(−)-STREMPELIOPINE. STEREOSELECTIVE TOTAL SYNTHESIS AND THE DETERMINATION OF ABSOLUTE CONFIGURATION*,**

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Dedicated to Prof. J. Tomko on the occasion of his 65th birthday.

A synthesis of (±)-strempeliopine (*II*) is described, the key step of which is the stereoselective reductive rearrangement of 18-methylene-1,2-dehydroaspidospermidine (*XI*). The absolute configuration of the natural (−)-base *II* was determined as (2*S*, 7*R*, 20*R*, 21*R*) on the basis of its synthesis from (+)-18-methylenevincadifformine (*XVII*) the configuration of which was derived from a comparison of circular dichroism properties of bases with a β-anilinoacrylate chromophore. The biogenesis of the alkaloids of the schizozygane type is discussed.

Among the alkaloids of aspidospermane type hexacyclic schizozygane alkaloids isolated almost exclusively from the plant *Schyzozygia caffaeoides* (BOJ.) BAILL.[1,2] are classified from the point of view of their biogenesis. They generally represent bases substituted on the aromatic nucleus; the main alkaloid of this plant, schizozygine[3] (*I*), is characteristic in an exceptional structural feature in the region of the indole bases, *i.e.* 10,11-methylenedioxy group. Several years ago the fundamental base of this group was also isolated[4] from the Cuban species *Strempeliopsis strempelioides* K. SCHUM. (*Apocynaceae*), *i.e.* (−)-strempeliopine (*II*). Biogenetic relationships permit the classification into this group of the bases of vallesamidine type which can be considered seco-schizozygane alkaloids. Their representatives are (−)-vallesamidine[5] (*III*), the structure of which was elucidated by X-ray analysis[6], and (−)-andrangine[7] (*IV*) the structure and absolute configuration of which was derived from the correlation with base *III*.

In 1971 studies were published concerning reductive rearrangements of indolenines[8,9] under the effect of zinc in hot acetic acid in the presence of cupric sulfate; in the case of 1,2-dehydroaspidospermidine (*V*) this route[10] gives 1-demethylvallesamidine (*VI*) in addition to unrearranged aspidospermidine (*VII*). It seemed that a suitable substitution of the ethyl group in the starting indolenine which would be capable of

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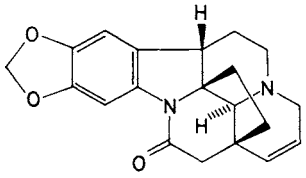
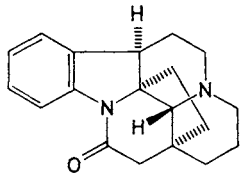
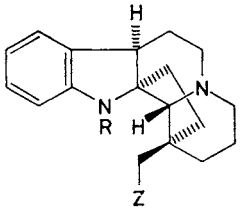
a conversion leading to the closure of the lactam cycle would be a convenient synthetic route to the schizozygane skeleton. In this communication we describe a total synthesis of the racemic form of base *II*, the preparation of natural (−)-strempeliopine (*II*) and the determination of its absolute configuration.



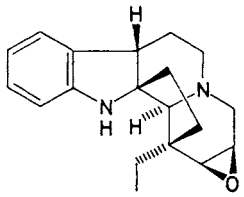
I



II



III, R = Z = CH_3
XII, R = H ; Z = $CH{=}CH_2$
XIII, R = CHO ; Z = $CH{=}CH_2$
XIV, R = Z = CHO
XV, R = CHO ; Z = COOH



IV

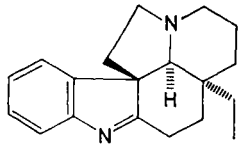
As model experiments we carried out the reductive rearrangement of (±)-1,2-dehydroaspidospermidine[11] (*V*) with zinc in acetic acid at 100–110°C in the presence of cupric sulfate pentahydrate[10]. It was observed (Table I) that the distribution of the products is entirely dependent on the zinc used*.

In experiment A predominantly the products of reduction and subsequent acetylation were obtained: (±)-aspidospermidine (*VII*), (±)-quebrachamine (*VIII*), and (±)-1-acetylaspidospermidine (*IX*).

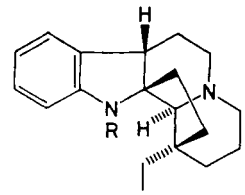
Reference samples were prepared from the same indolenine *V*, in the case of base *VIII* by reduction with sodium cyanoborohydride in acetic acid, in the case of base *VII* by reduction with lithium aluminum hydride in ether, from which N-acyl-derivative *IX* was obtained by acetylation under the conditions of Schotten–Baumann

* In both cases the origin of the zinc was unknown. No differences were found either in their morphology (oval to spherical particles) or other properties compared (trace elements *etc.*), except for the particle size. In zinc A the size of the majority of the particles was up to 5–7 μm, in the case of zinc B up to 17 μm.

