

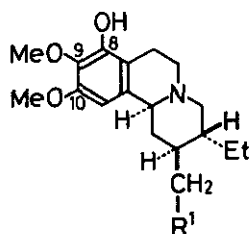
A NEW SYNTHETIC APPROACH TO BENZOQUINOLIZIDINE ALKALOIDS
ISOLATED FROM ALANGIUM LAMARCKII

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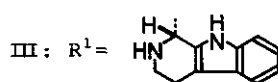
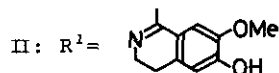
Abstract—— New general synthetic routes from 3-acetylpyridine (IV) to some ipecac and Alangium alkaloids possessing the 9,10-dimethoxy- and 8-hydroxy-9,10-dimethoxybenzo[a]quinolizidine skeletons have been established.

It has been known that Alangium lamarckii Thwaites (family Alangiaceae) contains a number of benzoquinolizidine alkaloids structurally related to the ipecac bases.¹ With a view to synthesizing these alkaloids, Fujii and co-workers invented the "lactim ether method" for the racemic series² and the "cincholoipon-incorporating method" for the chiral series³ and succeeded in the syntheses and structure determination of some Alangium alkaloids,¹ e. g., ankorine (I),^{4,5} alangicine (II),^{6,7} and alangimarckine (III).^{8,9} Now we wish to report the results of our further efforts in this area, which have established new general synthetic routes from 3-acetylpyridine (IV) to some ipecac and Alangium alkaloids having the 9,10-dimethoxy- and 8-hydroxy-9,10-dimethoxybenzo[a]quinolizidine skeletons.

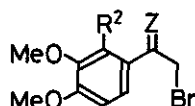
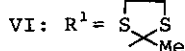
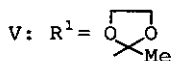
The lactam XVIa, prepared from 3-(1,1-ethylenedioxyethyl)pyridine (V) and 3,4-dimethoxyphenacyl bromide (VIIa) through the intermediates IXa, XIIa, XIIIa, and XIVa or from V and 3,4-dimethoxyphenethyl bromide (VIIIa) through the intermediates Xa, XXVIa, and XVa according to the reported procedure,¹⁰ was converted into XVIIa¹¹ in 82% yield by means of Wolff-Kishner reduction [80% aq. $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$, KOH, $(\text{CH}_2\text{OH})_2$, 120°C, 1 h, then 190–195°C, 3 h]. The same compound XVIIa was also obtained in 84% yield by desulfurization (Raney Ni, boiling 70% aq. EtOH, 3 h) of XXVIIa^{10a} available from an initial quaternization of 3-(1,1-ethylenedithioethyl)pyridine (VI) with VIIIa and subsequent alkaline ferricyanide oxidation of the pyridinium salt XIa. Sulfenylation¹² of XVIIa was effected by the use of diphenyl disulfide in the presence of lithium diisopropylamide and hexamethylphosphoramide (THF, -78°C, 2 h),



