STEREOSPECIFIC TOTAL SYNTHESIS OF (+)-18-METHYLENEVINCADIFFORMINE* **

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The synthesis and the resolution of (±)-18-methylenevincadifformine (*VIII*) is described. Its key step is the reaction of methyl 1-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-carboxylate (*XIII*) with 2-allyl-5-chloropentanal (*XVI*).

The discovery of biomimetic rearrangements[1-3] of 1,2-dehydroaspidospermidine (*I*) and vincadifformine (*II*) opened new possibilities in the syntheses of bases of the vallesamidine (*III*, *IV*) and the eburnane type (for example *V*). However, till recently the compounds of the group *I* and *II* were difficult to obtain, because their precursors[4], bases of the vincadifformine type, were demanding in their preparation[5-7]. Their preparation by dehydrogenation[8] of saturated compounds of type *VI* is also preparatively unsatisfactory. A fundamental change in this situation arose from Kuehne's[9] elegant biomimetic total synthesis of (±)-vincadifformine (*II*) which also makes the key indolenine *I* accessible for synthetic use[4].

Recently we described[10] the synthesis of (±)-ethyl vincadifforminate (*VII*) where we used this approach. In this paper we describe a stereospecific synthesis of (±)-18-methylenevincadifformine (*VIII*) based on the same principle, as well as its resolution. This base, or the indolenine *IX* corresponding to it, is postulated as a universal intermediate in the syntheses of aspidospermane bases of the schizozygane (*X*), 18-oxoaspidospermane*** (*XI*) and aspidoalbine (*XII*) type.

One of the starting compounds for the synthesis of base *VIII* was methyl 1-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-carboxylate[9] (*XIII*) which we obtained, in addition to a small amount of the free acid[12] *XIV*, in 83% yield by base-catalysed transesterification of the corresponding ethyl ester *XV*, using sodium methoxide in boiling methanol. For the preparation of the second component, *i.e.* 2-allyl-5-chloropentanal (*XVI*), we used 4-pentenal[13] (*XVII*) as starting component which was reacted with cyclohexylamine to give imine *XVIII* in 75% yield. The latter was alkylated[14] with 1-bromo-3-chloropropane in the presence of lithium diisopropyl-

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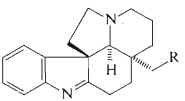
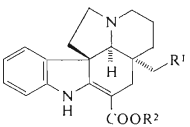
*** The synthesis of the alkaloids of this type from 12-methoxy analogue of base *IX* is known[11].

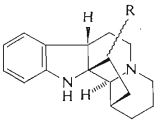
amide at −78°C; hydrolysis[10] of the reaction mixture at pH 3–4 led to aldehyde *XVI* in high yield. Its structure was confirmed by ^{1}H NMR spectroscopy, *i.e.* the presence of an allylic A_2B system and a doublet of the aldehydic proton at δ 9·62 ppm (J = = 1 Hz).



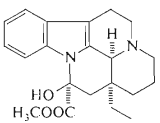
I, R = CH_3
IX, R = $CH{=}CH_2$



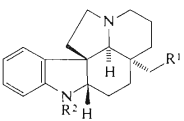
II, $R^1 = R^2 = CH_3$
VII, $R^1 = CH_3$, $R^2 = CH_2CH_3$
VIII, $R^1 = CH{=}CH_2$, $R^2 = CH_3$



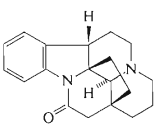
III, R = H
IV, R = $COOCH_3$



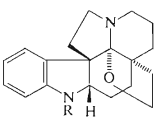
V



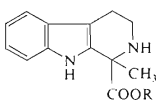
VI, $R^1 = CH_3$, R^2 = H
XI, $R^1 = COOCH_3$, $R^2 = COCH_3$



