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STRUCTURE AND SYNTHESIS OF DESMETHYLPSYCHOTRINE

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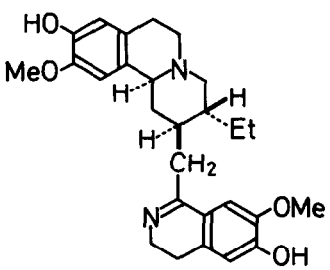
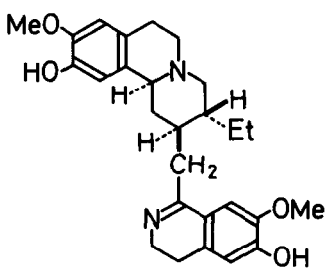
Abstract — (+)-9-Demethylpsychotrine (I) has been synthesized from ethyl cincholoiponate [(+)-III] and 3-benzyloxy-4-methoxyphenacyl bromide by the "cincholoipon-incorporating method" through the intermediates IV–VI and VIII–XVII. Identity of synthetic (+)-I with desmethylpsychotrine unequivocally established the structure of this Alangium alkaloid.

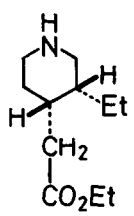
In a very recent communication[1] reporting the syntheses of (±)-9-demethylpsychotrine (I) and (±)-10-demethylpsychotrine (II), we suggested formula I as the most likely structure of desmethylpsychotrine,[2] an Alangium alkaloid. However, the identity of (±)-I with the natural desmethylpsychotrine could not be rigorously established owing to paucity of the alkaloid sufficient for solution IR and/or NMR spectra, the frequent difficulty of identifying an enantiomer with a racemic modification in the solid state by IR spectroscopy being well-known. We, therefore, decided to synthesize the chiral target molecule I (absolute configuration shown) for direct and unambiguous comparison with desmethylpsychotrine. Thus, a parallel route to our recent chiral syntheses of some of the Ipecac alkaloids[3] as well as the Alangium alkaloids, namely, ankorine,[4] alangicine,[5] and alangimarckine[6] by the "cincholoipon-incorporating method" was adopted for the synthesis of the enantiomer I as in the sequel.



(±)-I
(+)-I

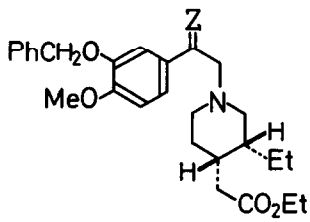


(±)-II

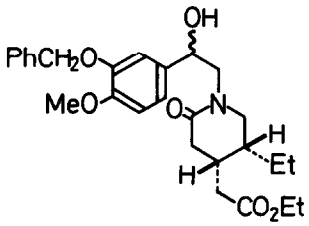


(+)-III

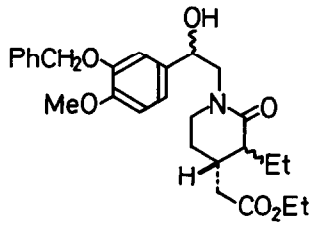
Condensation (benzene, K_2CO_3, 50–55°, 15 hr) of cincholoipon ethyl ester [(+)-III], prepared[7] from the Cinchona alkaloid cinchonine in 50% overall yield, with 3-benzyloxy-4-methoxyphenacyl bromide[8] furnished the amino ketone (+)-IV [71% yield; $[\alpha]_D^{13}$ +2.1° (c 2.39, EtOH)],[9] which was reduced ($NaBH_4$, EtOH, 0°, 6 hr, room temp., 14 hr) to a diastereoisomeric mixture of the amino



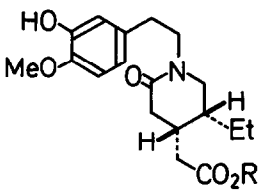
(+)-IV: Z = O
V: Z = H,OH



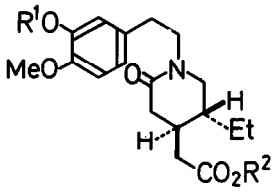
VI



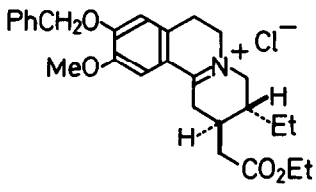
VII



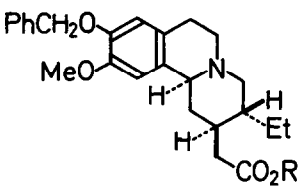
(–)-VIII: R = Et
(–)-IX: R = H



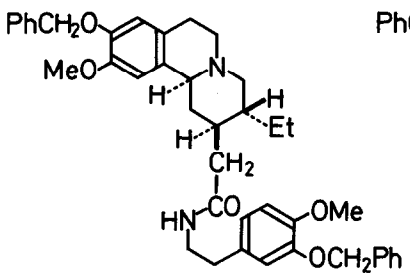
(+)-X: R^1 = H; R^2 = H
(+)-XI: R^1 = H; R^2 = Et
(+)-XII: R^1 = $PhCH_2$; R^2 = Et



