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TETRACYCLIC ALKALOIDS OF THE SPARTEINE GROUP. ^1H AND ^{13}C NMR SPECTROSCOPY AND CONFORMATIONAL ANALYSIS*

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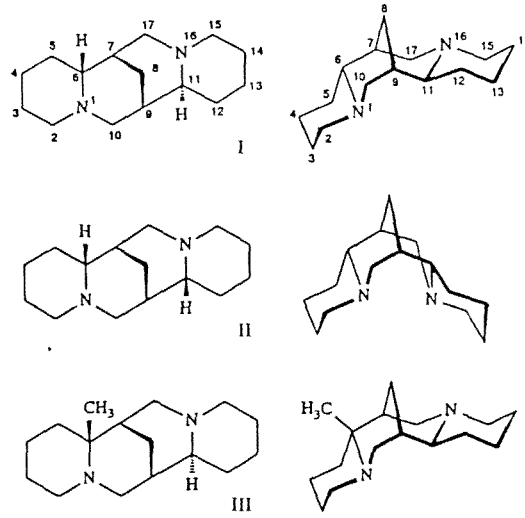
The ^1H and ^{13}C chemical shifts of 11 sparteine derivatives are reported. Substituent and group effects are interpreted in terms of structural properties. The conformational equilibrium of aphyllin is determined.

INTRODUCTION

The isolation, structure determination, chemical transformations, and spectroscopic identification of tetracyclic quinolizidine alkaloids of the sparteine group have been subjects of great interest [1-9]. Their biochemistry has been investigated [10-12]. In recent years NMR spectroscopy has contributed increasingly to a rapid advance in this area of alkaloid chemistry. Numerous ^1H and ^{13}C NMR results have been reported on structure elucidations and conformational analysis of natural lupine alkaloids and their derivatives [13-21]. This paper is devoted to NMR investigation of sparteine alkaloids (I-XI).

The ^{13}C NMR data of compounds V and VIII-X have been presented before [22-25]. The use of two-dimensional ^1H, ^1H and ^1H, ^{13}C NMR techniques (homo- and heteronuclear COSY) led to complete and unambiguous ^1H and ^{13}C NMR signal assignments [26-30].

Structures of I—XI



*Dedicated to Prof. N. S. Zefirov on the occasion of his 60th birthday.

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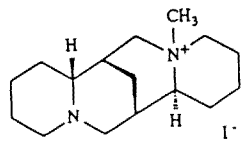

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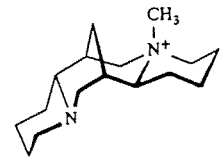

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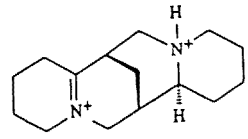

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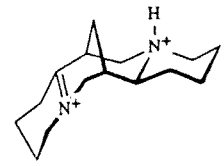

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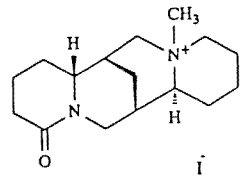

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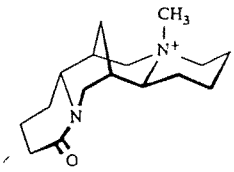

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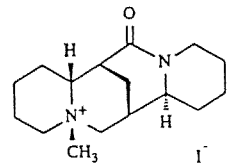

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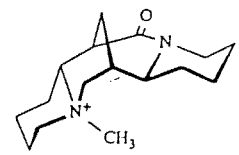

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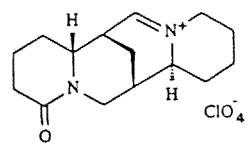

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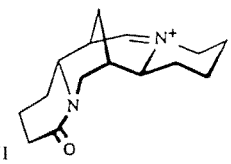

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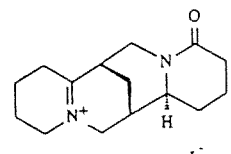

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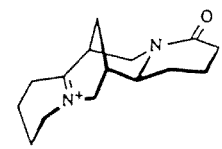

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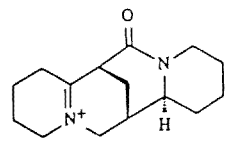

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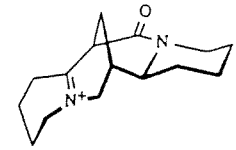