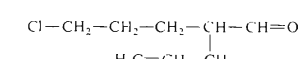
X



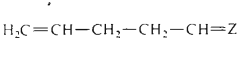
XII



XIII, R = CH_3
XIV, R = H
XV, R = CH_2CH_3



XVI



XVII, Z = O
XVIII, Z = N−C_6H_{11}

Condensation of aldehyde *XVI* with the base *XIII* was carried out in boiling toluene in the presence of 4-toluenesulfonic acid. The aldehyde was added in portions and the reaction course was followed by thin layer chromatography. When the base *XIII* disappeared after about 110 h, diazabicycloundecene was added to the mixture which contained a considerable amount of base *VIII* at this stage. Then the reaction was completed by 15 h refluxing. Thus the required 18-methylenevincadifformine (*VIII*) was obtained in a 50% yield. The structure of this base is in full agreement with the expected spectral properties. Its ultraviolet spectrum indicates the presence of a β-anilinoacrylate chromophore[15] and in its ^{1}H NMR spectrum the diagnostic A_2B system of the allylic side chain was present. However, its signals were shifted upfield by about 0·25 ppm, in comparison with the corresponding signals of the aldehyde *XVI*, which is due to the shielding effect of the chromophoric system, corresponding to an analogous situation in the base[10] *VII*. A final proof was given by its mass spectrum which displayed a typical fragmentation, parallel to that in the spectrum[16] of vincadifformine (*II*), with the only difference that the masses of corresponding fragments were higher by 12 mass units in the spectrum of base *VIII*, as consequence of the substitution $—CH_3 \rightarrow —CH=CH_2$.

Preliminary experiments aiming at the resolution of base *VIII* were carried out with a model substance, (±)-vincadifformine (*II*), which we prepared according to literature[9] in 53·7% yield. However, its diastereoisomeric salts with (−)-camphor-10-sulfonic acid and (+)-O,O′-di(4-toluyl)tartaric acid could not be prepared in a crystalline state. The use of (+)-*p*-nitrotartranilic acid was also unsuccessful. In this case, it is true, a crystalline salt of m.p. 109·5–113°C could be obtained from aqueous ethanol, but the base *II* set free from it had a very low specific rotation value, $[\alpha]$ −12·5° (*c* 0·8, ethanol). Finally (2*R*,3*R*)-(+)-tartaric acid proved to be an effective resolving agent. Even from once recrystallized salt (from ethanol; m.p. 167·5–171·5°C) a base could be set free with $[\alpha]$ +587° (*c* 0·68, ethanol). Still more effective was the use of tartaric acid in the case of 18-methylenevincadifformine (*VIII*). The salt with (2*R*,3*R*)-(+)-tartaric acid is poorly soluble and therefore we purified it merely by boiling with ethanol. Similarly, we completed the resolution of the base set free from the mother liquors *via* the salt with (2*S*,3*S*)-(−)-tartaric acid. The absolute optical rotation value of base *VIII* liberated from both salts was the same, within the experimental error, *i.e.* $[\alpha]$ + and −561° (ethanol) which indicates a 100% optical purity.

EXPERIMENTAL

The boiling points and the melting points (Boetius micro block) are not corrected. Samples for analysis were dried at room temperature and 1·4 Pa pressure for 6 h. The purity of the compounds was checked by thin-layer chromatography on commercial silica gel plates GF_{254} (Merck, GFR) in suitable solvent systems or by gas chromatography using a CHROM IV instrument

(Labora, Czechoslovakia). The ultraviolet spectra were measured in methanol on a SPECORD UV-VIS spectrophotometer (Zeiss, Jena, GDR) and are given in nm of λ_{max} and ($\log \varepsilon$). The infrared spectra were recorded on a UR-10 (Zeiss, Jena, GDR) instrument. The ^{1}H NMR spectra were measured on a BS 487 80 MHz instrument (Tesla, Czechoslovakia), the chemical shifts are given in ppm (δ-scale). Tetramethylsilane was used as internal standard. The mass spectra were recorded with the MAT 44S (Varian, USA) and MCH-1320 (USSR) instruments. Optical rotations were measured on a POLAMAT-A polarimeter at 578 nm wave-length, at 24–26°C.