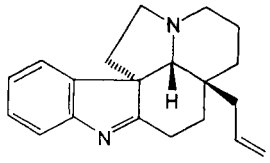
reaction. In contrast to this, in experiment B 1-demethylvallesamidine (*VI*) was obtained as the main product, the spectral characteristics of which were in agreement with literature[10] and which was further characterized as (±)-1-formyl-1-demethyl-



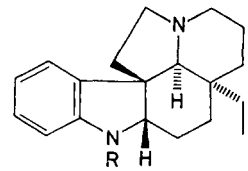
V



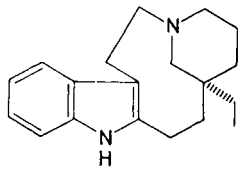
VI, R = H
X, R = CHO



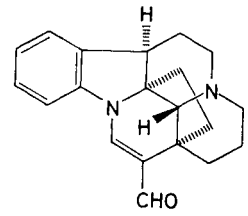
XI



VII, R = H
IX, R = $COCH_3$



VIII



XVI

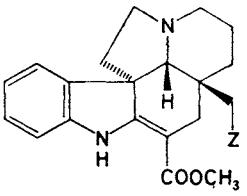
TABLE I

Yields of the products of the rearrangement of (±)-1,2-dehydroaspidospermidine (*V*)

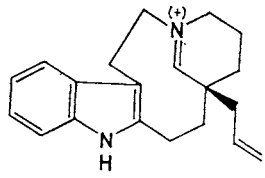
Experiment	*VI*	*VII*	*VIII*	*IX*
A	3	2	4	44
B	36	2	2	7

vallesamidine (*X*), formed from base *VI* by formylation with a mixture of formic acid and acetic anhydride. In view of the very close R_F values of bases *VI* and *VIII* it was convenient to separate first this mixture of indole and indolenine, submit it to formylation (which in this case is chemospecific) and finally to separate compounds *VIII* and *X* chromatographically, because their R_F values differ distinctly.

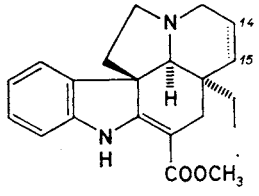
The rearrangement of (±)-18-methylene-1,2-dehydroaspidospermidine[11] (*XI*) was carried out under the conditions of experiment B and after formylation it afforded (±)-1-demethyl-1-formyl-18-methylenevallesamidine (*XIII*) in about 40% yield. In order to rebuild the allylic chain to a substance suitable for the closure of ring F, we first considered the amino aldehyde *XIV* as an intermediate, which we prepared by cleavage according to Lemieux and Johnson in about 50% yield. Its structure is confirmed mainly by the one-proton triplet in its ^{1}H NMR spectrum at δ 9·79 ppm (J = 2·5 Hz) which indicates the presence of the CH_2—CHO group. However, we found that this route is not feasible because the oxidation of compound *XIV* to acid *XV* would be complicated by side reactions. Thus, for example, on oxidation with monovalent silver in alkaline medium a non-acidic product was obtained in low yield to which we assigned the structure of vinylindoline *XVI*. This structure is supported both by UV spectrometry (λ_{max} 351 nm (log ε 3·98); β-anilinoacrylaldehyde chromophore) and by an analysis of its mass spectrum (*m/z* 306: M^+; $C_{20}H_{22}N_2O$) and ^{1}H NMR spectra (instead of the signal of the proton on $C_{(19)}$ the presence of singlets of the formyl and olefinic proton at δ 9·21 and 7·35 ppm, respectively).



XVII, Z = CH=CH$_2$
XIX, Z = C_2H_5



XVIII



XX
XXI, *14,15* - double bond

We focused our attention on conversions in which the aldehyde is not set free and the work is done in acid medium in order to block the atom $N_{(4)}$ against oxidation. Ozonization of formylindoline *XIII* in a mixture of methanol and hydrochloric acid at about 15°C and subsequent treatment with hydrogen peroxide afforded (±)-strempeliopine (*II*) directly, with m.p. 132–136°C, which was found to be identical, except its optical rotation with the natural (−)-strempeliopine. The base displays a mass fragmentation corresponding to schizozygane bases[12], namely the fragments *m/z* 266 and 265, as well as the ions at *m/z* 251 and 249. The 200 MHz ^{1}H NMR spectrum which is identical with the spectrum of natural alkaloid is also important.

The absolute configuration of (−)-strempeliopine (*II*) was determined on the basis of its synthesis from (+)-18-methylenevincadifformine (*XVII*) refs[13,14]; this synthesis is stereoselective. During the reductive rearrangement the absolute configuration on atom $C_{(20)}$ is preserved (see the intermediary structure *XVIII*). In addition to this it was necessary to determine the absolute configuration of base *XVII*. For its deduction the comparison of chiroptical properties of this base and its dihydroanalogue[13] *XIX* with those of compounds with the same β-anilinoacrylate chromophore of known absolute configuration was made use of, *i.e.* (−)-(7*R*,20*S*,21*S*)-vincadifformine (*XX*) and (−)-(7*R*,20*R*,21*S*)-tabersonine (*XXI*).

