(s)	151.4(s)	151.0(s)
7	34.0(d)	35.5(d)	35.3(d)	35.5(d)
8	25.0(t)	25.9(t)	25.3(t)	26.2(t)
9	33.1(d)	28.0(d)	27.8(d)	27.7(d)
10	48.0(t)	50.0(t)	49.9(t)	49.7(t)
11	63.3(d)	59.9(t)	62.1(t)	52.9(t)
12	27.5(t)	–	–	–
13	19.2(t)	60.2(t)	62.4(t)	53.8(t)
14	21.5(t)	56.9(t)	46.1(q)	–
15	54.8(t)	31.1(t)	–	–
16	–	136.2(d)	–	–
17	56.5(t)	115.4(d)	–	–

[a]TMS was used as internal standard; multiplcities (in parenthesis) were determined by APT and DEPT experiments.

(+)5,6-Dehydrolupanine 2

A colourless liquid; $[\alpha]_D^{25} = +62.4°$ (c=0.1, MeOH); UV λ_{MeOH} nm (ε): 253 (0.27×10^4); IR $\nu\,cm^{-1}$: 2920, 2840, 2780, 2710 (sh), 1650 (lactam carbonyl); ^{1}H-NMR (200 MHz, $CDCl_3$, δ): 4.9 (1H, t, j=4.2 Hz, H-5), 3.99 (1H, d, j=14.2, H-10_e) and 3.25 (1H, dd, j=14.2, 6.2 Hz, H-10_a); ^{13}C-NMR (Table I); MS (EI) m/z: M^+ 246 (17%), 167 (9%), 149 (15%), 136 (10%), 134 (12%), 112 (14%), 98 (100%), 97 (47%), 84 (37%), 69 (34%), 68 (32%) and 55 (32%).

(−)N-Methylcytisine 7

White crystals (MeOH); m.p 130-132°C (uncorrected), $[\alpha]_D^{25} = -194.7°$ (c=5, MeOH); UV λ_{MeOH} nm, (ε): 230 (0.19×10^5), 305 (0.204×10^5); IR $\nu\,cm^{-1}$: 3040, 2925, 2830, 2780, 2740, 1650 (lactam carbonyl), 1570, 1550 (conj. C=C); ^{1}H-NMR (200 MHz, $CDCl_3$, δ): 7.26 (1H, dd, j=8.8, 7.1 Hz, H-4), 6.4 (1H, dd, j=8.8, 1.3 Hz, H-3); 5.99 (1H, dd, j=7.1, 1.3 Hz, H-5), 4.1 (1H, d, j=14.2 Hz, H-10_e), 3.88 (1H, dd, j=14.2, 6.2 Hz, H-10_a); ^{13}C-NMR: (Table I); MS (EI) m/z: M^+ 204 (100 %), 160 (10%), 146 (21%), 117 (15%). 58 (52%), 42 (20%).

Catalytic Hydrogenation of 2

(+)-5,6-Dehydrolupanine (**2**; 5 mg) in ethanol (15 ml) was hydrogenated with nascent hydrogen using 10% Pd/C (10 mg) at room temperature. The catalyst was removed by filtration and the solvent was removed under reduced pressure at 40°C. The product was

identified as lupanine by GLC [3% OV-17 on Chromosorb WHP 80/100 mesh (3 mm×200 cm), isothermal at 250°C, Injector temp. 300°C, FID detector at 300°C, N_2 as inert gas at a flow rate 30 ml/min] and two TLC systems on Silica gel G [S_1; MeOH-NH_4OH (131 : 2) and S_2; EtOAc-toluene-diethylamine (14 : 5 : 1)]. The product of hydrogenation was indistinguishable from authentic lupanine (R_t: 4.00 min.; R_f: S_1, 0.44 and S_2, 0.43) and was quite distinguishable from **2** (R_t: 3.52 min., R_f: S_1, 0.62 and S_2, 0.52). Determination of $[\alpha]_D$ of the obtained lupanine proved it the (−)-form.

The spectral data and $[\alpha]_D$ values of each of (−)-anagyrine **5**, (−)-lupanine **4**, (−)-cytisine **6** and (+)-sparteine **3** were identical with those reported (Bohlmann and Schumann, 1965; Wiewiorowski *et al.*, 1967; Choa and Martin, 1971; Bohlmann and Zeisberg, 1975; Hatifield *et al.*, 1980; Wink *et al.*, 1981; Murakoshi *et al.*, 1982; Tosun *et al.*, 1986) and are available upon request.

