SYNTHESES OF (+)-9-DEMETHYLPSYCHOTRINE AND (+)-10-DEMETHYLPSYCHOTRINE

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Abstract — The synthesis of (+)-9-demethylpsychotrine (I) has been achieved by an initial condensation of 3-benzylxy-4-methoxyphenacyl bromide (Xa) with the lactum ether IX, derived from the lactam ester VIII, and the subsequent steps proceeding through the intermediates Xla, XIIa, XIIIc, XIIIa, XIVa, XVa, XVIa, XVIIa, and XVIIIa. A parallel synthesis starting with 4-benzylxy-3-methoxyphenacyl bromide (Xb) and IX afforded (+)-10-demethylpsychotrine (II).

Desmethylpsychotrine, a phenolic base, was encountered1 among a number of benzoquinolizidine alkaloids in Alangium laurinarckii Thw. (family Alangiaceae). On the basis of its conversion into O-methylpsychotrine (IV) and its formation from psychotrine (III) by acid hydrolysis and from the mass spectral evidence, some of us proposed2 for this compound the structure I or II, a differentiation of which was however not possible at that time. In the present work the two target molecules, (+)-9-demethylpsychotrine (I) and (+)-10-demethylpsychotrine (II), were selected for synthesis with a view to establishing the exact location of the phenolic function in ring A of the natural base. The "lactim ether method",2 so successfully employed in the syntheses of ring-A-modified benzoquinolizidine alkaloids such as emetine,3 ankorine (V),4 alangicine (VI),5 and alangimarckine (VII),6 was also adapted for the syntheses of (±)-I and (±)-II.

Treatment of the lactum ether IX, prepared from ethyl (±)-trans-5-ethyl-2-oxo-4-piperidineacetate (VIII)7 according to the previously reported procedure,3,8 with 3-benzylxy-4-methoxyphenacyl bromide (Xa)9 in HCONMe2 at 60°C for 8 h furnished the keto lactam Xla10 in 64% overall yield (from VIII). The NaBH4 reduction (EtOH, room temp., 3 h) of Xla and hydrogenolysis (10% Pd-C/H2, EtOH-70% aq. HClO4, room temp., 1 atm, 12 h) of the resulting diastereoisomeric mixture of the hydroxy lactam XIIa produced the phenolic lactam XIIIc (92% overall yield; mp 109-110°C), which was then benzylated (PhCH2Br, K2CO3,
I: $R^1 = H; R^2 = Me; R^3 = H$
II: $R^1 = Me; R^2 = H; R^3 = H$
III: $R^1 = Me; R^2 = Me; R^3 = H$
IV: $R^1 = Me; R^2 = Me; R^3 = Me$
V: $R = CH_2OH$
VI: $R = CH_3OH$
VII: $R = H$

$Xa, b$: $Z = O$

$XIIa, b$: $Z = H, OH$

$XVIIa, b$: $R^3 = Et$

$XVIa, b$: $R^3 = H$

$a$: $R^1 = CH_2Ph; R^2 = Me$

$b$: $R^1 = Me; R^2 = CH_2Ph$

$c$: $R^1 = H; R^2 = Me$

$d$: $R^1 = Me; R^2 = H$
boiling acetone, 48 h) to give the O-benzyl derivative XIlA in 74% yield. The Bischler-Napieralski reaction (POCl₃, boiling toluene, 1.5 h) of XIlA and catalytic hydrogenation (PtO₂, EtOH, room temp., 1 atm, 50 min) of the resulting quaternary salt XIVA afforded the tricyclic ester XVA [77% overall yield from XIlA; mp 89.5-90.5°C; IR (CHCl₃): 2815, 2760 (trans-quinolizidine ring), 1725 cm⁻¹ (ester CO)]. That all the chemical operations proceeding from VIII to XVA did not affect the stereochemical relationship already established in the starting material and the correctness of the configuration at C-11b in XVA were supported by the recent application of the above reaction sequence to a formal synthesis of (+)-emetine, the stereochemistry of which is unequivocally established. On alkaline hydrolysis (2 N aq. NaOH-EtOH, room temp., 20 h), the tricyclic ester XVA provided the amino acid XVIa [mp 182-184°C (dec.)] in 83% yield. Condensation of XVIa with 3-benzyloxy-4-methoxyphenethylamine by the diethyl phosphorocyanidate method (Et₃N, HCONMe₂, room temp., 6 h) gave the amide XVIIa [97% yield; mp 178-180°C (dec.)], which was then cyclized with POCl₃ (boiling toluene, 1.5 h) to the base XVIIIa in 82% yield. Finally, debenzylation of XVIIIa was effected with 10% aq. HCl-EtOH (reflux, 18 h) to produce (±)-9-demethylpsychotrine (I) [90% yield; mp 224-226°C (dec.)].

For the synthesis of the alternative target molecule [(±)-II], a parallel synthetic route starting from the lactim ether IX and 4-benzyloxy-3-methoxyphenacyl bromide (Xb) was followed through the intermediates Xlb (75% yield; mp 118.5-119.5°C), XIIb (99%), XIIIId (97%), XIVb, XVb (73% from XIlb; mp 72-73°C), XVIb (89%; mp 78-79°C), XVIIb (85%; mp 145-147°C), and XVIIIb (81%). Debenzylation of XVIIIb as above furnished (±)-10-demethylpsychotrine (II) [mp 242-244°C (dec.)] in 91% yield.

While the UV spectra (in EtOH, 0.1 N aq. HCl, or 0.1 N aq. NaOH) of both (±)-I and (±)-II were found to match those of natural (+)-desmethylpsychotrine (mp 166-168°C), the mass spectrum of the latter corresponded to that of (±)-I rather than (±)-II. The solid state IR spectrum of the natural base was also quite different from that of (±)-II but was very close to the corresponding spectrum of (±)-I, the small difference being perhaps due to the sample of (±)-I crystallizing as a racemic compound. Unfortunately, unambiguous identification was precluded owing to lack of sufficient amount of natural desmethylpsychotrine for solution IR and/or NMR spectra.

The above results thus suggested that the formula I is a likely structure for desmethylpsychotrine though the final conclusion must await the completion of a chiral synthesis of I, currently under way in our laboratories.

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REFERENCES

10. The assigned structures of all new compounds were supported by ir, nmr, and mass spectral evidence and/or satisfactory elemental analyses.
13. Recrystallized from EtOH-AcOEt. This sample was found to contain 1/3 equivalent mole of EtOH on crystallization.
16. Recrystallized from EtOH. The analysis pointed to the formula C2H4N4O4·2.5EtOH.
18. The analysis pointed to the formula C2H4N4O4·H2O.

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