From Table II it follows that the (+)-enantiomer has the absolute configuration shown in formula *XVII*, *i.e.* (7*S*,20*S*,21*R*). This assignment of absolute configuration is supported by the comparison of the CD spectra of corresponding indolenines, namely (+)-*XI* and (−)-(7*R*,20*S*,21*S*)-*V* (ref.[15]), prepared in the above mentioned manner from bases (+)-*XVII* and (−)-*XX*.

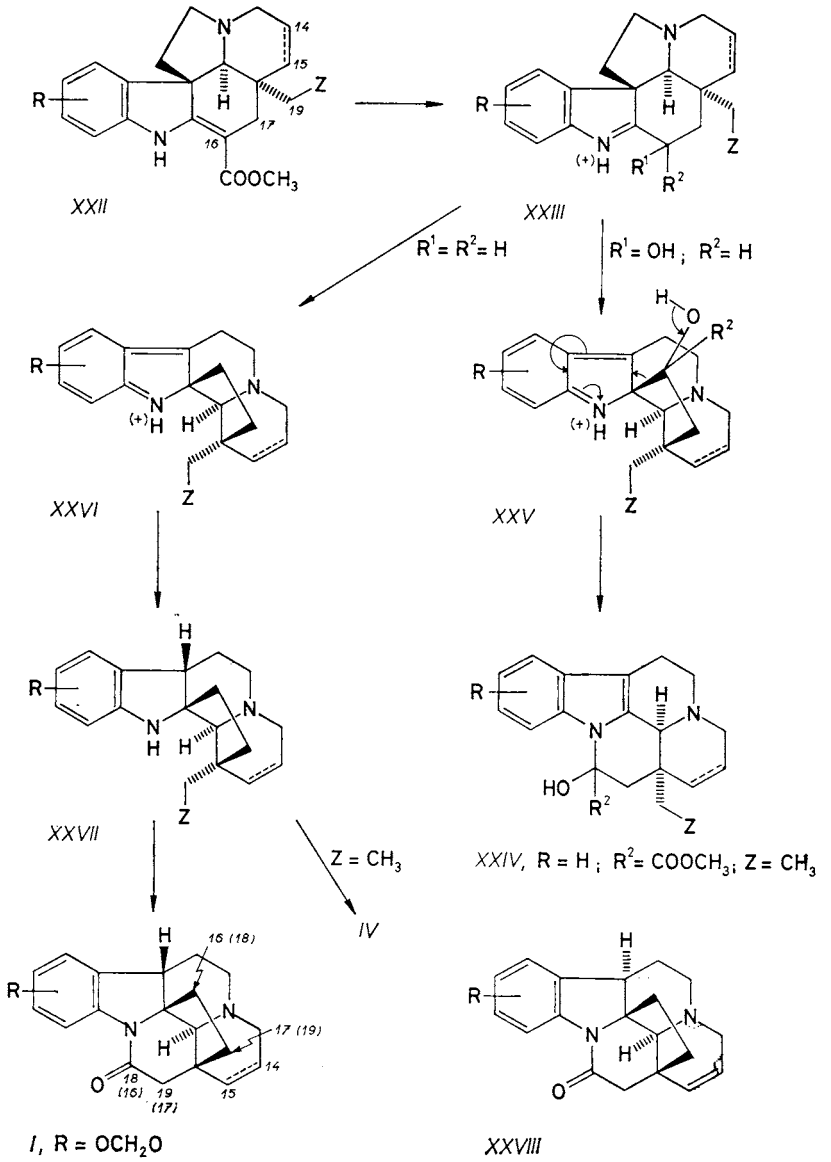
With the knowledge of absolute configuration of the starting bases we approached the synthesis and thus the simultaneous determination of the absolute configuration of the natural (−)-strempeliopine (*II*). The starting (+)-(7*S*,20*R*,21*R*)-18-methylene-1,2-dehydroaspidospermidine (*XI*) was reductively rearranged and formylated under

TABLE II

CD spectra of bases with β-anilinoacrylate or indolenine chromophore (in methanol)

Compound	λ_{max}, nm (Δε)		
(+)-*XVII*	324·5 (+31·3)	285·0 (−4·3)	236·0 (−17·5)
(+)-*XIX*	325·0 (+32·3)	285·0 (−2·4)	237·0 (−16·6)
(−)-*XX*	324·0 (−35·7)	286·0 (+3·2)	237·0 (+17·2)
(−)-*XXI*	324·5 (−24·7)	288·0 (+6·1)	238·5 (+18·2)
(+)-*XI*	270·5 (+20·1)	—	—
(−)-*V*	269·0 (−22·5)	—	—

formation of (−)-(2*S*,7*R*,20*R*,21*R*)-base *XIII* which was ozonized and eventually converted to (−)-(2*S*,7*R*,20*R*,21*R*)-strempeliopine (*II*), $[\alpha]_{578}$ −25·4° (*c* 2, methanol). Since the starting base is optically pure[14] and during the reaction racemization could hardly have taken place the published data[4] concerning specific rotation, $[\alpha]_D$ −120° (methanol), may be considered with certainty as erroneous.



