

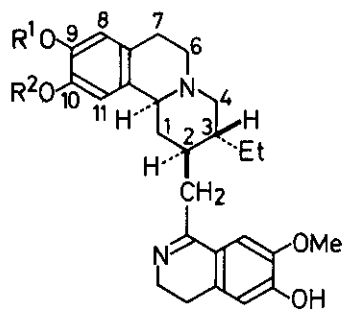
SYNTHESES OF (-)-9-DEMETHYLPROTOEMETINOL AND (±)- AND (-)-10-DEMETHYLPROTOEMETINOLS

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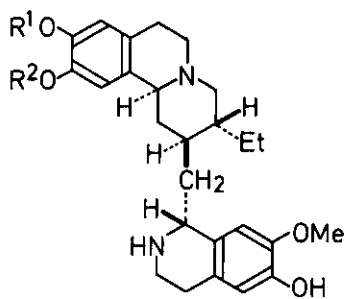
Abstract — The synthesis of (-)-9-demethylprotoemetinol (X) was achieved by LiAlH₄ reduction of the (-)-tricyclic ester XIV followed by catalytic hydrogenolysis of the resulting (-)-tricyclic alcohol XI. Acetylation of (-)-X yielded the (-)-diacetate XVII. Parallel synthetic routes starting with the isomeric (±)- and (-)-tricyclic esters XV gave (±)- and (-)-10-demethylprotoemetinols (XII) and the corresponding diacetates [(±)- and (-)-XVIII] through the (±)- and (-)-tricyclic alcohols XIII, respectively.

The isolation of psychotrine (I),¹⁻³ cephaeline (IV),¹⁻⁴ and tubulosine (VII),³⁻⁷ together with their demethylated bases such as 9-demethylpsychotrine (II),^{3,8,9} demethylcephaeline (V or VI),^{3,10} and 10-demethyltubulosine (VIII),^{7,11} from Alangium lamarckii Thwaites (family Alangiaceae) suggested the possibility of co-occurrence of the 9-demethylated (X) and/or 10-demethylated (XII) bases of protoemetinol (IX), already encountered in A. lamarckii.^{4,12} To facilitate the search from the natural source, we undertook the synthesis of (-)-9-demethylprotoemetinol (X)¹³ and (±)- and (-)-10-demethylprotoemetinols (XII).

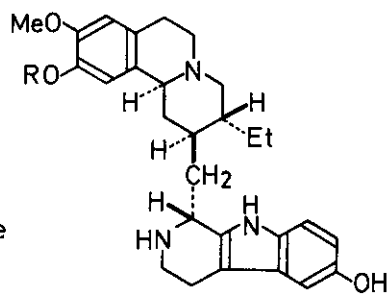
The first target selected for synthesis was (±)-10-demethylprotoemetinol (XII). It seemed accessible from the known (±)-tricyclic ester XV, the key intermediate used for the syntheses of (±)-10-demethylpsychotrine (III)¹⁴ and (±)-10-demethyltubulosine (VIII),¹¹ through a route closely parallel to that¹⁵ adopted by Fujii *et al.* for the synthesis of yet another Alangium alkaloid, ankorine (XVI).^{12,15,16} Thus, reduction



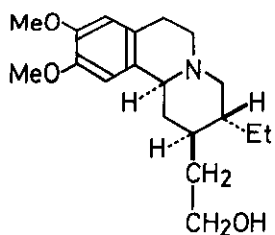
I: $R^1 = R^2 = \text{Me}$
 II: $R^1 = \text{H}; R^2 = \text{Me}$
 III: $R^1 = \text{Me}; R^2 = \text{H}$



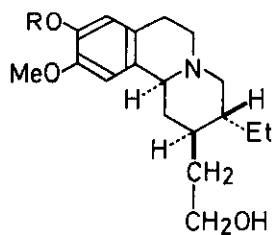
IV: $R^1 = R^2 = \text{Me}$
 V: $R^1 = \text{H}; R^2 = \text{Me}$
 VI: $R^1 = \text{Me}; R^2 = \text{H}$