RESULTS AND DISCUSSION

From the alcoholic extract of the leaves and stems of *A. foetida* L., seven alkaloids were isolated by column chromatography and/or chromatotron separations. Five of these alkaloids, namely sparteine **3**, lupanine **4**, anagyrine **5**, cytisine **6** and N-methylcytisine **7**, previously reported in this species, were isolated and identified by comparison of their spectral data (UV, IR, NMR(^{1}H, ^{13}C) and MS) with the reported values (Ing, 1933 & 1935; Bohlmann and Schumann, 1965; Wiewiorowski *et al.*, 1967; Adzet *et al.*, 1970; Orjales Venero, 1971; Nakano *et al.*, 1974; Bohlmann and Zeisberg, 1975; Viguera Lobo *et al.*, 1977; Wink *et al.*, 1981; McCoy and Stermitz, 1983; Tosun *et al.*, 1986; Cordell, 1989). In addition, two other alkaloids **1** and **2** are reported for the first time in this species. Since no data on ^{1}H-NMR and ^{13}C-NMR for compound **1** and ^{13}C-NMR for compound **2** could be traced in literature, these are discussed in detail.

Rhombifoline **1**, was obtained as a yellowish oil, $[\alpha]_D^{25} = -232.4°$ (c=2.13, EtOH), in a yield of (0.0091 %). The IR spectrum showed absorption bands at ν_{max} 2760-2790 cm^{-1} (trans-quinolizidine), 1650 cm^{-1} (lactam carbonyl) and 1560 cm^{-1} (conjugated double bond) (Atta-ur-Rahman, 1991). The UV spectrum showed absorption at λ_{max} 232 and 306 nm, suggesting the presence of pyridone moiety (Ohmiya *et al.*, 1981; Atta-ur-Rahman *et al.*, 1991). The MS of **1** showed a weak $[M]^+$ at m/e 244 (4%), with a predominant ion at m/e 203 (73%), which corresponds to the loss of an allyl group (M^+-41). In addition, it showed ions at m/e 160 (13%) and 146 (11%) characteristic of lupine alkaloids containing α-pyridone ring (Ohmiya *et al.*, 1974, Ohmiya *et al.*, 1979; Murakoshi *et al.*, 1981). The ^{1}H-NMR showed signals at (δ) 6.45 (dd, J=8.8, 1.2 Hz), 7.27 (dd, J=8.8, 7.1 Hz) and 6.02 (dd, j=7.1, 1.2 Hz) corresponding to protons at C-3, C-4 and C-5, respectively. The C-10 protons were very characteristic for quinolizidine alkaloids with this type of substitution for ring A and were quite similar to C-10 protons in cytisine, N-methylcytisine and anagyrine. The H-10_a appeared at δ 3.86 (dd, J=14.2, 6.2 Hz) which was coupled to H-10_e at 4.01 (d, j=14.2 Hz). These low field chemical shift values for H-10_a & H-10_e are characteristic for pyridone-type quinolizidine alkaloids (Atta-ur-Rahman *et al.*, 1991).

The ^{13}C-NMR showed the presence of a conjugated carbonyl carbon at 163.6 ppm (C-2), one quaternary aromatic carbon at 151.6 ppm (C-6) and three aromatic C-H carbons at 116.4 (C-3), 138.7 (C-4) and 104.6 (C-5). The two olefinic signals at 136.2 and 115.4 ppm were assigned to C-16 and C-17, respectively. The upfield chemical shift observed for C-8 at 25.9 ppm is characteristic for the tricyclic quinolizidine alkaloids, as well as H-9/H-11 trans-oriented tetracyclic quinolizidines (Bohlmann and Zeisberg, 1975; Waterman and Faulkner, 1982). From the previous data, compound **1** is identified as rhombifoline.

5,6-Dehydrolupanine **2** was obtained as a colourless oil, $[\alpha]_D^{25} = +62.4°$ (c=0.1, MeOH). The IR spectrum showed absorption bands at 2780-2840 cm^{-1} (trans-quinolizidine) and 1650 cm^{-1} (lactam carbonyl). The UV spectrum showed absorption at λ_{max} 253 nm, indicative of a vinylamide (Murakoshi *et al.*, 1982). The MS of **2** showed $[M^+]$ at m/e 246 (17%) and a base peak at m/e 98 (100%), which results from a fragmentation pathway involving the D ring, via charge localization at N-16 (Choa and Martin, 1971). The low intensity of the fragment ions at m/e 136 (10%) and 149 (15%), the most two characteristic ions in lupanine, supports the $\Delta^{5,6}$ position of the double bond, which inhibits the cleavage of the molecule at the A/B ring junction upon electron impact (Choa and Martin, 1971).

The identity of compound **2** as 5,6-dehydrolupanine was confirmed from ^{1}H- and ^{13}C-NMR-spectra. The ^{1}H-NMR showed an olefinic proton at (δ) 4.9 (t, j=4.2 Hz), which could be assigned to C-5 proton. In addition, the signal at δ 3.99 (d, j=14.2 Hz) was assigned to the strongly deshielded C-10_e proton, while the C-10_a proton appeared at 3.25 (dd, j=14.2, 6.2 Hz), more upfield than that observed for rhombifoline. The ^{13}C-NMR (Table I) showed the presence of carbonyl at 170.9 (C-2) and two olefinic carbons at 142.9 (C-6) and 102.4 (C-5). The upfield chemical shift value of C-8 at 25.0 is indicative of quinolizidine with trans-oriented H-9/H-11 (Bohlmann and Zeisberg, 1975; Waterman and Faulkner, 1982), reflecting the shielding effect due to the spatial proximity to N-16. This is

