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[â]quinolizidine skeletons have been established.

It has been known that Alangium lamarckii Thwaites (family Alangiacese) 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 alanginamarckine (III)6,8. 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[â]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. NH2NH2•H2O, KOH, (CH2OH)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 XXVIIa12 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),

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affording XVIIIa as a diastereomeric mixture in 91% yield. Oxidation of XVIIIa with sodium metaperiodate (aq. MeOH, room temp., 18 h) and dehydrosulfenylation (CaCO₃, boiling toluene, 1 h) of the resulting sulfoxide XIXa provided the α,β-unsaturated lactam XXa 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. The Michael addition of diethyl malonate to XXa was carried out according to the previously reported procedure, giving XXIa in 69% yield. De-ethoxycarbonylation of
the adduct XXIa by heating with NaCl in moist dimethyl sulfoxide\textsuperscript{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 \textsuperscript{13}C nmr spectroscopy. The lactan acid (t)-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 (t)-XXIVa were confirmed by its identity with an authentic sample, which was prepared from XXa via XXIa and XXIIIa by the method of Battersby and Turner.\textsuperscript{14} In view of the previous conversions of (t)-XXIVa into (-)-emetine,\textsuperscript{14} (+)-O-methyl-

psychotrine,\textsuperscript{16} (t)-cephaline,\textsuperscript{17} (t)-tubulosine,\textsuperscript{18} (t)-deoxytubulosine,\textsuperscript{19} (t)-protoemetinol,\textsuperscript{14} (t)-protoemetine,\textsuperscript{17} and (t)-emetamine\textsuperscript{20} through the ethyl ester (t)-XXVa, which is also obtainable by the "lactim ether method",\textsuperscript{15} the present synthesis of (t)-XXIVa constitutes formal new syntheses of these ipecac and/or \textit{Alangium} alkaloids.
On the other hand, a parallel synthesis of (±)-XXVb started with quaternization of V with 2-benzyloxy-3,4-dimethoxyphenacyl bromide (VIIb). The resulting salt IXb (mp 169-169.5°C (dec.))\textsuperscript{21} was reduced with hydrogen and Adams catalyst (50% aq. EtOH, 1 atm, room temp., 18 h) and then with NaBH\textsubscript{4} 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)\textsubscript{2}-EDTA oxidation of XIIIb was carried out according to the previously reported standard procedure,\textsuperscript{11} and the 6-piperidone XIVb was obtained in 82% yield as a diastereomeric mixture. Catalytic hydrogenolysis (10% Pd-C/H\textsubscript{2}, EtOH-70% aq. HClO\textsubscript{4}, 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 XVIIc (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).\textsuperscript{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 LiAlH\textsubscript{4} 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 reagent\textsuperscript{23} (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,\textsuperscript{11} producing the 6-oxidation products XXVb (83% yield from V) and XXVIIb (42% yield from VI; mp 72-74°C),\textsuperscript{24} respectively. On catalytic hydrogenation (Raney Ni/H\textsubscript{2}, 1 atm, 35°C, 13 h) and subsequent acid hydrolysis (HCl, boiling aq. EtOH, 2 h), the 6-pyridone XXVb 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/H\textsubscript{2}, 1 atm, room temp., 3.5 h) gave the 3-ethyl-6-piperidone XVIIc in 82% yield.

The lactam phenol XVIIc thus obtained was then benzylated (PhCH\textsubscript{2}Br, K\textsubscript{2}CO\textsubscript{3}, boiling acetone, 24 h) to furnish the benzyl ether XVIIb (96% yield), which was converted
into the trans-lactam ester (t)-XXVb in 43% overall yield from XVIIb through the intermediates XVIIIb, XIXb, XXb, XXlb, XXlb (cis: trans = 11: 89), and (t)-XXIVb (mp 126-128°C) in a manner similar to that described above for the a-series. The trans-lactam acid (t)-XXIVb was also prepared by a route via alkaline hydrolysis (NaOH, aq. EtOH, 50°C, 20 h) of XXlb 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 (t)-XXVb thus synthesized was identical with an authentic sample prepared by Fujii et al., according to the "lactim ether method". Since (t)-XXVb has already been converted into (t)-ankorine (I), (t)-alangicinc (II), (t)-alangimarckine (III), the present synthesis of (t)-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), the method used for the above syntheses may be called "3-acetylpyridine method" for convenience of ready reference.

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21. Satisfactory spectral data and/or elemental analyses have been obtained for all new compounds described herein.
24. The elemental analysis suggested that this sample is a hemihydrate.

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