SYNTHESES OF (±)-9-DEMETHYLPSYCHOTRINE AND (±)-10-DEMETHYLPSY-
CHOTRINE

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

Desmethylpsychotrine, a phenolic base, was encountered[1] among a number of benzoquinolizidine alka-

loids in Alangium lamarckii Thw. (family Alangiaceae). On the basis of its conversion into O-methylpsy-

chotrine (IV) and its formation from psychotrine (III) by acid hydrolysis and from the mass spectral evi-

dence, some of us proposed[1] for this compound the structure I or II, a differentiation of which was how-

ever 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 success-

fully employed in the syntheses of ring-A-modified benzo[a]quinolizidine 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 lactim ether IX, prepared from ethyl (±)-trans-5-ethyl-2-oxo-4-piperidineacetate (VIII)[7]

according to the previously reported procedure,[3,8] with 3-benzyloxy-4-methoxyphenacyl bromide (Xa)[9]

in HCONMe2 at 60°C for 8 h furnished the keto lactam XIa[10] in 64% overall yield (from VIII). The NaBH4

reduction (EtOH, room temp., 3 h) of XIa 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

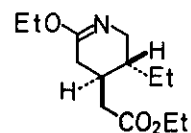phenolic lactam XIIIc (92% overall yield; mp 109−110°C), which was then benzylated (PhCH2Br, K2CO3,
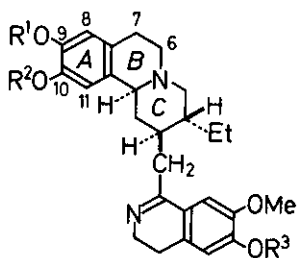
I: $R^1 = H$; $R^2 = Me$; $R^3 = H$
II: $R^1 = Me$; $R^2 = H$; $R^3 = H$
III: $R^1 = Me$; $R^2 = Me$; $R^3 = H$
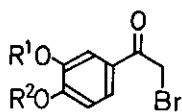IV: $R^1 = Me$; $R^2 = Me$; $R^3 = Me$

V: $R = CH_2OH$

VI: $R =$

VII: $R =$
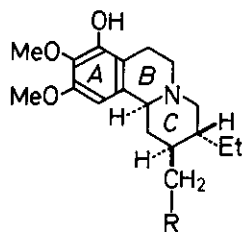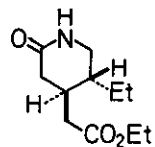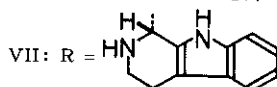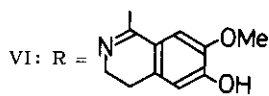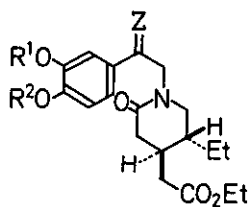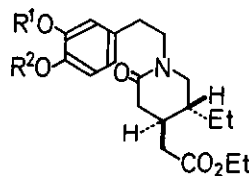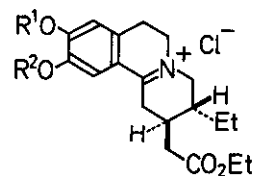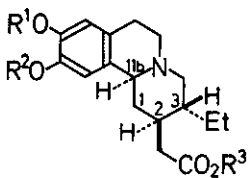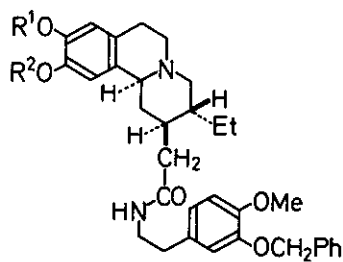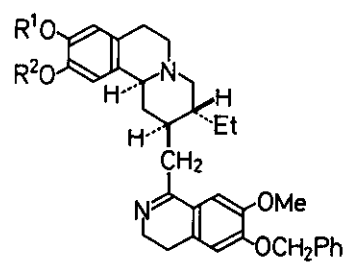
VIII

IX

Xa, b

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

XIIIa, b, c, d

XIVa, b

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

XVIIa, b

XVIIIa, b

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 XIIIa in 74% yield. The Bischler-Napieralski re-action (POCl₃, boiling toluene, 1.5 h) of XIIIa and catalytic hydrogenation (PtO₂, EtOH, room temp., 1 atm, 50 min) of the resulting quaternary salt XIVa afforded the tricyclic ester XVa [71% overall yield from XIIIa; mp 89.5—90.5 °C; ir (CHCl₃): 2815, 2760 (<u>trans</u>-quinolizidine ring),[11] 1725 cm⁻¹ (ester CO)]. That all the chemical operations proceeding from VIII to XVa did not affect the stereochemical relation-ship already established in the starting material and the correctness of the configuration at C-11b in XVa were supported by the recent application[3,4] of the above reaction sequence to a formal synthesis of (±)-emetine, the stereochemistry of which is unequivocally established.[12]

On alkaline hydrolysis (2 N̲ aq. NaOH—EtOH, room temp., 20 h), the tricyclic ester XVa provided the amino acid XVIa [mp 182—184 °C (dec.)][13] in 83% yield. Condensation of XVIa with 3-benzyloxy-4-me-thoxyphenethylamine[14] by the diethyl phosphorocyanidate method[15] (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.)][16]].

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)[17] was followed through the intermediates XIb (75% yield; mp 118.5—119.5 °C), XIIb (99%), XIIId (97%), XIIIb (72%), XIVb, XVb (73% from XIIIb; mp 72—73 °C), XVIb (89%; mp 78—79 °C),[18] 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 N̲ aq. HCl, or 0.1 N̲ aq. NaOH) of both (±)-I and (±)-II were found to match those of natural (+)-desmethylpsychotrine (mp 166—168 °C),[1] the mass spectrum of the latter corre-sponded 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.[19] Unfortunately, unambig-uous 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 labo-ratories.

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