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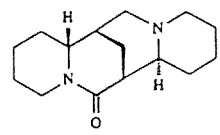

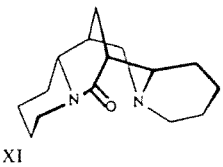

XI

TABLE 1. ^{13}C Chemical Shifts of Compounds I-XI[a]

C	I[b]	II[b]	III[b]	IV[c]	V[c]	VI[c]	VII[c]	VIII[c]	IX[c]	X[c]	XI[b]
2	56,0	57,2	49,6 -5,4	54,5 -1,5	53,5	171,2 +116,7	67,5	169,6	53,5	52,9	42,2
3	25,6	25,3	26,2 +0,6	24,9 -0,7	19,7	32,5 +7,6	21,9	32,3	20,0	19,8	25,0
4	24,5	24,9	20,3 -4,2	21,6 -2,9	16,1	19,1 -2,5	18,7	19,4	16,3	16,1	24,6
5	29,1	30,0	33,2 +4,1	28,4 -0,7	31,6	26,4 -2,0	24,0	27,1	31,7	32,1	28,8
6	66,3	66,3	55,4 -10,9	65,5 -0,8	186,9	61,1 -4,4	70,3	59,2	189,4	183,0	59,0
7	32,9	35,6	38,5 +5,6	30,5 -2,4	35,3	29,8 -0,7	32,9	37,6	33,7	46,2	32,4
8	27,4	36,4	20,6 -6,8	26,7 -0,7	16,5	25,9 -0,8	25,0	21,5	19,0	18,1	22,7
9	35,9	35,6	36,2 +0,3	32,4 -3,5	30,8	31,4 -1,0	40,8	31,9	32,7	30,8	43,8
10	61,8	55,8	55,7 -6,1	60,4 -1,4	58,6	46,3 -14,1	67,9	46,5	58,6	60,0	172,1
11	64,2	66,3	65,2 +1,0	71,4 +7,2	61,4	70,8 -0,6	59,8	66,5	54,7	62,0	58,7
12	34,5	30,0	34,4 -0,1	26,4 -8,1	22,1	26,3 -0,1	31,7	32,5	28,9	31,5	22,4
13	24,6	24,9	24,8 +0,2	23,6 -1,0	21,6	21,9 -1,7	24,2	22,2	18,1	24,4	25,4
14	25,8	25,3	25,9 +0,1	19,4 -6,4	17,4	19,4 0,0	24,5	26,0	32,3	24,6	18,8
15	55,2	57,2	55,5 +0,3	68,1 +12,9	52,8	67,8 +0,3	41,5	60,6	169,4	43,4	53,9
17	53,4	55,8	54,1 +0,7	63,8 +10,4	45,2	62,9 -0,9	166,3	177,9	42,4	160,8	46,6
CH_3	—	—	10,9	45,5	—	45,6	40,7	—	—	—	—

[a]In ppm; signals are referenced to the central peak of $CDCl_3$ (δ = 77.0) and DMSO-d_6 (δ = 39.5), respectively. Italicized values are substituent effects: III vs. I and IV vs. I, respectively: methyl SCS; VI vs. IV: effects of carbonyl oxygen introduction.
[b]In $CDCl_3$.
[c]In DMSO-d_6.

EXPERIMENTAL

NMR Spectroscopy

All compounds were recorded at 400.1 MHz (^1H) and 100.6 MHz (^{13}C) using a Bruker AM-400 spectrometer with an ASPECT 3000 computer and a $^1H/^{13}C$ dual probe head. Solutions were 0.3-0.5 molar in $CDCl_3$ or DMSO-d_6. The parameters for the homo- and heteronuclear COSY spectra were identical with those in [28].

