SYNTHESES OF (−)-9-DEMETHYLCEPHAELINE AND (−)-10-DEMETHYLCEPHAELINE

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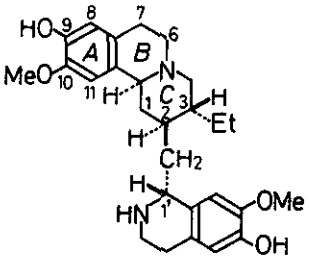
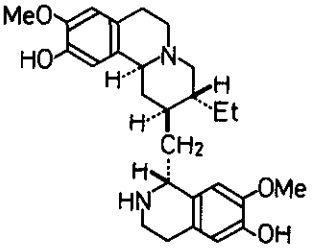
Abstract — The synthesis of (−)-9-demethylcephaeline (I) has been accomplished by reduction of (+)-O,O-dibenzyl-9-demethylpsychotrine (XIa) followed by debenzylation of the resulting (−)-tetrahydroisoquinoline derivative XIIa. A parallel synthesis starting with (+)-O,O-dibenzyl-10-demethylpsychotrine (XIb), prepared from the (−)-tricyclic amino ester VIIIb through the (−)-amino acid IXb and the (−)-amide Xb, gave (−)-10-demethylcephaeline (II).

(−)-Demethylcephaeline is a phenolic base among a number of benzoquinolizidine alkaloids in Alangium lamarckii Thw. (family Alangiaceae).[1] Based on its chemical correlation with the ipecac alkaloids cephaeline (III) and emetine (IV) and on the uv, ir, and mass spectral evidence, Pakrashi and Achari[1] have assigned the alternative structure I (absolute configuration shown) or II to this alkaloid, but a discrimination between the 9- and the 10-demethyl structures remains to be settled. We have recently shown that (+)-desmethylpsychotrine, another Alangium alkaloid,[2] has the 9-demethyl structure (V),[3] whereas (−)-demethyltubulosine, yet another phenolic Alangium alkaloid,[2,4] is not a 9-demethylated base,[5] but 10-demethyltubulosine (VI).[6] In the present study, therefore, both 9-demethylcephaeline (I) and 10-demethylcephaeline (II) were selected as the synthetic chiral targets with a view to elucidating the exact location of the phenolic function in ring A of natural (−)-demethylcephaeline.

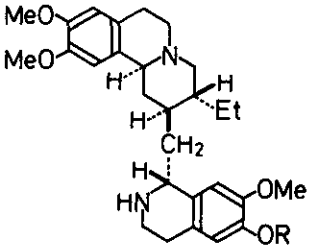
We first tried to synthesize the 9-demethyl structure I from (+)-O,O-dibenzyl-9-demethylpsychotrine (XIa), an intermediate prepared from (+)-ethyl cincholoiponate (VII) through (−)-VIIIa, IXa, and (−)-Xa and utilized in our recent synthesis[3] of (+)-9-demethylpsychotrine (V). On catalytic reduction (Pt/H_2, EtOH, 1 atm, 18°C, 1 h) and chromatographic separation (silica gel, $CHCl_3$–MeOH) of the hydrogenation products, (+)-XIa provided the (−)-base XIIa [47% yield; $[\alpha]_D^{26}$ −18.7° (c 0.82, EtOH); ^{13}C nmr ($CDCl_3$) δ:[7] 36.9 (C-2), 36.9 (C-1), 51.9 (C-1')][8] and its 1'-epimer (−)-XIIIa [30% yield; $[\alpha]_D^{26}$ −25.6° (c 0.66, EtOH); ^{13}C nmr ($CDCl_3$) δ:[7] 38.9 (C-2), 39.4 (C-1), 55.3 (C-1')] as glassy materials. The above formation of (−)-XIIa and (−)-XIIIa in a 1.6 : 1 molar ratio was comparable to