SCHEME 1

Only limited attention has so far been devoted to the mutual biogenetical relationship of the alkaloidal types within the class of aspidospermanoids. The proposed mechanism of biogenesis of eburnane bases[16] was rationalized by *in vivo* experiments[17]. The biogenesis of vallesamidine (*III*) also seems well elucidated[18] (for an improbable proposal of a precursor of schizozygane bases see ref.[2]). We believe that the biosynthesis of schizozygane bases is a parallel of the genesis of eburnane bases. This led us to the formulation of a common mechanism of biogenesis of both types of bases (Scheme 1)[19]. The precursors of both types of alkaloids are the bases of the aspidospermane type *XXII*, while the type of the generated alkaloids is already decided in the starting step (*XXII* → *XXIII*): the $C_{(16)}$-demethoxycarbonylation leads to the formation of a schizozygane base, while the $C_{(16)}$-hydroxylation represents the introductory step of the formation[16] of the eburnane alkaloid vincamine (*XXIV*). In the case where $R^1 = R^2 = H$, a fragmentation analogous to that in the intermediate *XXV* is prevented and the related intermediate *XXVI* then affords indoline *XXVII* on reduction* (ref.[13]). In the terminal phases this is transformed in dependence on the substituent Z to the alkaloids of the vallesamidine and schizozygane type. From these mechanistic views it follows that the alkaloids of the schizozygane type *I*, with a substitution in ring F similar to vincamine (*XXIV*) should not exist in nature. The numbering of the schizozygane skeleton, mentioned in the nomenclature proposal[21] (the numbers in formula *I* in brackets) also logically requires a correction in this sense.

EXPERIMENTAL

The melting points (Boetius microblock) are not corrected. The analytical samples were dried at room temperature and 1·4 Pa pressure for 6 h. The purity of the substances was checked by thin-layer chromatography on commercial silica gel GF_{254} plates or alumina plates (Merck, G.F.R.) in corresponding solvent systems, or by gas chromatography on a CHROM IV instrument (Labora, Czechoslovakia). The ultraviolet spectra were measured in methanolic solution on a SPECORD UVIS (Zeiss, Jena, G.D.R.) spectrophotometer and they are expressed in wavelengths of the absorption maxima λ(nm) and in corresponding log ε values. The infrared spectra were measured in chloroform on a UR-10 (Zeiss, Jena, G.D.R.) spectrophotometer. The ^{1}H NMR spectra were measured in deuteriochloroform on a BS 487 (80 MHz, Tesla, Czechoslovakia) or XL 200 (200 MHz, Varian, U.S.A.) instrument; the chemical shifts are in ppm (δ-scale), tetramethylsilane was used as internal reference. The mass spectra were taken with MAT 44S (Varian, U.S.A.) and MCH-1 320 (U.S.S.R.) instruments. The optical rotations were measured on a POLAMAT-A polarimeter at 578 nm, at 24—26°C.

* Originally the minor $C_{(7)}$-epimeric bases *XXVIII* were also described in addition to the schizozygane bases with a configuration given in formula *I* for which we have proposed the absolute configuration shown on the basis of speculative consideration[13]. Careful analysis[20] of the ^{13}C NMR spectra indicates, however, a different skeleton in the former bases.

Rearrangement of (±)-1,2-Dehydroaspidospermidine (*V*)

A) $CuSO_4 . 5 H_2O$ (0·03 g) and zinc (6·0 g) were added under nitrogen to a stirred solution of 0·42 g (1·50 mmol) of (±)-1,2-dehydroaspidospermidine[11] (*V*) in acetic acid (60 ml) and the mixture was heated to 105°C over 30 min and then kept at this temperature for 6 h, when TLC indicated the disappearance of the starting compound; during the heating, after 3 h reaction time, a further amount of zinc (3·0 g) and $CuSO_4 . 5 H_2O$ (0·02 g) was added. The mixture was filtered while hot and the remaining zinc was washed with hot acetic acid (20 ml). The combined filtrates were concentrated in a vacuum and the residue partitioned between ether (75 and 25 ml) and 7% aqueous ammonia (50 ml). The combined organic phases were washed with water (25 ml) and brine (25 ml), dried over Na_2SO_4 and evaporated. The residue was chromatographed on alumina (22 g). Elution with a light petroleum–benzene mixture (3—1 : 1) afforded a glassy product, 0·017 g (4·0%), identical with (±)-quebrachamine (*VIII*). Further elution with the light petroleum–benzene mixture (1 : 4—8) afforded 0·013 g (3·1%) of a glassy product which was identified as (±)-1-demethylvallesamidine (*VI*). Ultraviolet spectrum: 298 (3·39), 246 (3·86). Infrared spectrum: 3 405, 2 805, 2 755, 1 601, 1 470, 1 455 cm^{-1}. ^1H NMR spectrum: 7·1—6·45 (4 H, m; arom. **H**), 3·93 (1 H, bs; indoline =N**H**), 3·18 (1 H, bt, J = 3·5 Hz; $C_{(7)}\mathbf{H}—CH_2$), 0·88 (3 H, t, J = 7·0 Hz; $—CH_2—CH_3$). Mass spectrum, *m/z* (%): 283 (18; $[M + 1]^+$), 282 (100; M^+, $C_{19}H_{26}N_2$), 281 (24), 255 (7), 254 (65, $C_{17}H_{22}N_2$), 253 (27), 239 (19), 226 (8), 225 (25), 199 (10), 198 (14), 197 (12), 190 (16), 163 (33), 130 (66, C_9H_8N), 124 (56, $C_8H_{14}N$).

