A NEW SYNTHETIC APPROACH TO BENZOQUINOLIZIDINE ALKALOIDS ISOLATED FROM ALANGIUM LAMARCKII

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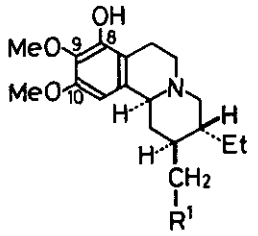
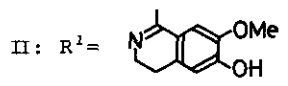
Abstract —— New general synthetic routes from 3-acetylpyridine (IV) to some ipecac and Alangium alkaloids possessing the 9,10-dimethoxy- and 8-hydroxy-9,10-dimethoxybenzo[a]quinolizidine skeletons have been established.

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 series[2] and the "cincholoipon-incorporating method" for the chiral series[3] 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.

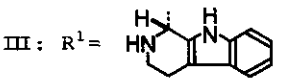
The lactam XVIa, prepared from 3-(1,1-ethylenedioxyethyl)pyridine (V) and 3,4-dimethoxyphenacyl bromide (VIIa) through the intermediates IXa, XIIa, XIIIa, and XIVa or from V and 3,4-dimethoxyphenethyl bromide (VIIIa) through the intermediates Xa, XXVIa, and XVa according to the reported procedure,[10] was converted into XVIIa[11] in 82% yield by means of Wolff-Kishner reduction [80% aq. $NH_2NH_2 \cdot H_2O$, KOH, $(CH_2OH)_2$, 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. Sulfenylation[12] of XVIIa was effected by the use of diphenyl disulfide in the presence of lithium diisopropylamide and hexamethylphosphoramide (THF, −78°C, 2 h),



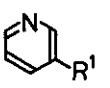
I: R^1= CH_2OH



II: R^1=



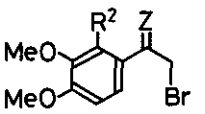
III: R^1=



IV: R^1= COMe

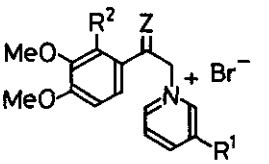
V: R^1=

VI: R^1=

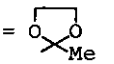


VIIa,b: Z = O

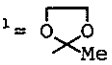
VIIIa,b: Z = H_2



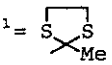
IXa,b: Z = O, R^1=

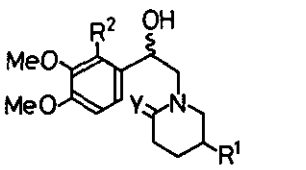


Xa,b: Z = H_2, R^1=



XIa,b: Z = H_2, R^1=

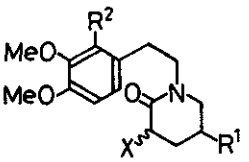




XIIa,b: Y = H_2, R^1=

XIIIa,b: Y = H_2, R^1= COMe

XIVa,b: Y = O, R^1= COMe



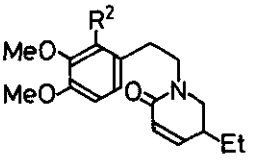
XVa,c: X = H, R^1=

XVIa,c: X = H, R^1= COMe

XVIIa,b,c: X = H, R^1= Et

XVIIIa,b: X = SPh, R^1= Et

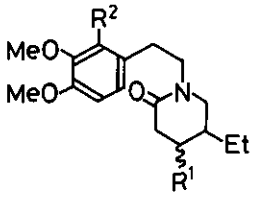
XIXa,b: X = SPh, R^1= Et
O



XXa,b

a: R^2= H, b: R^2= OCH_2Ph, c: R^2= OH

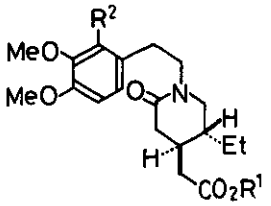
affording XVIIIa[13] as a diastereomeric mixture in 91% yield. Oxidation of XVIIIa with sodium metaperiodate (aq. MeOH, room temp., 18 h) and dehydrosulfenylation ($CaCO_3$, boiling toluene, 1 h) of the resulting sulfoxide XIXa provided the α,β-unsaturated lactam XXa[14] in 91% yield from XVIIIa. The 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



XXIa,b: R^1= $CH(CO_2Et)_2$

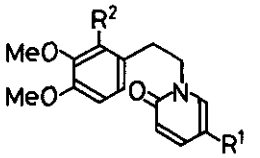
XXIIa,b: R^1= CH_2CO_2Et

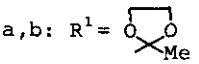
XXIIIa,b: R^1= $CH(CO_2H)_2$

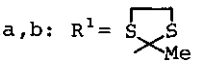


XXIVa,b: R^1= H

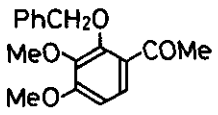
XXVa,b: R^1= Et



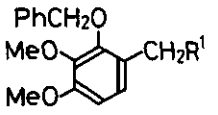
XXVIa,b: R^1= 

XXVIIa,b: R^1= 

a: R^2= H, b: R^2= OCH_2Ph



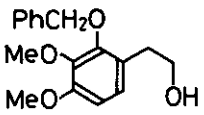
XXVIII



XXIX: R^1= 

XXX: R^1= CO_2H

XXXI: R^1= CO_2Et



XXXII

the adduct XXIa 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 ^{13}C 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* XXIa and XXIIIa 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 (±)-emetamine[20] 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 (±)-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 $NaBH_4$ 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 $Hg(OAc)_2$–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/H_2, EtOH–70% aq. $HClO_4$, 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).[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 $LiAlH_4$ 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[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,[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/H_2, 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/H_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 ($PhCH_2Br$, K_2CO_3, 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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