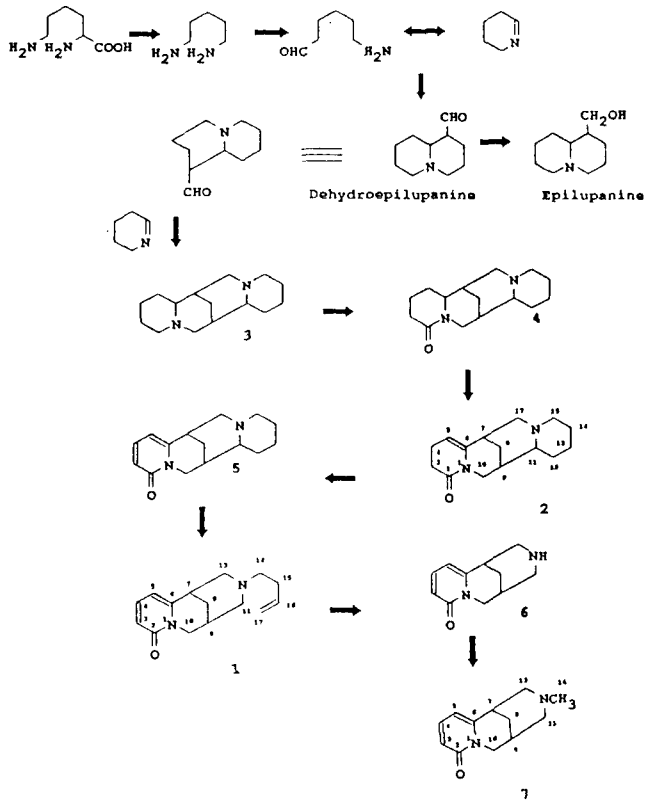

Fig. 1. Biosynthetic interrelationship of the alkaloids *A. foetida* L..

in contrast to the H-9/H-11 cis-quinolizidines, where C-8 was shown to resonate at values greater than 30 ppm (Bohlmann and Zeisberg, 1975; Waterman and Faulkner, 1982). Thus compound **2** is identified as 5,6-dehydrolupanine. This identity was confirmed through catalytic hydrogenation of **2** in ethanol, with 10% Pd/C, whereby (−)-lupanine was obtained. Thus (+)-5,6-dehydrolupanine **2** has the same absolute configuration as (−)-lupanine.

The ^{13}C-NMR data of rhombifoline is shown in Table I. In addition, the so-far unreported ^{13}C-NMR of 5,6-dehydrolupanine and N-methylcytisine are reported, the latter in comparison to those of cytisine.

Rhombifoline **1** and 5,6-dehydrolupanine **2** are reported here for the first time in *A. foetida* L. and from the genus *Anagyrus*. However, they have been isolated, as minor constituents, from certain species belonging to the quinolizidine-rich tribes of the family Leguminosae. Both alkaloids were shown to occur together in certain *Echinosophora* (Murakoshi *et al.*, 19 82), *Thermopsis* (Choa and Martin, 1971), *Clathrotropis* (Hatfield *et al.*, 1980) and *Petteria* (Veen *et al.*, 1992) species. Rhombifoline was also reported in certain *Genista* and *Ammodendron* species (Cordell, 1989), while 5,6-dehydrolupanine was reported in certain *Lupinus* (Kinghorn *et al.*, 1980; Cordell, 1989), *Sophora* (Hatfield *et al.*, 1980; Cordell, 1989) and *Sarothamnus* (Wink *et al.*, 1981) species. Both alkaloids, however, have a much limited distribution than other tetracyclic and tricyclic quinolizidine alkaloids.

Although rhombifoline and 5,6-dehydrolupanine are minor alkaloids in *A. foetida* L., they are plausible biosynthetic intermediates of several of the major alkaloids of the plant, particularly anagyrine, N-methylcytisine and cytisine (Choa and Martin, 1971; Nowacki and Waller, 1975), as is depicted in Fig. 1.

The results of this investigation indicates the presence of the tetracyclic quinolizidine alkaloids (+)-sparteine, (+)5,6-dehydrolupanine, (−)-lupanine, and (−)-anagyrine together with the tricyclic alkaloids (−)-rhombifoline, (−)-N-methylcytisine, and (−)-cytisine. These alkaloids possess the same absolute configuration of the C7/C9 methylene bridge i.e. (7R, 9R) and (7R, 9S) configuration respectively. Okuda *et al.* (1965) have generalized from their extensive stereochemical studies on lupine alkaloids, that alkaloids having the same absolute configuration of the C7/C9 bridge are found together in a given plant. This was generally found to hold true (Abdul-Halim *et al.*, 1992) with the exception of a few cases (Okuda *et al.*, 1965; Ohmiya *et al.*, 1984).

The results with *A. foetida* L. show that this plant accumulates only (7R, 9R) tetracyclic and (7R, 9S) tricyclic lupine alkaloids, both having the same absolute configuration of C7/C9 methylene bridge and is thus consistent with the above generalization.

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