Tetrahedron Letters No. 24, pp 1965 - 1968, 1975. Pergamon Press. Printed in Great Britain.

# ABSOLUTE CONFIGURATION OF ANKORINE: CHEMICAL CORRELATION WITH CINCHONA ALKALOIDS

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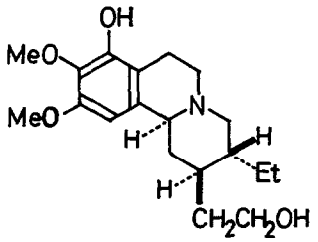
(Received in Japan 31 March 1975; received in UK for publication 1 May 1975)

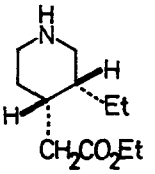
In quite a recent communication[1] from this laboratory, we have revealed that the Alangium lamarckii alkaloid ankorine[2,3] has the structure and relative stereochemistry as shown in formula I. For establishment of its absolute configuration, this knowledge allows a stereoselective synthesis starting with a substance of known absolute stereochemistry to be designed. Our previous success[4] in synthetic incorporation of cincholoipon ethyl ester (II) into the ipecac alkaloids is a valid model for the preparations of analogous alkaloids from the major cinchona alkaloids (III). We have now extended the scope of the synthetic incorporation to include ankorine.

Condensation of the optically active cis-ester (II),[5] prepared from commercially available cinchonine (IV) in 31% overall yield according to the classical degradation procedure,[5a,6] with 2-benzyloxy-3,4-dimethoxyphenacyl bromide[1] in benzene solution containing anhydrous $K_2CO_3$ gave amino ketone V [91% yield; $[\alpha]_D^{20}$ −6° (c 3, EtOH)],[7] which was reduced ($NaBH_4$, EtOH, 0°, 4 hr) to afford a diastereoisomeric mixture of amino alcohol VI [87%; $[\alpha]_D^{17}$ −5° (c 2, EtOH)]. Oxidation of the mixture (VI) with $Hg(OAc)_2$ — EDTA (1% aq. AcOH, reflux, 1.5 hr)[8,9] and column chromatographic separation (silica gel, $Et_2O$ — EtOH) of the products furnished 6-piperidone VII as a diastereoisomeric mixture [57% yield; $[\alpha]_D^{16}$ −5° (c 1, EtOH); IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$ : 3320 (OH), 1726 (ester CO), 1613 (lactam CO)] and an oily substance presumed to be a diastereoisomeric mixture of 2-piperidone VIII (19%). The assignments of both piperidone structures were based on analogy of the $Hg(OAc)_2$ — EDTA oxidation of a structurally related system[4] as well as simpler 3-alkylpiperidine derivatives[10] and on the following self-consistent reaction sequence.

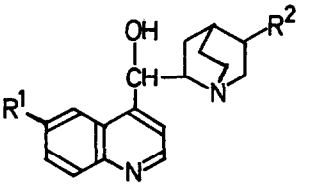
Hydrogenolysis of the diastereoisomeric mixture of VII ($Pd-C/H_2$, EtOH — 70% aq. $HClO_4$, 4.2 atm, 20°, 8 hr) yielded lactam phenol IX [88%; $[\alpha]_D^{17}$ −10.5° (c 1.5, EtOH)], which was then benzyl-



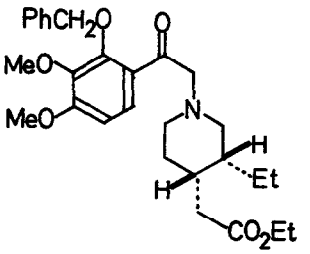
I



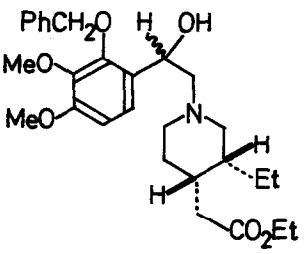
II



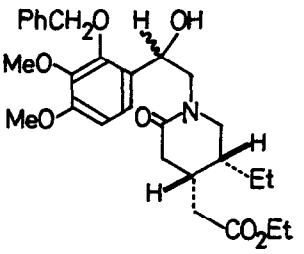
III, $R^1$ = H or MeO; $R^2$ = vinyl or Et
IV, $R^1$ = H; $R^2$ = vinyl