Isolation and Synthesis

The free base sparteine (I) was obtained from commercially available sparteine sulfate. α-Isosparteine (II) was prepared using a literature procedure [31]. V(6)-Methylsparteine (III) was obtained based on the method described by Leonard [31]: I was dehydrogenated by mercuric acetate to obtain the appropriate Δ^5-dehydrobase which, by addition of perchloric acid, was then converted into the $\Delta^{1(6)}$-immonium salt (monoperchlorate). The salt was carefully dried over P_2O_5 under reduced pressure and submitted to the reaction with the Grignard reagent CH_3MgI. The reaction was carried out under nitrogen in dry ether by

TABLE 2. ^{1}H Chemical Shifts of Compounds I-XI[a]

H[b]	I[c]	II[c]	III[c]	IV[c]	V[d]	VI[d]	VII[d]	VIII[d]	IX[d]	X[d]	XI[c]
2[a]	1,79	1,72	2,24	2,05	3,75	—	3,43	—	3,67	3,65	2,22
2[e]	2,53	2,70	2,18	2,69	3,75	—	3,48	—	3,67	3,65	4,64
3[a]	1,38	1,63	1,43	1,45	2,07	2,22	1,49	2,17	1,95	1,85	1,28
3[e]	1,38	1,48	1,43	1,52	1,90	2,45	1,74	2,17	1,80	1,85	1,50
4[a]	1,08	1,23	1,43	1,56	1,87*	1,56	1,65	1,57	1,80*	1,74	1,27
4[e]	1,55	1,71	1,43	1,69	1,73*	1,72	1,97	1,57	1,70*	1,55	1,72
5[a]	1,24	1,59	1,54	1,30	3,10	1,72*	1,90	2,10*	2,66	2,88	1,42
5[e]	1,12	1,24	0,83	1,19	2,88	1,42*	1,78	1,63*	2,94	2,88	1,42
6	1,58	1,89	—	1,89	—	3,40	3,66	3,67	—	—	3,11
7	1,69	1,45	1,53	2,10	3,29	2,33	2,59	3,23	3,15	3,54	1,82
8[f]	0,90	1,52	1,43	1,35	2,20	1,57	1,93	1,77	1,67	1,98	1,49
8'	1,91	1,52	1,73	2,30	1,90	2,33	2,08	1,98	1,46	2,21	1,78
9	1,32	1,45	1,28	1,76	2,57	1,90	2,26	2,09	2,29	2,42	21,9
10[a]	1,84	1,99	2,40	2,02	4,13	2,53	3,60	2,70	3,76	3,97	—
10[e]	2,38	2,90	2,02	2,57	3,82	4,25	3,68	4,59	3,58	3,81	—
11	1,83	1,89	1,73	3,31	3,71	2,53	3,46	3,74	3,22	3,43	2,92
12[a]	1,35	1,59	1,38	1,90	1,68	1,79	1,60	1,72*	1,95*	1,61	1,71
12[e]	1,21	1,24	1,22	1,74	2,18	1,79	1,60	1,95*	1,67*	1,61	1,01
13[a]	1,15	1,23	1,19	1,17	1,60	1,40	1,54	1,74	1,75	1,51	1,35
13[e]	1,55	1,71	1,61	1,67	1,78	1,72	1,80	1,74	1,64	1,80	1,72
14[a]	1,43	1,63	1,45	1,92	1,75	1,88	1,24	1,72	2,23	1,23	1,46
14[e]	1,43	1,48	1,45	1,68	1,75	1,70	1,60	1,90	2,23	1,58	0,98
15[a]	1,86	1,72	1,90	3,24	3,29	3,40	2,41	3,87	—	2,44	2,62
15[e]	2,63	2,70	2,71	3,54	3,29	3,48	4,44	4,14	—	4,36	2,58
17[a]	2,20	1,99	2,42	3,16	3,49	3,08	?	8,92	4,49	—	2,39
17[e]	2,54	2,90	2,55	3,65	4,01	3,71	?	8,92	2,88	—	2,93
CH_3	—	—	0,85	3,12	—	3,13	2,86	—	—	—	—
NH	—	—	—	—	9,20	—	—	—	—	—	—

[a]In ppm; signals are referenced to $CHCl_3$ (δ = 7.24) and DMSO-d_6 (δ = 2.49), respectively.

[b]Letters "a" and "e" denote the stereochemical position of the respective hydrogen: "a" for axial or quasi-axial or boat-axial and "e" for equatorial or quasi-equatorial or boat-equatorial (cf. Scheme 1).

[c]In $CDCl_3$.

[d]In DMSO-d_6.

[e]Values marked by "*", "+" or "&" may be interchanged pairwise; "?": not identified.

