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TRANSFORMATION OF EPIPACHYSANDRINE-A INTO PACHYSTERMINE-A AND -B

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Pachystermine-A (I) and -B (II), isolated from Pachysandra terminalis SIEB. et ZUCC.(Buxaceae), are unique in that they carry a β-lactam ring system in the molecule[1]. These alkaloids have now been synthesized starting from epipachysandrine-A (III), a minor alkaloid present in the same source[2].

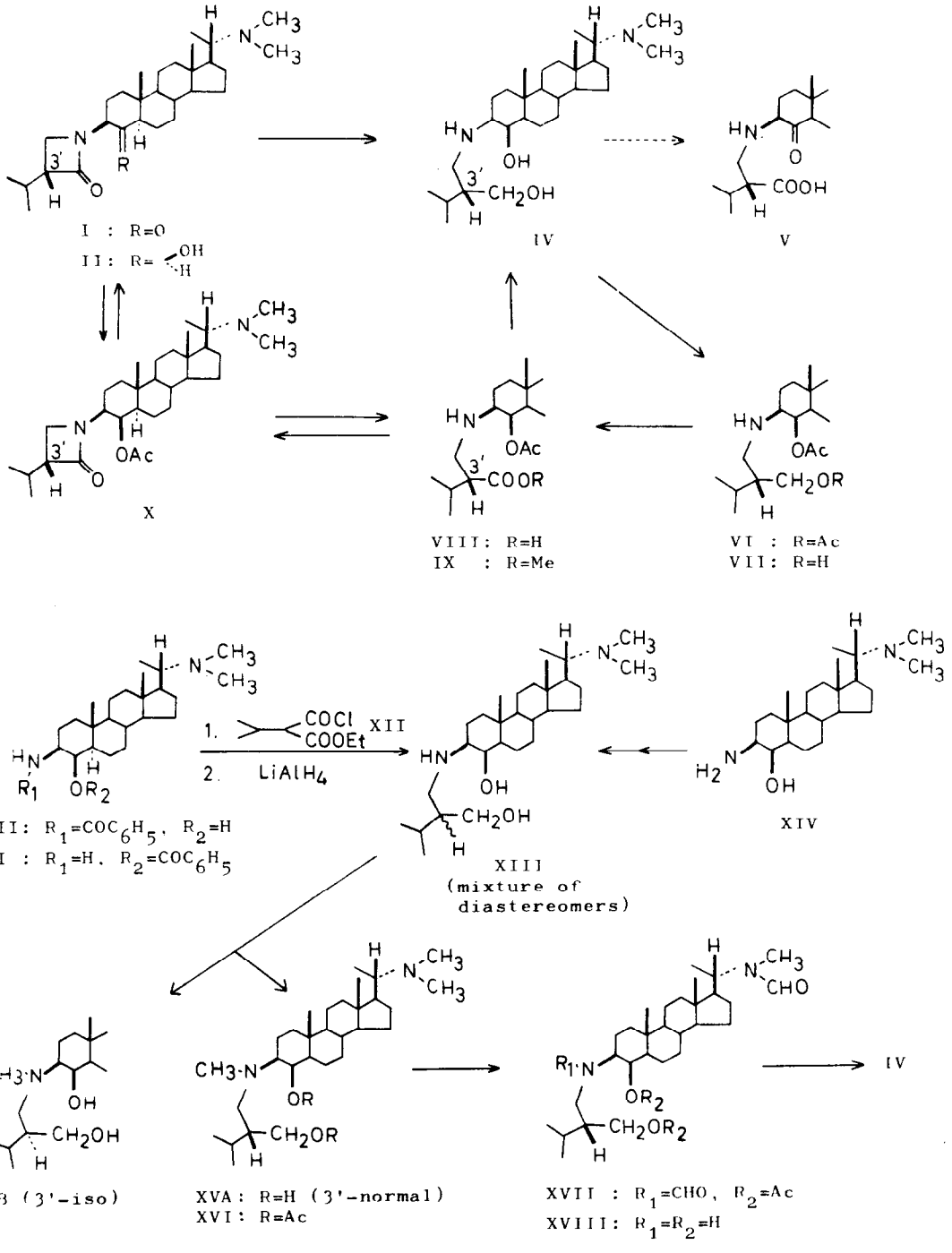
For this synthesis a possible route is the conversion of epipachysandrine -A (III) through pachystermine-diol (IV) to an amino-acid (VIII), which in turn is expected to give the β-lactam on cyclization. Since pachystermine-diol (IV) is readily obtained by $LiAlH_4$ reduction of pachystermine-A (I)[1], our effort was first made on the transformation of IV into I and II.

Initial attempts at oxidizing the diol (IV) to a keto-acid (V) with CrO_3 were unsatisfactory, leading only to an unseparable mixture in poor yield. An alternative approach was then undertaken as outlined in Chart 1.

Acetylation of IV with Ac_2O-AcOH in the presence of p-TsOH gave an O,O-diacetate (VI), $C_{33}H_{58}O_4N_2$*, m.p. 131-134°*, $[\alpha]_D$ +6°*. Partial hydrolysis of VI proceeded smoothly by heating with AcOH-15% aq.HCl (1:1) to afford a mono-acetate (VII), $C_{31}H_{56}O_3N_2$, m.p. 165-168°, $[\alpha]_D$ -4°, IR* 1726 cm^{-1}; NMR* 4.73 (1H, m., -CH(OAc)), 6.32 (2H, m., $-CH_2OH$), 7.17 (2H, m., NH-CH_2-), 7.83 ($N(CH_3)_2$), 7.91 (OAc), 9.07, 9.36 (two tert.CH_3), 9.09 (d., $-CH(CH_3)_2$), 9.12 τ (d., sec. CH_3). Oxidation of the latter with CrO_3-H_2SO_4-AcOH[3] yielded the expected amino acid (VIII), IR 3300 and 1580 cm^{-1}, in almost quantitative yield, whose methyl ester (IX), $C_{32}H_{56}O_4N_2$, showed m.p. 186-188°, $[\alpha]_D$ +2°.

