(-)-4α-HYDROXYSPARTEINE, A NEW NATURAL PRODUCT FROM ACOSMIUM PANAMENSE

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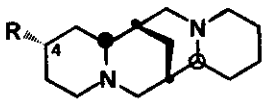
Abstract - (-)-4α-Hydroxysparteine (1) was obtained for the first time as a natural product from a methanol extract of the bark of Acosmium panamense (Leguminosae). The structure and stereochemistry of 1 were confirmed by gc/ms comparison of the acetylated product of 1 with authentic samples of 4α-acetoxysparteine (2) and 4β-acetoxysparteine (6). 4α-Hydroxysparteine (1) and 2,4-d_2-4α-hydroxysparteine (7) were prepared by reduction of multiflorine (3) with sodium borohydride and sodium borodeuteride in methanol, respectively.

The bark of Acosmium panamense (Benth.) Yakovlev (syn. Sweetia panamensis Benth.) was formerly used as the official drug Cascara Amarga in the United States for the treatment of chronic skin diseases, scrofula, anemia and colds[1,2]. A methanol extract (211 g) of A. panamense bark (2.3 kg) was subjected to an acid-base partition procedure. On combined gc/ms[3], 1 was found to occur in a chloroform-soluble, diethyl ether-insoluble fraction (26.5 g), and was calculated to represent approximately 0.07% w/w of the bark. (-)-4α-Hydroxysparteine (1, 2 mg) was purified by preparative tlc and was found to exhibit the following data: oil; $[\alpha]_{589}^{23}$ -31°, $[\alpha]_{578}^{23}$ -33°, $[\alpha]_{546}^{23}$ -36°, $[\alpha]_{436}^{23}$ -60° and $[\alpha]_{365}^{23}$ -103° (c 0.1, ethanol); gc/ms, R_t: 11.8 min, ms: m/z 250 (M^+, $C_{15}H_{26}N_2O$, 27%), 233 (M-OH, 5), 221 (5), 209 (35), 153 (100), 136 (41), 122 (11), 114 (71), 110 (22), 98 (56), 97 (34), 96 (19), 84 (15), 55 (24) and 41 (39); R_f[4]: 0.50 (cyclohexane-diethylamine, 7:3), 0.04 (methanol-28% ammonia, 65:1).

The presence of a secondary hydroxyl group in 1 was established by its quantitative conversion, under mild acetylation conditions, into the O-acetyl derivative, 2; gc/ms, R_t: 14.4 min, ms: m/z 292 (M^+, $C_{17}H_{28}N_2O_2$, 40%), 263 (5), 251 (37), 249 (12), 233 (27), 231 (13), 195 (81), 156 (42), 150 (32), 136 (93), 135 (100), 134 (40), 122 (21), 110 (37), 98 (94), 97 (60), 96 (98), 82 (36), 55 (45) and 41 (64).

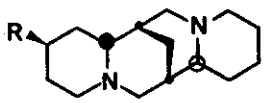
The mass spectrum of 1 exhibited a fragmentation pattern that was suggestive of a sparteine nucleus with ring A hydroxyl-substitution, but this mass spectrum was not comparable to any of

those previously reported for hydroxysparteines[5-7]. Since 1 was unaffected by treatment with sodium borohydride in methanol, the occurrence of the -OH group as part of a carbinolamine functionality could be ruled out. The identification of multiflorine (3) in another species of the genus Acosmium[8] suggested on biogenetic grounds that the position of -OH substitution in the sparteine nucleus of 1 might be at C-4. Thus, when an authentic sample of multiflorine (3)[9] was reduced with sodium borohydride in methanol, a product was quantitatively obtained that was identical to 1 by gc/ms and tlc.



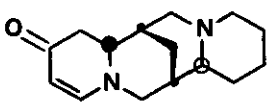
1 R = OH

2 R = OAc



4 R = OH

6 R = OAc



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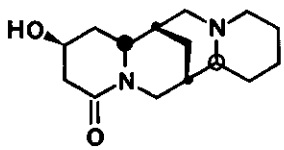