[f]H-8 is directed towards N-1 and H-8' to N-16.

stirring and refluxing for several hours. The course of the reaction was monitored by TLC. The reaction mixture was worked up according to reference [31], and the product was isolated and purified by high vacuum distillation at ca. 0.133 Pa (10^{-3} torr).

Sparteine methiodide (IV) was obtained by reaction of sparteine with an excess of methyl iodide [32]. Δ^5-Dehydrosparteinium diperchlorate (V) was obtained by mercuric acetate dehydrogenation of sparteine to Δ^5-dehydrosparteine and protonation of the latter with a methanolic solution of perchloric acid at pH = 2.0 [26]. 2-Oxosparteine methiodide (VI) was obtained by reaction of 2-oxosparteine with an excess of methyl iodide [33, 34]. Lupanine (2-oxosparteine) was isolated from *Lupinus angustifolius* seeds [35]. 17-Oxosparteine methiodide (VII) was obtained by reaction of 17-oxosparteine with methyl iodide. 17-Oxosparteine was formed by oxidation of sparteine with potassium ferricyanide [36, 37]. $\Delta^{11(16)}$-Dehydrolupaninum perchlorate monohydrate (VIII) was obtained by mercuric acetate dehydrogenation of lupanine to $\Delta^{11(16)}$-dehydrolupanine and addition of perchloric acid [38].

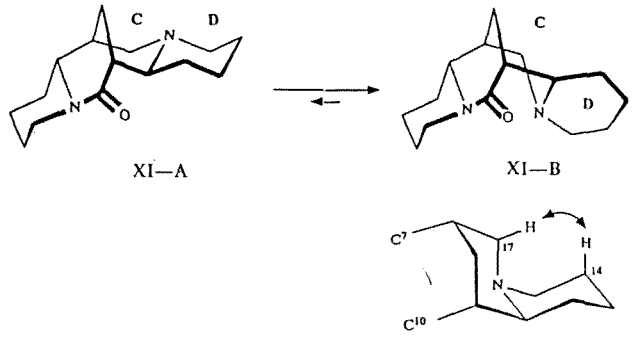

Fig. 1. Conformational equilibrium of aphyllin XI.

$\Delta^{1(6)}$-Dehydro-15-oxosparteine monohydrate IX was obtained by dehydrogenation of 15-oxosparteine with mercuric acetate complexed with EDTA [39]. $\Delta^{1(6)}$-Dehydro-17-oxosparteine monohydrate (X) was obtained by mercuric acetate dehydrogenation of 17-oxosparteine to Δ^5-dehydro-17-oxosparteine followed by perchloric acid addition [40]. 10-Oxosparteine (aphylline, XI) was a natural product extracted from the plant *Anabasis aphylla* [41].

RESULTS

All signals were assigned using standard one- (DEPT) and two-dimensional correlation techniques (HH COSY and HC COSY) as well as ^1H, ^1H NOE-difference techniques [42, 43]. In addition, inspection of ^1H signal splittings in terms of the presence or absence of large *vicinal* three-bond couplings in *antiperiplanar* hydrogen–hydrogen orientations and the identification of cross-peaks in the HH COSY spectra were very useful for stereochemical assignments of proton signals since they indicate four-bond W-couplings. Sometimes an unequivocal stereochemical assignment of diasterotopic protons within a given methylene group was not possible so that analogy arguments by comparison with other derivatives had to be accepted. In no case, however, leads this to an uncertainty in the conformational discussion.

The ^1H and ^{13}C NMR spectra of sparteine I have been published by Golembiewski et al. [27] and by Bohlmann et al. [13], respectively. Some corrections were made later by Shaka and Freemen [22] which were confirmed by our data. It is interesting to note that the ^1H chemical shifts of I in C_6D_6 are generally smaller than in $CDCl_3$, and that even their sequences are not identical. The ^{13}C NMR spectrum of α-isosparteine II has been published by Bohlmann et al. [13]; the assignment of C-2 and C-10 is revised in the present paper.