Elution with benzene–chloroform (5—1 : 1—10) afforded a mixture of two substances (0·224) the ratio of which was determined by GC analysis. The less polar substance was identified as (±)-aspidospermidine (*VII*; 2% per starting *V*), the major component was the N-acetyl derivative *IX* (44%). Treating this mixture with acetyl chloride led to the disappearance of the minor component.

B) Procedure *A* was applied, with the difference that another type of zinc was used (see the remark on p. 1732). From 1·5 mmol of (±)-*V* 2% of (±)-*VIII*, 36% of (±)-*VI*, 2% of (±)-*VII*, and 7% of (±)-*IX* were obtained.

(±)-1-Formyl-1-demethylvallesamidine (*X*)

A) Acetic anhydride (0·5 ml) was added dropwise to a stirred solution of 0·080 g (0·28 mmol) of (±)-*VI* in formic acid (1·5 ml) and the mixture was allowed to stand overnight. The residue was partitioned between ether and 3% aqueous ammonia. The organic phase was washed with water and brine, dried and evaporated in a vacuum. The residue was crystallized from a benzene–hexane mixture, yield 0·078 g (89%), m.p. 138—139·7°C. Literature[10] gives m.p. 127—128°C for an optically pure compound. For $C_{20}H_{26}N_2O$ (310·4) calculated: 77·38% C, 8·44% H, 9·03% N; found: 77·67% C, 8·40% H, 9·09% N. Ultraviolet spectrum: 288 (3·50), 281 (3·56), 253 (4·01). Infrared spectrum: 2 798, 2 755, 1 638, 1 580, 1 470, 1 455, 1 372 cm^{-1}. ^1H NMR spectrum (200 MHz): 8·66 (1 H, s; =N—C**H**=O), 7·99 (1 H, bd, $J_{11,12}$ = 8·0 Hz; arom. $C_{(12)}\mathbf{H}$), 7·27 to 7·05 (3 H, m; arom. **H**), 3·19 (1 H, dd, $J_{7,6}$ = 8·5 Hz, $J_{7,6'}$ = 5·0 Hz; $C_{(7)}\mathbf{H}—C_{(6)}H_2—$), 2·13 (1 H, s; $C_{(21)}\mathbf{H}$), 0·87 (3 H, t, J = 7·5 Hz; $—CH_2—CH_3$). Mass spectrum, *m/z* (%): 311 (16; $[M + 1]^+$), 310 (62; M^+), 309 (15), 283 (19), 282 (100), 281 (34), 267 (22), 255 (14), 254 (95), 253 (29), 239 (31), 190 (47), 163 (59), 134 (70), 130 (65).

B) The rearrangement of 0·70 g (2·5 mmol) of (±)-*V* was carried out according to procedure *B* from the preceding section. The crude product was applied on a column of alumina (10 g) and eluted with a light petroleum–benzene mixture (1—0 : 1), affording after evaporation of the solvent 0·29 g of an oil which was dissolved in formic acid (3 ml). The solution was stirred and additioned with acetic anhydride (1 ml). After 6 h standing at room temperature the mixture

was evaporated in a vacuum and worked up. Chromatography on alumina (4 g) gave first (±)-*VIII* (0·014 g) (elution with light petroleum–benzene 5—3 : 1) and then 0·27 g of crystals (elution with benzene) which were recrystallized from benzene–hexane. Yield, 0·24 g (31%), m.p. 138·5—140°C, identical with the product obtained under *A*.

(±)-Quebrachamine (*VIII*)

Sodium cyanoborohydride (0·17 g; 2·7 mmol) was added in portions to a solution of 0·095 g (0·34 mmol) of (±)-*V* in acetic acid (3 ml) at 10°C under stirring. After 2 h stirring the mixture was evaporated in a vacuum. Water (10 ml), 5% ammonia (up to pH 10), and ether (20 ml) were added to the residue and the organic phase was separated, evaporated in a vacuum, dissolved in benzene, and filtered through a small column of alumina. The eluate was evaporated, affording a residue, homogeneous according to TLC. Yield, 0·066 g (69%), m.p. 109·5—111·5°C (light petroleum–acetone). Literature[22] gives m.p. 113—116°C. ^{1}H NMR spectrum: 7·88 (1 H, bs; indole =NH), 7·65—7·05 (4 H, m; arom. H), 3·31 (1 H, m), 0·87 (3 H, t, J = 7 Hz; —CH_2—CH_3). Mass spectrum, m/z: 282 (M^+, $C_{19}H_{26}N_2$).