I: $R^1 = \text{CH}_2\text{OH}$

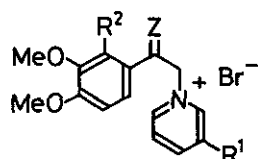


IV: $R^1 = \text{COMe}$



VIIa,b: $Z = \text{O}$

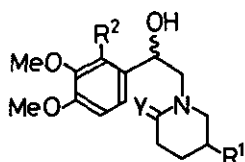
VIIIa,b: $Z = \text{H}_2$



IXa,b: $Z = \text{O}$, $R^1 =$

Xa,b: $Z = \text{H}_2$, $R^1 =$

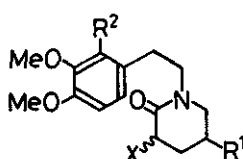
XIa,b: $Z = \text{H}_2$, $R^1 =$



XIIa,b: $Y = \text{H}_2$, $R^1 =$

XIIIa,b: $Y = \text{H}_2$, $R^1 = \text{COMe}$

XIVa,b: $Y = \text{O}$, $R^1 = \text{COMe}$



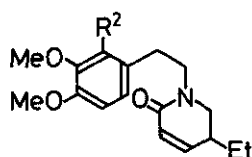
XVa,c: $X = \text{H}$, $R^1 =$

XVIa,c: $X = \text{H}$, $R^1 = \text{COMe}$

XVIIa,b,c: $X = \text{H}$, $R^1 = \text{Et}$

XVIIIa,b: $X = \text{SPh}$, $R^1 = \text{Et}$

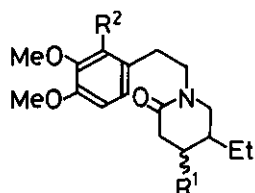
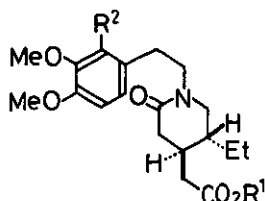
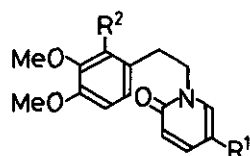
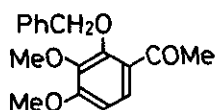
XIXa,b: $X =$



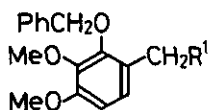
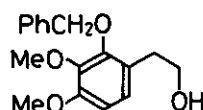
XXa,b

a: $R^2 = \text{H}$, b: $R^2 = \text{OCH}_2\text{Ph}$, c: $R^2 = \text{OH}$

affording XVIIIa¹³ as a diastereomeric mixture in 91% yield. Oxidation of XVIIIa with sodium metaperiodate (aq. MeOH, room temp., 18 h) and dehydrosulfenylation (CaCO_3 , boiling toluene, 1 h) of the resulting sulfoxide XIXa provided the α,β -unsaturated lactam XXa¹⁴ in 91% yield from XVIIIa. The conversion of XVIIa to XXa via XVIIIa and XIXa by a similar method has also been reported by Takano *et al.*¹³ The Michael addition of diethyl malonate to XXa was carried out according to the previously reported procedure,¹⁵ giving XXIa in 69% yield. De-ethoxycarbonylation of

XXIIa,b: $R^1 = \text{CH}(\text{CO}_2\text{Et})_2$ XXIIa,b: $R^1 = \text{CH}_2\text{CO}_2\text{Et}$ XXIIa,b: $R^1 = \text{CH}(\text{CO}_2\text{H})_2$ XXIVa,b: $R^1 = \text{H}$ XXIVa,b: $R^1 = \text{Et}$ XXVIa,b: $R^1 = \text{O} \begin{array}{c} \diagup \diagdown \\ \text{Me} \end{array}$ XXVIIa,b: $R^1 = \text{S} \begin{array}{c} \diagup \diagdown \\ \text{Me} \end{array}$ a: $R^2 = \text{H}$, b: $R^2 = \text{OCH}_2\text{Ph}$ 

XXVIII

XXIX: $R^1 = \text{CN} \begin{array}{c} \diagup \diagdown \\ \text{O} \end{array}$ XXX: $R^1 = \text{CO}_2\text{H}$ XXXI: $R^1 = \text{CO}_2\text{Et}$ 

XXXII

the adduct XXIIa by heating with NaCl in moist dimethyl sulfoxide^{13,16} (160–165°C, 8 h) furnished XXIIa (85% yield), which was shown to be a 9 : 91 mixture of the *cis* and the *trans* isomers by means of ¹³C nmr spectroscopy. The lactam acid (±)-XXIVa was then obtained in 84% yield by alkaline hydrolysis (NaOH, aq. EtOH, room temp., 24 h) of the mixture XXIIa and fractional recrystallization of products from 50% aq. acetone. The structure and the *trans* stereochemistry of (±)-XXIVa were confirmed by its identity with an authentic sample, which was prepared from XXa via XXIIa and XXIIa by the method of Battersby and Turner.¹⁴

In view of the previous conversions of (±)-XXIVa into (–)-emetine,¹⁴ (+)-O-methylpsychotrine,¹⁴ (±)-cephaeline,¹⁷ (±)-tubulosine,¹⁸ (±)-deoxytubulosine,¹⁹ (±)-protoemetinol,¹⁴ (±)-protoemetine,¹⁷ and (±)-emetamine²⁰ through the ethyl ester (±)-XXVa, which is also obtainable by the "lactim ether method",¹⁵ the present synthesis of (±)-XXIVa constitutes formal new syntheses of these ipecac and/or Alangium alkaloids.