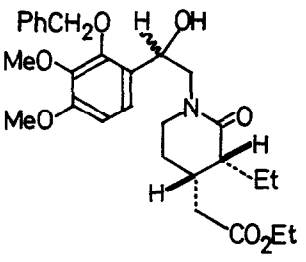
V



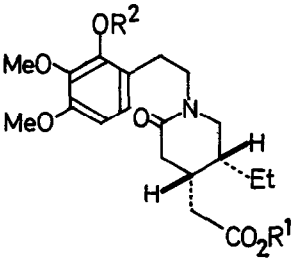
VI



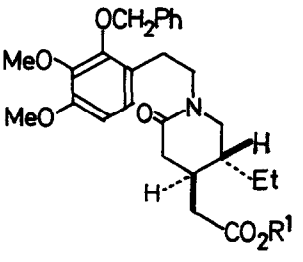
VII



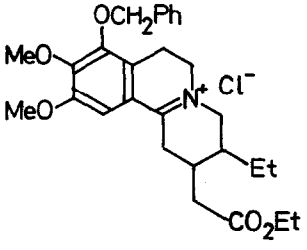
VIII



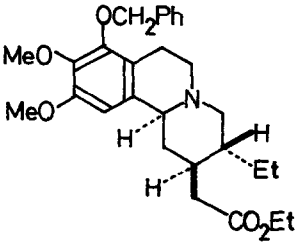
IX, $R^1$ = Et; $R^2$ = H
X, $R^1$ = Et; $R^2$ = $PhCH_2$
XI, $R^1$ = H; $R^2$ = $PhCH_2$



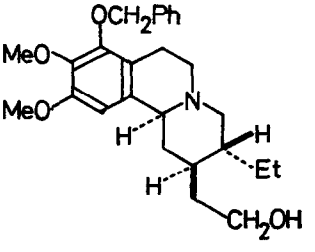
XII, $R^1$ = H
XIII, $R^1$ = Et



XIV



XV



XVI

ated ($PhCH_2Br$, $K_2CO_3$, refluxing acetone, 15 hr) to ether X. On alkaline hydrolysis (1 N aq. NaOH-EtOH, 40°, 10 hr), the O-benzyl derivative (X) provided cis-acid XI [99% overall yield from IX; mp 74–75°; $[\alpha]_D^{17}$ +0.9° (c 1, EtOH); IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$ : 1710 ($CO_2H$), 1597 (lactam CO)]. Thermal isomerization of the lactam acid (XI) to the trans isomer was carried out at 180° for 80 min as in the case of model compounds,[4,11] giving a hardly separable 63 : 37 mixture (90% yield; mp 118–119°)[12] of the trans (XII) and the cis isomer (XI). This mixture was then esterified (HCl — EtOH, room temperature, 12 hr), and the resulting mixture (95% yield) of lactam esters XIII and X was cyclized ($POCl_3$, benzene, reflux, 2.5 hr) to a mixture of trans- and cis-XIV. Catalytic hydrogenation of the quaternary salt (XIV) ($PtO_2$, EtOH, 1 atm, 20°, 2.5 hr) and column chromatographic purification of the basic product (silica gel, hexane — AcOEt) furnished tricycle XV as an unstable oil [10% overall yield based on the trans-acid (XII); $[\alpha]_D^{16}$ −16° (c 1.6, EtOH)]. The structure and stereochemistry of this base as expressed in XV were confirmed by its IR and NMR spectra and thin-layer chromatographic behavior identical with those of authentic (±)-XV.[1]

Reduction of tricyclic ester XV to alcohol XVI was effected with $LiAlH_4$ in refluxing ether for 4 hr. Debenzylation of XVI by hydrogenolysis (Pd-C/$H_2$, EtOH, 1 atm, 20°, 2 hr) led to the ultimate compound (I) [64% overall yield from XV; mp 176–177°; $[\alpha]_D^{16}$ −58° ± 1° (c 0.23, $CHCl_3$)], which was identical [by mixed melting-point test and comparison of UV (EtOH or 0.1 N aq. NaOH), IR (KBr or $CHCl_3$), NMR ($CDCl_3$), and mass spectra, chromatographic behavior, and specific rotation] with a natural sample of ankorine [mp 175–177°; $[\alpha]_D^{16}$ −54° ± 2° (c 0.18, $CHCl_3$)] kindly provided by Professor Battersby.[3]

The above chemical correlation, along with the results previously described,[1] defines the absolute configuration of all the asymmetric centers in ankorine; one and the same stereoformula as I is a complete expression for this phenolic alkaloid. These stereochemical relationships correspond to those in the 8-deoxy relatives, e. g., emetine, which also occur in A. lamarckii.[13] Therefore, the same may be applicable to the absolute stereochemistry in the benzoquinolizidine moiety of yet other phenolic A. lamarckii alkaloids, alangicine[14] and alangimarckine.[3]

Acknowledgment —— The authors wish to thank Professor A. R. Battersby and Dr. R. S. Kapil (Cambridge) for the generous gift of ankorine which made this work possible. Thanks are also due to Professor S. Sugasawa (Tokyo) and Professor Y. Ban (Sapporo) for their interest and encouragement.

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