(±)-Aspidospermidine (*VII*)

A solution of 0·21 g (0·75 mmol) of (±)-*V* (ref.[11]) in 15 ml of ether was added dropwise to a stirred suspension of 0·15 g of lithium aluminum hydride in ether (20 ml). After 30 min of stirring at room temperature and 15 min boiling the mixture was cooled and decomposed by dropwise addition of a saturated sodium chloride solution (0·7 ml). After 1 h stirring the solid phase was filtered off under suction and washed with ether (25 ml). The combined organic phases were extracted with 7% hydrochloric acid (15 and 10 ml). The aqueous extracts were alkalized with ammonia and extracted with ether. The ethereal solution was washed with brine and evaporated in a vacuum. The residue was dissolved in methylene chloride and filtered through a short column of silica gel. The evaporated eluates were crystallized from light petroleum, giving 0·165 g (78%) of platelets melting at 108—110°C. For (±)-*VII* literature[23] gives m.p. 99—103°C. ^{1}H NMR spectrum: 7·13—6·49 (4 H, m; arom. H), 3·46 (1 + 1 H, dd, J = 11 Hz, J = 6·5 Hz; —NH—$C_{(2)}$H—), 3·11—2·9 (2 H, m), 0·58 (3 H, def. t, J = 6·5 Hz; —CH_2—CH_3).

(±)-N-Acetylaspidospermine (*IX*)

Acetyl chloride (0·075 ml; 1 mmol) was added to a stirred two-phase mixture of 0·110 g (0·39 mmol) of (±)-*VII*, potassium carbonate (0·28 g; 2·0 mmol), dichloromethane (4 ml), and water (4 ml) at 15°C. After 30 min dichloromethane (15 ml) was added and the organic phase separated. After washing it with 5% ammonia solution, water and brine the organic phase was dried and evaporated in a vacuum. Yield, 0·127 g (about 100%) of a colourless glassy residue, homogeneous according to TLC. Literature[24] describes the acetanilide (±)-*IX* as a colourless resin. ^{1}H NMR spectrum: 8·12 (1 H, m; arom. $C_{(12)}$H), 7·35—6·9 (3 H, m; arom. H), 4·02 (1 H, dd, J = 11 Hz, J = 6 Hz; =N—$C_{(2)}$H—), 2·21 (3 H, s; =N—$COCH_3$), 0·60 (3 H, def. t, J = 6·5 Hz; —CH_2—CH_3). Mass spectrum, m/z: 324 (M^+, $C_{21}H_{28}N_2O$).

(±)-N-Formyl-N-demethyl-18-methylenevallesamidine (*XIII*)

Cupric sulfate pentahydrate (0·15 g) and zinc (25 g) were added to a stirred solution of 2·3 g (7·86 mmol) of (±)-18-methylene-1,2-dehydroaspidospermidine[11] (*XI*) in glacial acetic acid (250 ml) at 60°C and under nitrogen. The heterogeneous mixture was heated at 102°C and after another 2 h additional 3 g of zinc and 0·03 g of cupric sulfate pentahydrate were added. After

another 2 h heating at the same temperature the mixture was filtered while hot and the solid phase was washed with acetic acid (50 ml). The liquid phases were concentrated in a vacuum. The residue was partitioned between ether (200, 75 ml) and 5% ammonia (100 ml). The organic phases were washed with brine, dried and evaporated. The residue was put on a column of neutral alumina (80 g) and eluted with benzene–chloroform (100—10 : 0—1). The eluate was evaporated and the residue dissolved in formic acid (9 ml) and acetic anhydride (3 ml) was added at 10°C. After 9 h standing at room temperature the mixture was worked up and the crude product was chromatographed on a column of alumina (40 g). The benzene–chloroform eluates (20—5 : 1) were evaporated, affording a residue which was recrystallized from benzene–hexane. Yield, 0·85 g (34%), m.p. 136—137·5°C. For $C_{21}H_{26}N_2O$ (322·4) calculated: 78·22% C, 8·13% H, 8·69% N; found: 78·43% C, 8·05% H, 8·73% N. Ultraviolet spectrum, nm (log ε): 286 (3·53), 279 (3·58), 252 (4·00). Infrared spectrum: 3 010, 2 805, 2 760, 1 652, 1 596, 1 475, 1 463 cm^{-1}. ^1H NMR spectrum (200 MHz): 8·68 (1 H, s; =N—CH=O), 7·97 (1 H, bd, $J_{11,12} = 8·0$ Hz; arom. $C_{(12)}H$); 7·28—7·06 (3 H, m; arom. H), 5·76 (1 H, m; $J_{trans} = 17·0$ Hz, $J_{cis} = 10·0$ Hz, $J_{vic} = 7·0 + 7·0$ Hz; $-CH_2-CH=CH_2$), 5·15—5·06 (2 H, m; $-CH_2-CH=CH_2$), 3·23 (1 H, dd, $J_{7,6} = 7·0$ Hz, $J_{7,6'} = 5·0$ Hz; $-C_{(7)}H-CH_2-$), 2·16 (1 H, bs; $-C_{(21)}H$). Mass spectrum m/z (%): 323 (12, $[M + 1]^+$), 322 (41, M^+), 294 (36), 282 (26), 281 (100), 254 (19), 253 (81), 252 (27), 161 (17), 160 (21), 134 (87), 130 (50).

