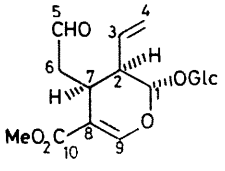
Stereoconservative Synthesis of Ipecac Alkaloids from Secologanin

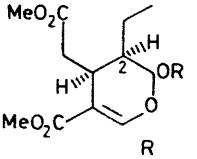
By RICHARD T. BROWN,* ANDREW G. LASHFORD, and SIMON B. PRATT
(*Department of Chemistry, The University, Manchester* M13 9PL)

Summary Methyl 3,4-dihydrosecoxyloganin (**2a**), readily obtained from secologanin (**1**), has been converted with retention of chirality at C-2 and C-7 into a piperidone (**5**) which acts as a general synthetic precursor for Ipecac alkaloids exemplified by deoxytubulosine (**8b**), cephaeline (**9b**), and emetine (**9c**).

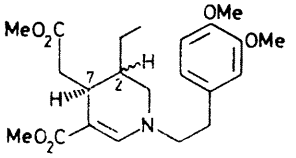
THE Ipecac alkaloids, *e.g.* (**8b**) and (**9b,c**), constitute a closely related group formed in the main by condensation of a dopamine or tryptamine with protoemetine (**6**), which itself is comprised of a dopamine residue and a C_9 unit derived from the monoterpene secologanin (**1**). Identical absolute configurations at C-2 and C-7† in (**6**) and (**1**) reflect the biosynthetic relationship. Because of the clinical importance of emetine (**9c**) in particular, the Ipecac alkaloids have been targets for several syntheses, which have involved problems in stereochemical control and resolution of racemic intermediates.[1] Provided chirality can be conserved at C-2 and C-7 many difficulties can be avoided by using as starting material the natural precursor secologanin, and we now report its conversion into representative Ipecac alkaloids.



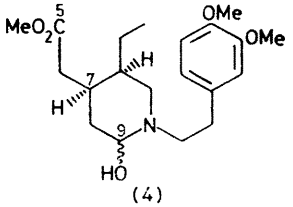
(1)



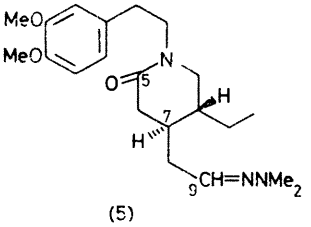
(2) a; Glc
b; Glc(OAc)$_4$
c; H



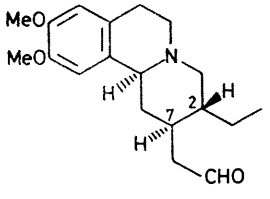
(3) a; α
b; β



(4)



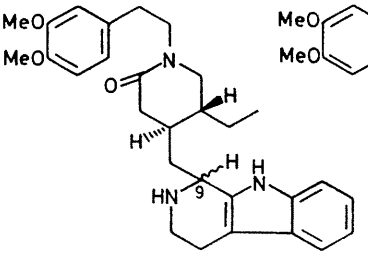
(5)

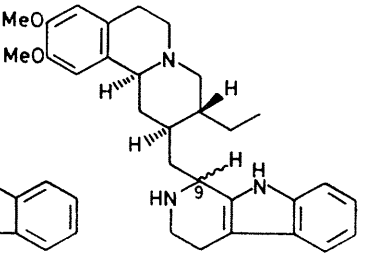


(6)

Methyl 3,4-dihydrosecoxyloganin tetra-acetate‡ (**2b**), m.p. 131—132 °C, $[\alpha]_D^{25}$ — 114° (MeOH), was prepared from secologanin by acetylation, oxidation, methylation, and catalytic hydrogenation,[2] in 63% isolated yield. Zemplen deacetylation and removal of the sugar with β-glucosidase in pH 5 buffer afforded the aglycone (**2c**) which was treated with 2-(3,4-dimethoxyphenyl)ethylamine and $NaCNBH_3$ in methanol for 15 min to give the oily tetrahydropyridine (**3a**), $[\alpha]_D^{25}$ +33°, as the major product (42% overall isolated yield). That this procedure did not result in any significant inversion was established by equilibrating the aglycone C-2 isomers *via* the ring-opened form by treatment with NaOMe in methanol for several hours. Upon repeating the reductive amination the major product (4:1 by t.l.c. and h.p.l.c.) was now a less polar epimer (**3b**), due to inversion of the ethyl group in the aglycone giving the preferred *trans* diequatorial orientation of the C-2 and C-7 substituents. Alternatively, the tetrahydropyridine (**3a**) could be obtained in a 'one-pot' procedure[3] but in lower yield.