On the other hand, a parallel synthesis of ($\pm$)-XXVb started with quaternization of V with 2-benzyloxy-3,4-dimethoxyphenacyl bromide (VIIb). The resulting salt IXb [mp 169–169.5°C (dec.)]²¹ was reduced with hydrogen and Adams catalyst (50% aq. EtOH, 1 atm, room temp., 18 h) and then with NaBH₄ to afford a diastereomeric mixture of the piperidinoethanol XIIb in 81% yield. Deketalization of XIIb with 1 N hydrochloric acid (40°C, 2 h) gave the ketone XIIIb in 98% yield. The Hg(OAc)₂-EDTA oxidation of XIIIb was carried out according to the previously reported standard procedure,¹¹ and the 6-piperidone XIVb was obtained in 82% yield as a diastereomeric mixture. Catalytic hydrogenolysis (10% Pd-C/H₂, EtOH-70% aq. HClO₄, 1 atm, room temp., 6 h) of the mixture XIVb and Wolff-Kishner reduction of the resulting compound XVic (89% yield; mp 123–124°C) provided the lactam phenol XVIc (84% yield; mp 119.5–120.5°C).

Alternative syntheses of the lactam phenols XVIc and XVIIc were also tried through routes utilizing alkaline ferricyanide oxidation. For this purpose, we first synthesized 2-benzyloxy-3,4-dimethoxyphenethyl bromide (VIIIb) from 2-benzyloxy-3,4-dimethoxyacetophenone (XXVIII).²² Treatment of XXVIII with sulfur and morpholine (80°C, 1 h, then refluxing, 4 h) afforded the thiomorpholide XXIX (62% yield; mp 110–111°C), which was hydrolyzed (KOH, boiling aq. EtOH, 9 h) to furnish the acid XXX (mp 113–114°C) in 93% yield. When esterified with ethanolic HCl (room temp., 20 h), XXX produced the ester XXXI (97% yield), and subsequent LiAlH₄ reduction of XXXI in ether (room temp., 4 h) gave the alcohol XXXII in 97% yield. The desired bromide VIIIb (mp 45.5–47°C) was obtained from XXXII in 88% yield via the agency of the N-bromosuccinimide/triphenylphosphine reagent²³ (benzene, room temp., 2 h).

The pyridinium salts Xb and XIb were then prepared from V and VI, respectively, by quaternization with VIIIb in benzene. The alkaline ferricyanide oxidations of Xb and XIb were effected under the standard conditions described in the literature,¹¹ producing the 6-oxidation products XXVIb (83% yield from V) and XXVIIb (42% yield from VI; mp 72–74°C),²⁴ respectively. On catalytic hydrogenation (Raney Ni/H₂, 1 atm, 35°C, 13 h) and subsequent acid hydrolysis (HCl, boiling aq. EtOH, 2 h), the 6-pyridone XXVIb was converted into the lactam phenol XVIc in 95% yield through XVc (mp 99–101°C), whereas desulfurization (Raney Ni, boiling 70% aq. EtOH, 6 h) of XXVIIb followed by catalytic hydrogenation (Raney Ni/H₂, 1 atm, room temp., 3.5 h) gave the 3-ethyl-6-piperidone XVIIc in 82% yield.

The lactam phenol XVIc thus obtained was then benzylated (PhCH₂Br, K₂CO₃, boiling acetone, 24 h) to furnish the benzyl ether XVIIb (96% yield), which was converted

into the trans-lactam ester (±)-XXVb in 43% overall yield from XVIIb through the intermediates XVIIIb, XIXb, XXb, XXIb, XXIIb (cis:trans = 11:89), and (±)-XXIVb (mp 126–128°C) in a manner similar to that described above for the a-series. The trans-lactam acid (±)-XXIVb was also prepared by a route via alkaline hydrolysis (NaOH, aq. EtOH, 50°C, 20 h) of XXIb in 73% yield (from XXb) and decarboxylation (boiling 60% aq. AcOH, 6 h) of the resulting dicarboxylic acid XXIIIb in 74% yield.

The lactam ester (±)-XXVb thus synthesized was identical with an authentic sample prepared by Fujii *et al.*⁴ according to the "lactim ether method". Since (±)-XXVb has already been converted into (±)-ankorine (I),⁴ (±)-alangicine (II),⁶ and (±)-alangimarckine (III),⁸ the present synthesis of (±)-XXVb represents formal new syntheses of these three Alangium alkaloids. In addition, since the starting material V or VI is easily obtainable from 3-acetylpyridine (IV),²⁵ the method used for the above syntheses may be called "3-acetylpyridine method" for convenience of ready reference.

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