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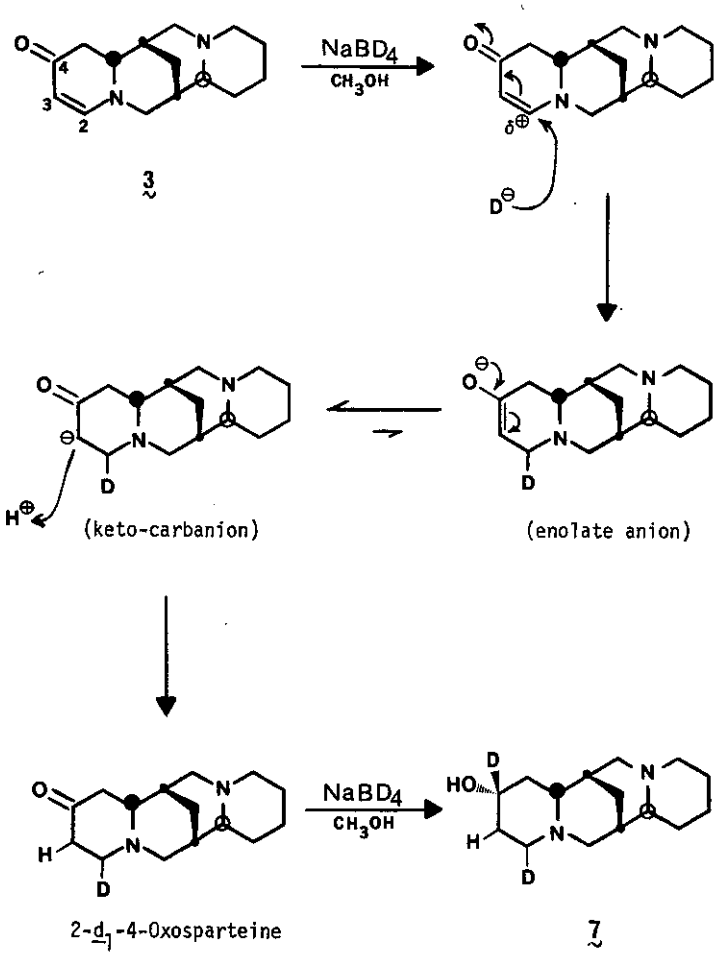
While the 4-OH group of 1 was assumed to be in the equatorial (α) position, since 4α-hydroxysparteine (1) is exclusively formed when multiflorine (3) is completely reduced with lithium aluminum hydride[10], it was decided to prove the stereochemistry of 1 by comparison with 4β-hydroxysparteine (4), obtained by reduction of nuttalline (5)[9] with sodium borohydride in methanol[11]. The product (4) was not readily distinguishable from its 4α-epimer (1) by gc/ms or tlc, but its O-acetate (6) was found to exhibit the following data by gc/ms; R_t: 13.9 min, ms: m/z 292 (M^+, not observed), 234 (9%), 233 (49), 156 (8), 150 (7), 148 (7), 136 (16), 135 (22), 134 (18), 122 (9), 110 (11), 98 (100), 97 (15), 96 (31), 82 (13), 55 (28), 43 (48) and 41 (55). Since 2 and 6 were clearly distinguishable on comparison of their mass spectra, the alkaloid obtained from A. panamense bark was assigned the structure (-)-4α-hydroxysparteine (1). Additional physical and spectral data have previously been reported for 1 when obtained by partial synthesis from multiflorine (3)[10].

The facile reduction of the vinylogous lactam function of multiflorine (3) with sodium boro-

hydride, which has not been previously reported, provided an opportunity to specifically deuteriate ring A of this compound. Reduction of multiflorine (3) with sodium borodeuteride quantitatively produced 2,4-d_2-4α-hydroxysparteine (7) via the probable mechanism indicated in Scheme 1. Gc/ms data for this compound were as follows: R_t: 12.3 min, ms: m/z 252 (M^+, $C_{15}H_{24}D_2N_2O$, 24%), 251 (16), 235 (M-OH, 4), 223 (3), 211 (19), 155 (100), 154 (51), 150 (17), 137 (22), 136 (55), 134 (16), 122 (13), 116 (61), 115 (39), 110 (28), 98 (55), 97 (42), 96 (11), 84 (16), 55 (22) and 41 (39). Comparison of the mass spectrum of this deuterium-labeled product with those of 1 and 2 afforded yet further proof that the hydroxyl group of 1 is located in ring A of the sparteine nucleus.



Scheme 1

Investigation of a diethyl ether-soluble fraction of the methanol extract of A. panamense bark by gc/ms and tlc led to the identification of additional lupine-type quinolizidine alkaloids: α-isosparteine (0.03% w/w); sparteine (0.006% w/w); 5,6-dehydro-α-isosparteine (0.003% w/w) and aphylline (0.02% w/w).

Acosmium Schott is the most primitive New World genus in the tribe Sophoreae of the legume subfamily Papilionoideae[12]. Since the only published reports of the occurrence of alkaloids in this genus refer to the identification of the Ormosia-type quinolizidine alkaloid (±)-6-epipodopetaline[2,13], the observation in A. panamense bark of 1 and the other lupine-type quinolizidine alkaloids mentioned above is of potential chemotaxonomic significance.

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3. Gc/ms was carried out in a glass column over 3% OV-17 on Gas Chrom Q (100-120 mesh), with helium flow rate 18 ml/min. The column was temperature programmed 180-310° at 4°/min.
4. Silica gel GHLF, precoated plates, 250 μm.
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