(+)-(7*S*,20*R*,21*R*)-18-Methylene-1,2-dehydroaspidospermidine (*XI*)

This was prepared from (+)-(7*S*,20*S*,21*R*)-18-methylenevincadifformine[13,14] (*XVII*) using a procedure described in refs[11,13], in 92% yield. The oil had [α] +319° (*c* 1·3, benzene). For the CD spectrum see Table II.

(−)-(2*S*,7*R*,20*R*,21*R*)-1-Formyl-1-demethyl-18-methylenevallesamidine (*XIII*)

This was obtained in 42% yield when the procedure for the racemic base was applied and (+)-*XI* used as starting material. The compound had [α] −27·1° (*c* 1·6; methanol) and m.p. 94—96°C (benzene–hexane).

(±)-1-Formyl-1-demethyl-18-oxovallesamidine (*XIV*)

A crystal of osmium tetroxide was added under nitrogen to a solution of 60 mg (0·19 mmol) of (±)-*XIII* in 80% aqueous acetic acid (30 ml), followed after 30 min (blackening) by the addition, over 20 min, of powdered sodium periodate (95 mg). After 24 h another portion (20 mg) of sodium periodate was added and the mixture was allowed to stand overnight. It was then evaporated in a vacuum and the residue partitioned between chloroform and 0·5M-Na_2CO_3. The chloroform phase was washed with water, dried and concentrated, and then filtered through a short column of silica gel. After evaporation of the eluates 30 mg (50%) of chromatographically pure glassy product were obtained. ^1H NMR spectrum: 9·79 (1 H, t, $J = 2·5$ Hz; $-CH_2-CH=O$), 8·69 (1 H, s; =N—CH=O), 7·40 — 7·05 (4 H, m; arom. H), 3·32 (1 H, m; $-C_{(7)}H-CH_2-$). Mass spectrum, m/z: 324 (M^+).

(±)-10-Formyl-18,19-didehydroschizozygane (*XVI*)

A solution of 27·0 mg (0·083 mmol) of *XIV* in ethanol (0·90 ml) was added dropwise under nitrogen to a stirred solution of silver nitrate (33·0 mg; 0·19 mmol) in water (0·12 ml) and then potassium hydroxide (24·8 mg; 0·44 mmol) solution was added under cooling with cold water.

After 30 min stirring water (3·0 ml) was added and the mixture concentrated to 2/3 of its volume, and then extracted with ether (20, 2 × 10 ml). The aqueous phase was neutralized and extracted with dichloromethane; TLC indicated that it is a complex mixture. The combined ethereal extracts were washed with water and brine, dried and evaporated. The residue (12 mg) was purified by preparative TLC on a 20 × 20 cm silica gel plate (Merck; 0·25 mm thickness); the plate was developed with a chloroform–ethanol mixture (33 : 1). Yield, 6·3 mg of an amorphous product (25%). Ultraviolet spectrum, nm (log ε): 351 (3·98), 298 (3·59), 244 (3·65). Infrared spectrum: 2 800, 1 650, 1 598, 1 570 cm^{-1}. ^1H NMR spectrum (200 MHz): 9·21 (1 H, s; =N—CH=C—CH=O), 7·35 (1 H, s; =N—CH=C(CHO)—), 7·27–7·14 (2 H, m; arom. $C_{(9)}H$ and $C_{(11)}H$), 6·99 (1 H, dt, $J_{10,9} = 7·4$ Hz, $J_{10,11} = 7·4$ Hz, $J_{10,12} = 1·1$ Hz; arom. $C_{(10)}H$), 6·89 (1 H, dt, $J_{12,11} = 7·8$ Hz, $J_{12,10} = 1·1$ Hz, $J_{12,9} = 1$ Hz; arom. $C_{(12)}H$), 3·36 (1 H, bd, $J_{7,6} = 6·6$ Hz, $J_{7,6'} \neq 0$, $J \neq 0$; $—C_{(7)}H—CH_2—$), 2·22 (1 H, bs; $—C_{(21)}H$). Mass spectrum, *m/z* (%): 306 (100, M^+, $C_{20}H_{22}N_2O$), 278 (61), 277 (73), 249 (46), 138 (33), 130 (25), 125 (31), 124 (38).