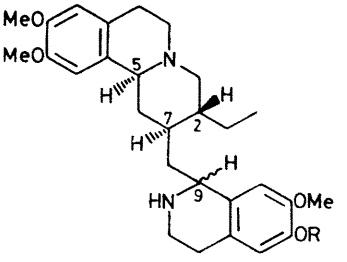
Selective hydrolysis and decarboxylation of (**3a**) to the carbinolamine (**4**) was achieved with 1% HCl in refluxing aqueous methanol for 1 h. Under these conditions there was neither appreciable hydrolysis of the C-5 ester, nor Pictet–Spengler cyclisation of C-9 to the aromatic ring. After basifying with triethylamine, refluxing with an excess of *NN*-dimethylhydrazine opened the carbinolamine ring to form a hydrazone from the C-9 aldehyde, followed by lactam formation from the liberated secondary amine and the C-5 ester to afford the piperidone (**5**), $[\alpha]_D^{25}$ +47° (MeOH), in 85% yield. The structure of the product was indicated *inter alia* by a lactam carbonyl i.r. absorption at 1627 cm^{-1} and n.m.r. signals for an imine proton triplet at τ 3·42 and a six-proton singlet due to NMe_2 at τ 7·31.





9-H
(7) a; α
b; β

9-H
(8) a; α
b; β



9-H R
(9) a; α H
b; β H
c; β Me

From the key intermediate (**5**) various alkaloids could be obtained by two alternative routes. Bischler–Napieralski cyclisation with $POCl_3$ in toluene, subsequent reduction with $NaBH_4$, and hydrolysis of the *NN*-dimethylhydrazone with aqueous $Cu(OAc)_2$ by Corey's method[4] afforded the unstable protoemetine (**6**). Its identity was established by Pictet–Spengler condensation in aqueous acetic acid with

† Monoterpenoid numbering is used for all structures.

‡ Satisfactory analytical and spectroscopic data were obtained for all new compounds.

2-(3-hydroxy-4-methoxyphenyl)ethylamine to give cephaeline (**9b**), identical with an authentic sample, together with a smaller amount of isocephaeline (**9a**). Cephaeline can be converted into emetine (**9c**) by diazomethane.[5] A similar condensation with tryptamine gave deoxytubulosine (**8b**), and deoxyisotubulosine (**8a**), identical with authentic samples.

Alternatively, the *NN*-dimethylhydrazone group in (**5**) was hydrolysed first and the aldehyde condensed with tryptamine to give two epimers (**7a,b**) in a ratio of *ca.* 3 : 1. Since the major isomer, $[\alpha]_D^{25}$ +60° (MeOH), showed a negative Cotton effect in the 260—300 nm region of the c.d. spectrum ($[\theta]_{294}$ $-2{\cdot}14 \times 10^3$ deg cm^{-2} dmol^{-1}), it must have the 9-H $\beta(R)$ configuration corresponding to (**7b**); likewise the minor isomer, $[\alpha]_D^{25}$ +20° (MeOH), had a positive Cotton effect ($[\theta]_{288}$ $+2{\cdot}54 \times 10^3$) and is (**7a**).[6] Vincoside and strictosidine, an analogous epimeric pair of established stereochemistry[7,8] formed from secologanin and tryptamine show similar correlations and constitute good models for these assignments. Bischler–Napieralski cyclisation and reduction of (**7b**) afforded deoxytubulosine (**8b**) and incidentally corroborated the C-9 chirality assigned from molecular rotation differences.[9] The yield of (**8a**) and (**8b**) from (**5**) by this second route was 42%.

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