DISCUSSION

Substituent Effects on ^1H and ^{13}C Chemical Shifts

Golembiewski [27] has already discussed enhanced ^1H chemical shift differences [$\Delta\delta = \delta(H^{ax}) - \delta(H^{eq}) < 0$] of *geminal* protons in α position to a nitrogen (CH_2-N), as compared to cyclohexanes. In addition, he reported reversed sequences ($\Delta\delta > 0$) when the axial hydrogen is in *syn-diaxial* position with respect to a nitrogen lone pair [27]. Consequently, these positive $\Delta\delta$-values turn back to negative when going from the tertiary amines I–III to the ammonium ion V. For example, a comparison of the H-12-$\Delta\delta$-values affords +0.14 in I, +0.35 in II, +0.16 in III but −0.50 in V. However, the presence of an additional methyl group at the nitrogen atom in IV (CH_3-N-16) causes again a sign reversal of $\Delta\delta = \delta(H^{ax}-12) - \delta(H^{eq}-12) = +0.16$. This corresponds to the well-known effect that hydrogens being in *δ-syn-diaxial* position with respect to an alkyl group are deshielded whereas their *geminal* counterparts are shielded, an effect which is observed for the methyl group at C-6 in III as well: H-2a, H-4a, H-8, and H-10a are deshielded rather uniformly by 0.35-0.56 ppm. The shieldings of equatorial hydrogens are apparently influenced, i.e., enhanced by the presence of an α-nitrogen: H-2e; −0.35 ppm and H-10e; −0.36 ppm, compared to H-4e; −0.12 ppm and H-8′; −0.18 ppm.

A subtraction of ^{13}C chemical shifts of 1 from those of II gives substituent effects of the methyl groups at C-6 (Table 1). The α effect (−10.9) is extremely low, even when it is compared with other highly congested molecules with quaternary α carbons [26-30]. The γ-*gauche* effects (γSCS) are in the expected range. Interestingly, there is a fair correlation between MM2-calculated interatomic distances d between the methyl carbon and the respective *syn-diaxial* hydrogen: d(C−16, H−8^{ax}) = 2.67 Å, γSCS(C−8) = −6.8; d(C−16,H−2^{ax}) = 2.75 Å, γSCS(C−2) = −5.4; d(C−16, H−10^{ax}) = 2.77 Å, γSCS(C−10) = −6.1; d(C−16, H−4^{ax}) = 2.86 Å, γSCS(C−4) = −4.2. In agreement with Grant and Cheney's steric constraint concept [44-47], the γ-*gauche* effects increase in their absolute values with decreasing interatomic distance.

^{13}C substituent effects of a methyl group attached to N-16 can be obtained when the data sets of IV and I are subtracted. Here, however, it has to be taken into account that, in addition to methyl substitution the molecule is converted from a tertiary amine to an ammonium salt. Moreover, the two data sets have been obtained in different solvents. Nevertheless, it can be stated that the two γ-*gauche* effects on C-7 and C-9 are rather small (−2.4 and −3.5, respectively) which is apparently due to the boat-conformation of that ring and the fact that the hydrogen atoms attached to C-7 and C-9 are directed away from the perturbing methyl group. On the other hand, γ-*gauche* effects within the ring with chair-conformation (−8.1 at C-12 and −6.4 at C-14) meet the expectation. It is noteworthy that the δ-effect on C-8 is negligible although, due to the considerable steric interference between the atoms involved, a stronger positive effect should occur [45, 48, 49].

Conformational Analysis of Aphylline (XI)

Apparently, NMR data of 10-oxo-derivatives in the sparteine group have not yet been published. However, on the basis of the present data it is possible to estimate the effects of the introduction of a doubly bonded oxygen on neighboring protons and carbons by comparing the chemical shifts of the two ammonium salts IV and VI, both measured in DMSO-d_6. Noticeable effects on sp^3 carbons larger than 2.5 ppm are observed only for C-3, C-6, and C-10 which are directly attached to the amide group (Table 1). Taking this into account and comparing the ^{13}C shieldings of XI and I one can see strong additional shielding effects on C-8, C-12, C-14, and C-17 which are associated to conformational conversion of the ring C and D from *trans*-boat-chair in XI-A, as present in I, to *cis*-chair-chair (XI-B, Fig. 1). Conformation XI-B is further confirmed by the observation of mutual NOE-induced signal intensity enhancements of H-14a and H-17a (double arrow in Fig. 1).

Apparently, the absence of an *endo*-oriented lone-pair at N-1 in XI allows N-16 to invert thereby avoiding the unfavorable boat conformation of ring C.

Acknowledgements

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