Methyl 1-Methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-carboxylate (*XIII*)

A 1M solution of sodium methoxide in methanol (20 ml) was added to a solution of 74·3 g (0·288 mol) of ethyl 1-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-carboxylate[10] (*XV*) in methanol (600 ml) and the mixture was refluxed for 1 h (checking with TLC). After cooling a 20% ammonium chloride solution (20 ml) was added and the mixture evaporated in a vacuum. The residue was partitioned between water (200 ml) and chloroform (700 and 2 × 200 ml); the undissolved residue was filtered off under suction and identified as 1-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*] indole-1-carboxylic acid (*XIV*), m.p. 210–213°C, or 213–215°C (after crystallization from ethanol). Lit.[12] gives m.p. 220°C. The combined chloroform layers were dried over anhydrous sodium sulfate. Crystallization of the residue from benzene–light petroleum gave 58·3 g (82·9%) of compound *XIII* with m.p. 136–139°C (lit.[9] gives m.p. 136–138°C).

N-(4-Pentenylidene)cyclohexylamine (*XVIII*)

Cyclohexylamine (84·3 g, 0·85 mol) was added dropwise and under stirring to 4-pentenal (*XVII*) (71·5 g, 0·85 mol) over 1·5 h at −5°C. After another 25 min of cooling and stirring ground potassium hydroxide was added and the mixture was allowed to stand at 10°C for 0·5 h under occasional shaking. The liquid phase was then separated and dried over solid potassium hydroxide in an ice-box for 15 h. Distillation on a 15 cm Vigreux column under nitrogen gave 104·7 g (74·5%) of an oil, b.p. 87–88·5°C /1·13 kPa. Infrared spectrum in chloroform: 1 649 cm^{-1} (C=N).

2-Allyl-5-chloropentanal (*XVI*)

A solution of imine *XVIII* (104·0 g, 0·629 mol) in tetrahydrofuran (100 ml) was added dropwise to a stirred solution of lithium diisopropylamide, prepared from diisopropylamine (65·17 g, 0·644 mol) and 302·8 ml of a 2·15M n-butyllithium solution (Bierce-Ventrom) in tetrahydrofuran (600 ml). The addition was carried out under nitrogen at −78°C over 45 min. After 30 min stirring 1-bromo-3-chloropropane (107·1 g, 0·680 mol) was added over 35 min at the same temperature. The mixture was cooled and stirred for 2·5 h, then allowed to warm up to room temperature, which lasted 4·5 h. Finally it was stirred for another 3 h at room temperature and then added dropwise over 15 min into a stirred solution of 110 ml of concentrated hydrochloric acid in water (875 ml). After 15 h stirring at room temperature the organic phase was separated and the aqueous phase extracted with ether (300 and 150 ml). The combined organic phases were washed with 3% hydrochloric acid (200 ml), water (2 × 200 ml) and brine (250 ml) and dried over anhydrous sodium sulfate. Distillation of the residue of the evaporated organic phases in a vacuum gave 78·8 g (78·0%) of an oil with b.p. 63°C/80 Pa (67–69°C/130 Pa) and a 98·5% purity according to GLC. Infrared spectrum in chloroform: 2 820, 2 700 (—CHO), 1 715 (—HC=O), 1 636 (C=C), 1 442, 1 435, 1 220, 982, 910 cm^{-1}. ^{1}H NMR spectrum in $CDCl_3$: 9·62 (1 H, d, J = 1 Hz; —C**H**=O); 5·70 (1 H, m; CH_2=C**H**—); 5·10 (2 H, m; C**H**$_2$=CH—); 3·55

(2 H, m; Cl—CH_2—CH_2—). Mass spectrum (CI ionization) (*m/z*): 161 ($[M+1]^+$, $C_8H_{14}ClO$, 100%). For $C_8H_{13}ClO$ (160·6) calculated: 59·81% C, 8·15% H, 22·07% Cl; found: 59·99% C, 8·04% H, 22·17% Cl.