(±)-Strempeliopine (*II*)

Ozone was introduced into a stirred solution of 0·322 g (1·0 mmol) of (±)-*XIII* in a mixture of methanol (2·0 ml) and 1M-HCl (7·5 ml) at room temperature until the starting compound had disappeared (according to TLC after about 30 min). After addition of 30% aqueous hydrogen peroxide (0·20 ml) the mixture was allowed to stand at room temperature for 15 h and then concentrated to 2/3 of its volume. Water (5 ml) and ammonia were then added to the concentrated solution until its pH was 9·5. The dichloromethane extracts (25, 2 × 10 ml) were washed with water and a brine, dried over anhydrous sodium sulfate and evaporated. The residue was chromatographed on an alumina column (Merck, act. I), using benzene and benzene–chloroform (100–10 : 1) for elution. The combined eluates were evaporated and the residue crystallized from methanol–hexane to yield 0·145 g (49%) of crystals melting at 132–136°C, identical according to TLC with the natural (−)base (alumina, benzene–acetone 25 : 2, benzene–chloroform 50 : 1, silica gel, dichloromethane–methanol 20 : 1). For $C_{19}H_{22}N_2O$ (294·4) calculated: 77·52% C, 7·53% H, 9·52% N; found: 77·39% C, 7·61% H, 9·40% N. Ultraviolet spectrum: 291 (3·61), 281 (3·69), 255 (4·10). Infrared spectrum: 2 805, 2 765, 1 643, 1 597, 1 473, 1 460, 1 395, 1 370 cm^{-1}. ^1H NMR spectrum (200 MHz): 8·05 (1 H, bd, $J_{12,11} = 8·0$ Hz, $J_{12,10} = 1·1$ Hz, $J_{12,9} \approx 0$ Hz; arom. $C_{(12)}H$), 7·23 (1 H, bt, $J_{11,12} = 8·0$ Hz, $J_{11,10} = 7·4$ Hz, $J_{11,9} \approx 1·0$ Hz; arom. $C_{(11)}H$), 7·17 (1 H, bd, $J_{9,10} = 7·4$ Hz, $J_{9,11} = 1·0$ Hz, $J_{9,12} \approx 0$ Hz; arom. $C_{(9)}H$), 7·06 (1 H, dt, $J_{10,11} = 7·4$ Hz, $J_{10,9} = 7·4$ Hz, $J_{10,12} = 1·1$ Hz; arom. $C_{(10)}H$), 3·25 (1 H, bt, $J_{7,6} = J_{7,6'} = 7·2$ Hz; $—C_{(7)}H—CH_2—$), 2·97 (1 H, ddd, $J_{5,5'} = 11·3$ Hz, $J_{5,6} = 8·0$ Hz, $J_{5,6'} = 5·3$ Hz; $=N—H'C_{(5)}H—$), 2·86 (1 H, bdt, $J_{3,3'} = 11·2$ Hz, $J_{3,14} = 3·2$ Hz, $J_{3,14'} = 3·2$ Hz; $=N—H'C_{(3)}H—$), 2·63 (1 H, d, $J_{19,19'} = 18·2$ Hz; $—CO—H'C_{(19)}H—$), 2·46 (1 H, dd, $J_{19',19} = 18·2$ Hz, $J_{19',15} = 2·4$ Hz; $—CO—HC_{(19)}H'—$), 2·23 (1 H, dt, $J_{3',3} = 11·2$ Hz, $J_{3',14'} = 6·0$ Hz; $=N—HC_{(3)}H'—CH_2—$), 2·09 (1 H, dq, $J_{6,6'} = 14·1$ Hz, $J_{6,5} = J_{6,5'} = J_{6,7} = 6·2$ Hz; $=N—CH_2—H'C_{(6)}H—C_{(7)}H—$), 2·04 (1 H, ddd, $J_{5',5} = 11·2$ Hz; $=N—HC_{(5)}H'—CH_2—$), 2·03 (1 H, s; $—C_{(21)}H$), 1·96 (1 H, m; $=N—CH_2—HC_{(6)}H'—$). Mass spectrum, *m/z* (%): 295 (22, $[M + 1]^+$), 294 (100, M^+), 293 (93), 266 (28), 265 (20), 251 (15), 249 (7), 238 (17), 237 (17), 160 (7), 147 (10), 144 (9), 143 (9), 130 (16).

(−)-(2*S*,7*R*,20*R*,21*R*)-Strempeliopine (*II*)

This was prepared in 35% yield from (−)-(2*S*,7*R*,20*R*,21*R*)-*XIII* in the manner described above (the starting compound is much less soluble in a mixture of methanol and hydrochloric acid than

the racemate). The product had m.p. 150·5—153°C (2× crystallized from methanol) and $[\alpha]_D$ —25·4° (*c* 1·8; methanol) and it was identical with the natural (—)-base according to TLC (as in (±)-*II*), ^{1}H NMR, infrared, and mass spectra. Literature[4] gives m.p. 152—154°C.

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Note added in proof: In Scheme 1 below the formula *XXIII* for $R^1 = OH$; $R^2 = H$ should read $R^1 = OH$; $R^2 = COOCH_3$.