On the other hand, acid hydrolysis of pachystermine-B acetate (X) afforded an amino-acid (VIII), which on treatment with CH_2N_2 gave rise to a methyl ester (IX), $C_{32}H_{56}O_4N_2$, m.p. 188-190°, $[\alpha]_D$ +6°. Since the $LiAlH_4$ reduction of IX gave only pachystermine-diol (IV) and no trace of 3'-iso compound[1], it is

Chart 1.


I : R=O
II: R=
IV
V
X
VIII: R=H
IX : R=Me
VI : R=Ac
VII: R=H
1. COCl COOEt XII
2. LiAlH4
III: R1=COC6H5, R2=H
XI : R1=H, R2=COC6H5
XIII
(mixture of
diastereomers)
XIV
XVB (3'-iso)
XVA: R=H (3'-normal)
XVI: R=Ac
XVII : R1=CHO, R2=Ac
XVIII: R1=R2=H
IV

evident that the configuration of 3'-position remained unchanged during the acid hydrolysis, in contrast to the result observed in alkaline hydrolysis which gave a mixture of 3'-epimeric pair.

The two methyl esters (IX) described above were proved to be identical with each other by IR comparison (KBr), thus indicating the 3'-normal stereochemistry in the amino-acid (VIII) prepared by oxidation of VII.

When the crude amino-acid (VIII) was allowed to react with DCC in CH_2Cl_2 at room temperature for 5 days, was obtained a β-lactam (X), $C_{31}H_{52}O_3N_2$, m.p. 242-245°, $[\alpha]_D$ -20°, in approximately 25% yield. This compound was identified as pachystermine-B acetate (X) by direct comparison (mixed m.p. and IR (KBr)).

The next problem is the conversion of X to pachystermine-B. Since direct hydrolysis under acidic or basic condition would cause the undesired ring-opening of the β-lactam moiety, our attention was directed to the preferential reduction of ester grouping with $LiAlH_4$ over amide grouping, which was successfully utilized in this case. The compound (X) was thus treated with $LiAlH_4$ for a short period of time at -10~-20°C in tetrahydrofuran to give pachystermine-B (II). $C_{29}H_{50}O_2N_2$, m.p. 258-259°, $[\alpha]_D$ -28°, in a yield of 50%. Identity was confirmed by direct comparison. Pachystermine-B (II) can be easily transformed into pachystermine-A (I) by CrO_3 oxidation as reported previously.[1)]

The second phase of the present work is concerned with the conversion of epipachysandrine-A(III) to pachystermine-diol (IV). In the course of structure elucidation of pachystermine-A and -B[1)] we have reported the synthesis of a mixture of 3'-epimeric diols (XIII) by a sequence of reactions (XIV→O,N-diacyl compound→XIII) starting from the amino-alcohol (XIV) which is a degradation product of pachystermine-B.

In analogous manner, we carried out the Schotten-Baumann reaction of XI[2)], an acyl-migration product of epipachysandrine-A, with the acid chloride (XII), the condensation product being reduced with $LiAlH_4$ to afford a mixture of 3'-epimeric diols (XIII), m.p. 200-205°. However, all the efforts to isolate each diastereomer at this stage, even through its salts and acyl derivatives, resulted in failure. Attention was therefore turned to the possible use of N-methylpachystermine-diol (XVA) which could readily be separated by chromatography of the mixture (XVA, XVB)[1)]. Initially we examined the selective von Braun degradation

in expectation of the preferential de-N-methylation at 3-position, but it was shown to be unpractical.

Then we attempted the CrO_3-pyridine oxidation of 0,0-diacetyl-N-methylpachystermine-diol (XVI), $C_{34}H_{60}O_4N_2 \cdot H_2O$, m.p. 130-132°, $[\alpha]_D$ -5°, whereupon was obtained a neutral diformate (XVII) as a sole product, which showed IR 1733(OAc), 1660 cm^{-1} (amide); NMR 1.73 (1H, $\underline{H}CON(CH_2R)$-), 1.92, 2.04 (1H, $\underline{H}CON(CH_3)$-, two peaks), 7.21, 7.27 τ (3H, amide N-CH_3, two peaks). The latter was partially hydrolysed by refluxing with Na_2CO_3 in aq. MeOH to give a mono-amide (XVIII), $C_{29}H_{52}O_3N_2$, m.p. 192-195°, $[\alpha]_D$ +2°, IR 1660 cm^{-1}; NMR 1.92, 2.04 (1H, two peaks, $\underline{H}CON(CH_3)$-), 7.21, 7.27 τ (3H, two peaks, amide N-CH_3). Subsequent $LiAlH_4$ reduction of XVIII gave rise to IV, m.p. 196-198°, $[\alpha]_D$ -6°, which was found to be identical with pachystermine-diol (IV) by mixed m.p. and IR (KBr) comparisons.

Thus the transformation of epipachysandrine-A (III) into pachystermine-A (I) and -B (II) was completed.

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* All compounds given by formula in this communication gave satisfactory elemental analyses. All melting points were determined on a Kofler type microscopic hot stage and are uncorrected. Optical rotations were taken at 20-30°C in $CHCl_3$. Unless otherwise stated, IR spectra were measured in $CHCl_3$ and NMR spectra in $CDCl_3$ with $SiMe_4$ as the internal standard.

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