18-Methylenevincadifformine (*VIII*)

Amino ester *XIII* (53·0 g; 0·217 mol), chloroaldehyde *XVI* (48·0 g) and 4-toluenesulfonic acid (0·17 g, 1 mmol) were mixed in toluene (4 400 ml) and the mixture was refluxed in an apparatus provided with a separator of water. After 30 h and 50 h boiling additional chloroaldehyde *XVI* was added (9·0 g each time, *i.e.* a total of 66·0 g, *i.e.* 0·411 mol). After 110 h boiling, base *XIII* was no longer present, as indicated by thin-layer chromatography. Diazabicycloundecane (63·9 g, 0·420 mol) was then added and the mixture refluxed for another 15 h. The toluene solution was separated while hot and then evaporated in a vacuum. The residue was dissolved in chloroform, filtered and prepurified by filtration through a column of silica gel (150 g). The main fraction was chromatographed on a silica gel column (400 g) with benzene and benzene with 10% of chloroform. The eluted material was an oil which crystallized from acetonitrile. Yield, 38·4 g (50·5%) of yellowish crystals with m.p. 108·5—110·5°C. Ultraviolet spectrum in methanol: 331 (4·08), 300 (3·95), 227 (4·03). Infrared spectrum in chloroform: 3 340 (NH), 2 903, 2 819, 2 747, 1 665 (conjugated ester), 1 600 (arom. vibration), 1 476, 1 455, 1 429, 1 286, 1 235, 1 146, 1 036, 909 cm^{-1}. ^1H NMR spectrum in $CDCl_3$: 8·90 (1 H, bs; NH); 7·20 to 6·60 (4 H, m; arom. H); 5·50 (1 H, m; CH_2=CH—); 4·82 (1 H, d, with str, J = 10·0 Hz; *cis*—HCH=CH—); 4·63 (1 H, d with str., J = 16·0 Hz; *trans*-HCH=CH—); 3·71 (3 H, s; —$COOCH_3$); 3·23—1·10 (15 H, m). Mass spectrum (*m/z*): 350 (M^+, 12·8%), 309 ($M^+ - CH_2$=$CHCH_2$, 3·5%), 136 (100%). For $C_{22}H_{26}N_2O_2$ (350·4) calculated: 75·40% C, 7·48% H, 7·99% N; found: 75·23% C, 7·62% H, 7·88% N.

Resolution of Base *VIII*

A mixture of the (±)-base *VIII* (8·76 g, 25·0 mmol) and (2*R*,3*R*)-(+)-tartaric acid (3·68 g, 24·5 mmol) was dissolved in boiling ethanol (40 ml) and the solution concentrated to 3/4 of its original volume. After standing at room temperature for 3 days the separated crystals were filtered off under suction and boiled for 5 min with 15 ml of ethanol. The mixture was set aside overnight. Then the crystals were filtered off, washed with a small amount of ethanol and dried in air. Yield, 5·92 g (78·6%) of the salt, m.p. 137-141·5°C, [α] +341° (*c* 0·75, dimethyl formamide–ethanol 2 : 5). This salt (4·83 g, 9·65 mmol) was partitioned between a 0·7M potassium hydrogen carbonate solution in water (60 ml) and dichloromethane (150 and 50 ml). The combined organic phases were washed with 0·3M aqueous potassium hydrogen carbonate solution (20 ml), water (2 × 25 ml) and brine (30 ml). After drying over anhydrous sodium sulfate the solution was evaporated to dryness. The residue (a glassy mass) weighed 3·27 g (96·7%), with [α] +560·5° (*c* 1·15, ethanol).

The original mother liquors were evaporated in a vacuum and the residue was treated as above to set free the base *VIII*. Thus 5·15 g (14·7 mmol) of base *VIII* were obtained which was dissolved in boiling ethanol (17 ml) together with 2·21 g (14·7 mmol) of (2*S*,3*S*)-(−)-tartaric acid. The solution was filtered and the filtrate set aside for one day at room temperature. The separated salt was filtered off under suction and boiled with ethanol (12 ml). The mixture was allowed to stand at room temperature for 2 days and the crystals formed were filtered off under suction, washed with ethanol and dried. Yield, 5·34 g (85·4%) of the salt, m.p. 137·5—142°C and [α] −344° (*c* 0·87, dimethylformamide–ethanol 2 : 5), from which a glassy base was set free, having [α] −561° (*c* 1·12, anhydrous ethanol), or [α] −546° (*c* 1·03, from 96% ethanol).

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