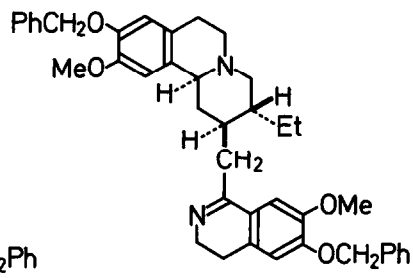
XIII



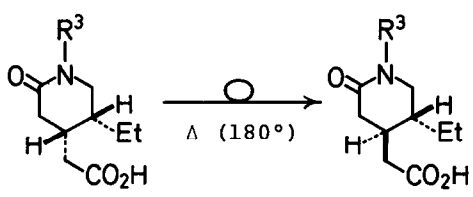
(–)-XIV: R = Et
XV: R = H



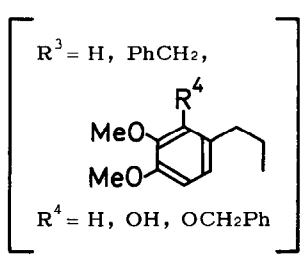
(–)-XVI



(+)-XVII



XVIII XIX



alcohol V [94%; $[\alpha]_D^{13}$ −2.5° (c 1.63, EtOH)]. The $Hg(OAc)_2$–EDTA oxidation (1% aq. AcOH, reflux, 1.5 hr) of the mixture V followed by column chromatography (alumina or silica gel, AcOEt–hexane) yielded the 6-piperidone VI as a diastereoisomeric mixture [55% yield; $[\alpha]_D^{18}$ −11.8° (c 2.00, EtOH); IR ($CHCl_3$): 3340 (OH), 1727 (ester CO), 1617 cm^{-1} (lactam CO)] and an oily substance, presumed to be a diastereoisomeric mixture of the cis- and the trans-2-piperidones VII [20% yield; $[\alpha]_D^{18}$ +15.1° (c 2.00, EtOH); IR ($CHCl_3$): 3350 (OH), 1726 (ester CO), 1611 cm^{-1} (lactam CO)]. The two piperidone structures, assigned in analogy with the similar oxidation products of structurally related systems[3,4] and simpler 3-alkylpiperidine derivatives,[10] were also substantiated by the following self-consistent reaction sequence.

On catalytic hydrogenolysis (Pd-C/H_2, EtOH–70% aq. $HClO_4$, 3.4–3.8 atm, 30–35°, 36 hr), the diastereoisomeric mixture of VI produced the lactam phenol (−)-VIII [91%; $[\alpha]_D^{20}$ −4.2° (c 2.00, EtOH)], which was then hydrolyzed (2 N aq. NaOH–EtOH, room temp., 30 hr) to the lactam acid (−)-IX [97%; $[\alpha]_D^{30}$ −0.2° (c 2.00, EtOH)]. Conversion of the cis-acid (−)-IX into the trans isomer was effected by thermal isomerization analoguous to the structurally parallel systems XVIII → XIX,[3,4,5,11] assumed[11] to proceed through an intramolecular acidolysis of the lactam bond. When heated at 180° for 1.5 hr, (−)-IX was transformed into the trans-acid (+)-X [mp 130–132°; $[\alpha]_D^{31}$ +72.0° (c 0.50, EtOH)] in 74% yield. Esterification (EtOH–HCl, room temp., 20 hr) of (+)-X and treatment of the resulting ester (+)-XI [96%; $[\alpha]_D^{31}$ +69.3° (c 0.50, EtOH)] with benzyl bromide (K_2CO_3, boiling acetone, 24 hr) provided the ether (+)-XII [98%; $[\alpha]_D^{33}$ +52.8° (c 0.50, EtOH)].[12]

The later part of the synthetic scheme was essentially the same as adopted recently for the racemic series.[1] Thus, the Bischler-Napieralski cyclization of (+)-XII was effected with $POCl_3$ (boiling toluene, 1.5 hr) and the resulting immonium salt XIII was reduced (Pt/H_2, EtOH, room temp., 1 atm, 40 min) to give the tricyclic amine (−)-XIV [73% overall yield from (+)-XII; mp 61.5–62.5°;[12] $[\alpha]_D^{25}$ −56.4° (c 0.44, EtOH); IR ($CHCl_3$): 2815, 2760 (trans-quinolizidine ring),[13] 1725 cm^{-1} (ester CO)]. Conversion of (−)-XIV into the amide (−)-XVI [71% overall yield; mp 152–154°; $[\alpha]_D^{17}$ −20.8° (c 0.50, EtOH)][12] was achieved through the amino acid XV[12] by alkaline hydrolysis (2 N aq. NaOH–EtOH, room temp., 20 hr, 82% yield) followed by the condensation with 3-benzyloxy-4-methoxyphenethylamine[14] (diethyl phosphorocyanidate,[15] Et_3N, $HCONMe_2$, room temp., 6 hr, 87% yield). Ring closure of the amide (−)-XVI ($POCl_3$, boiling toluene, 1.5 hr) furnished the base (+)-XVII [81%; $[\alpha]_D^{24}$ +45.6° (c 1.37, EtOH)], which was then debenzylated (10% aq. HCl–EtOH, reflux, 15 hr) to the desired phenolic base (+)-I [82%; mp 166–170° (sintered at 148°);[16] $[\alpha]_D^{16}$ +58.6° (c 0.50, MeOH)], identical [by IR (Nujol), UV (EtOH, 0.1 N aq. HCl, or 0.1 N aq. NaOH), and mass spectra] with natural desmethylpsychotrine[2] [mp 166–168°; $[\alpha]_D$ +67.9° (c 0.50, MeOH)]. Conformity of the synthetic base (+)-I to the racemic base (±)-I that was prepared recently[1] by a different stereospecific synthesis proved the stereospecificity of the synthetic operations proceeding from (+)-III to (+)-I via the intermediates IV–VI and VIII–XVII.

The present results have thus established the structure of the Alangium alkaloid desmethylpsychotrine[2] as 9-demethylpsychotrine [(+)-I]. Interestingly enough, the positions of the methoxyl and the hydroxyl groups in both the isoquinoline moieties in the compound are identical.

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16. The analysis pointed to the formula $C_{27}H_{34}N_2O_4 \cdot 2.5EtOH$.

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