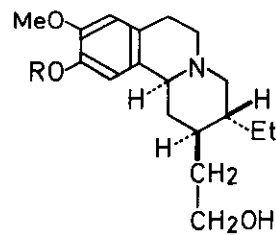
VII: $R = \text{Me}$
 VIII: $R = \text{H}$



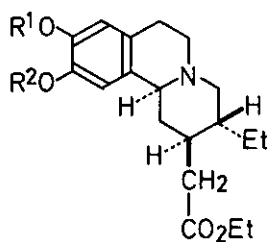
IX



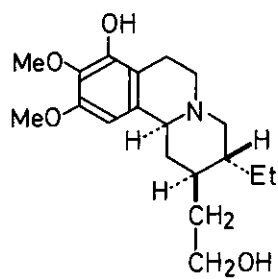
X: $R = \text{H}$
 XI: $R = \text{PhCH}_2$



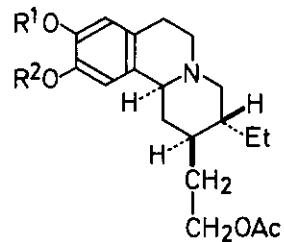
XII: $R = \text{H}$
 XIII: $R = \text{PhCH}_2$



XIV: $R^1 = \text{PhCH}_2; R^2 = \text{Me}$
 XV: $R^1 = \text{Me}; R^2 = \text{PhCH}_2$



XVI



XVII: $R^1 = \text{Ac}; R^2 = \text{Me}$
 XVIII: $R^1 = \text{Me}; R^2 = \text{Ac}$

of (±)-XV with LiAlH_4 in ether afforded the (±)-tricyclic alcohol XIII¹⁷ (mp 98.5–99.5°C) in 91% yield. On catalytic hydrogenolysis (10% Pd-C/H₂, EtOH, room temp., 1 atm, 2 h), (±)-XIII gave (±)-10-demethylprotoemetinol (XII) (mp 151–152°C) in 96% yield. The (±)-diacetate XVIII (mp 97–98°C) was obtained from (±)-XII in 85% yield by acetylation (Ac_2O /pyridine, 60°C, 0.5 h).

A parallel route starting with the known (–)-tricyclic ester XV,¹⁸ the key intermediate utilized in our recent synthesis of (–)-10-demethylcephaeline (VI),¹⁰ provided the second target (–)-10-demethylprotoemetinol (XII) [glass, $[\alpha]_D^{17}$ –35.2° (c 0.50, EtOH)] and the corresponding (–)-diacetate XVIII [oil, $[\alpha]_D^{25}$ –29.7° (c 0.38, CHCl_3)] in excellent overall yields via the (–)-tricyclic alcohol XIII [mp 85–86°C; $[\alpha]_D^{16}$ –50.6° (c 0.50, EtOH)].

Finally, the same sequence of reactions with the known isomeric (–)-tricyclic ester XIV,⁹ the key intermediate for our recent syntheses of (+)-9-demethylpsychotrine (II)⁹ and (–)-9-demethylcephaeline (V),¹⁰ produced the third target (–)-9-demethylprotoemetinol (X) [mp 157–158.5°C; $[\alpha]_D^{25}$ –61.0° (c 0.50, EtOH)] and its (–)-diacetate XVII [oil, $[\alpha]_D^{25}$ –34.3° (c 0.40, CHCl_3)] in high overall yields through the (–)-tricyclic alcohol XI [mp 103–104°C; $[\alpha]_D^{25}$ –35.0° (c 0.50, EtOH)].

Recently, Pakrashi's group¹⁹ has isolated two new alkaloids from the seeds of *A. lamarkii* and inferred them to be 9-demethylprotoemetinol (X) and 10-demethylprotoemetinol (XII). The structure and relative stereochemistry of the latter alkaloid were confirmed by comparison of the ir and nmr spectra of its diacetate [$[\alpha]_D$ –15.8° (CHCl_3)] with those of synthetic (±)-10-demethylprotoemetinol diacetate (XVIII) described above. The absolute stereochemistry was, however, deduced from the identity of sign of the specific rotations of the diacetate of the natural base and synthetic (–)-XVIII. On the other hand, a direct comparison of the other alkaloid, inferred to be 9-demethylprotoemetinol, with synthetic (–)-X was not possible owing to paucity of the natural base.¹⁹

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