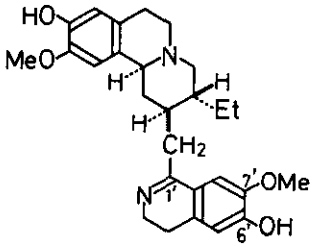
I



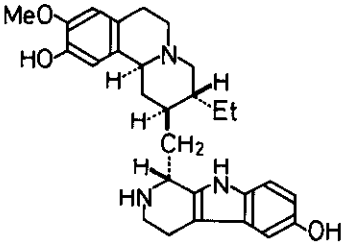
II



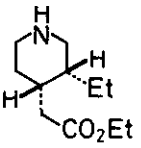
III: R = H
IV: R = Me



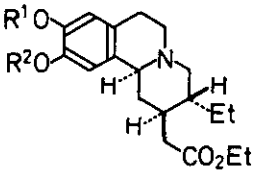
V



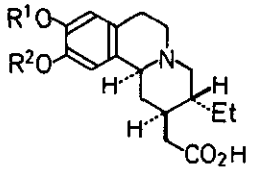
VI



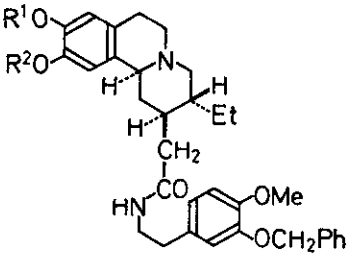
VII



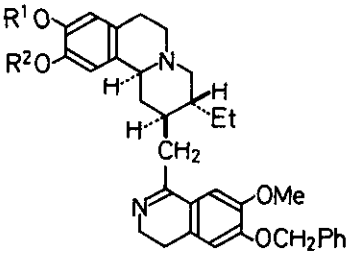
VIIIa,b



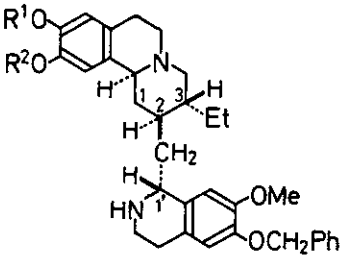
IXa,b



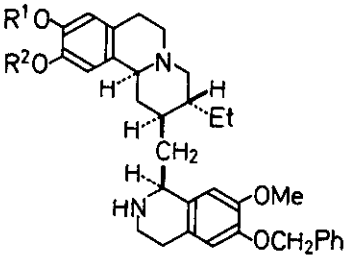
Xa,b



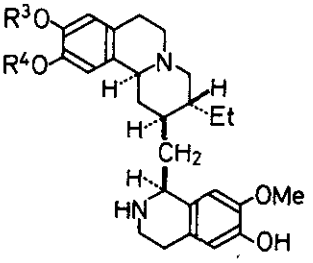
XIa,b



XIIa,b



XIIIa,b



XIV: R^3 = H; R^4 = Me
XV: R^3 = Me; R^4 = H

a: R^1 = $PhCH_2$; R^2 = Me
b: R^1 = Me; R^2 = $PhCH_2$

that of emetine (IV) and its 1'-epimer (isoemetine) in a 1.7 : 1 molar ratio in a similar hydrogenation of O-methylpsychotrine (V, MeO for OH at C-9 and C-6').[9] On tlc analysis (silica gel, $CHCl_3$–EtOH), (–)-XIIa moved faster than (–)-XIIIa, and this difference in mobility corresponded to that observed for a pair of emetine (IV) and isoemetine. In the ^{13}C nmr spectra in $CDCl_3$, the C-1, C-2, and C-1' carbon signals of (–)-XIIa resonated at higher field than the corresponding signals of (–)-XIIIa by 2.0–3.4 ppm (vide supra). These findings permitted us to assign the configuration at C-1' of (–)-XIIa and (–)-XIIIa by the analogy of the stereochemical assignments in structurally related systems.[5,6,10,11]

The (–)-base XIIa was then hydrogenolyzed [Pd-C/H_2, MeOH–AcOH (1 : 1, v/v), 1 atm, 18°C, 3 h] to give the desired (–)-phenolic base I [mp 147°C (sintered at 124°C); $[\alpha]_D^{12}$ –55.0° (c 0.50, $CHCl_3$)] in 82% yield. A similar debenzylation of the epimeric base (–)-XIIIa furnished (–)-XIV [mp 178–180°C; $[\alpha]_D^{12}$ –94.0° (c 0.36, $CHCl_3$)][12] in 73% yield.

The synthesis of the alternative target structure II was tried next. Alkaline hydrolysis (2 N aq. NaOH–EtOH, room temp., 24 h) of the (–)-tricyclic amino ester VIIIb, prepared from (+)-VII according to the recently reported[13] procedure ("cincholoipon-incorporating method"),[3,14-17] gave the (–)-amino acid IXb [98%; $[\alpha]_D^{18}$ –56.8° (c 0.50, EtOH)]. Condensation of (–)-IXb with 3-benzyloxy-4-methoxyphenethylamine[18] by the diethyl phosphorocyanidate method[19] [$(EtO)_2POCN$, Et_3N, $HCONMe_2$, room temp., 6 h] yielded the (–)-amide Xb [90%; mp 149–151°C; $[\alpha]_D^{20}$ –22.2° (c 0.50, EtOH)], which was then cyclized ($POCl_3$, boiling toluene, 1.5 h) to furnish (+)-O,O-dibenzyl-10-demethylpsychotrine (XIb) [87%; $[\alpha]_D^{26}$ +39.9° (c 0.96, EtOH)]. The subsequent steps to II were essentially the same as described above for the 9-demethyl series, affording first an epimeric pair of (–)-XIIb [48% yield from (+)-XIb; $[\alpha]_D^{30}$ –33.2° (c 0.50, EtOH); ^{13}C nmr ($CDCl_3$) δ:[7] 36.7 (C-2), 36.7 (C-1), 51.8 (C-1')] and (–)-XIIIb [29% yield from (+)-XIb; $[\alpha]_D^{30}$ –30.9° (c 0.50, EtOH); ^{13}C nmr ($CDCl_3$) δ:[7] 39.0 (C-2), 39.2 (C-1), 55.2 (C-1')], and then (–)-10-demethylcephaeline (II) [73% yield from (–)-XIIb; mp 148°C (sintered at 129–130°C); $[\alpha]_D^{17}$ –53.0° (c 0.50, $CHCl_3$)][20] and its 1'-epimer (–)-XV [77% yield from (–)-XIIIb; mp 114–116°C; $[\alpha]_D^{17}$ –50.0° (c 0.34, $CHCl_3$)].[20]

Now that the two target compounds, (–)-I and (–)-II, became available, it was possible to compare them with natural (–)-demethylcephaeline [lit.[1] mp 147–149°C; $[\alpha]_D$ –53.5° ($CHCl_3$)] by spectroscopic means. The uv (in EtOH or 0.1 N ethanolic NaOH), ir (in Nujol), and mass spectra of the three were so closely similar, respectively, that they were impracticable as the means of identification. Although the nmr spectra (in $CDCl_3$) of (–)-I and (–)-II were clearly differentiated from one another, that of the natural alkaloid was not available then. Unfortunately, lack of sufficient amount of natural (–)-demethylcephaeline for an nmr spectrum and/or mixture melting point test precluded us from identifying either (–)-I or (–)-II with this alkaloid.

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