5a-Carboxystrictosidine[†]

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OH

Me

NH2

CO₂Me

OC6H2(OAc)

Summary The isolation, structural elucidation, biosynthesis, and partial synthesis of 5α -carboxystrictosidine and related compounds are described.

CURRENT views on the biosynthesis of indole alkaloids imply that the first nitrogenous intermediate is produced by condensation of secologanin (1) with tryptamine (2).¹ However, van Tamelen² speculated on the possible significance of the corresponding tryptophan analogues and recently demonstrated their potential importance by the biogenetically modelled synthesis of ajmaline (12).³ Furthermore, the isolation of cordifoline,⁴ a 10-hydroxy- β carboline analogue, demonstrates that at least in Adina cordifolia such precursors are likely. Accordingly our studies of *Rhazya* species were extended in a search for

Me

(12)

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(3) $R^1 = CO_2H$, $R^2 = H$

(4) $R^1 = H, R^2 = CO_2 H$

С

(2) $R^1 = R^2 = H$

(30)

[26) $R^1 = CO_2 H R^2 = Me 3\beta, 5\beta$ amino-acid glycosides. We now report the presence of substantial amounts of three such intermediates (each > 0.2% dry weight) in *R. orientalis* root extracts, and summarise the investigations which have led to the elucidation of their complete structures.

The amorphous nature of the new amino-acid glycosides complicates their characterisation and only 5α -carboxy-strictosidine (8) m.p. 232° [α]_D -280° (MeOH) has so far

† For indole alkaloid numbering see preceding communication.

been obtained completely homogeneous. The structures (7) and (9) are however consistent with the properties of the other glycosides which were characterised by conversion into strictosidine $(5)^5$ and 5α -methoxycarbonylstrictosidine (11) respectively.



Esterification of (7), (8), and (9) with diazomethane or diazoethane afforded their respective esters and N-alkyl esters, whose comparative study, together with their 18,19-dihydro-derivatives and acetates, by mass, i r., u.v., and n.m.r. spectroscopy⁵ fully confirmed the structures. The main problem was then the determination of the stereochemistry of 5α -carboxystrictosidine (8).

Initially it was necessary to confirm the expected 5α configuration and this was readily achieved by the excellent incorporation (10%) of [³H]-generally labelled-(L)-tryptophan using *R. orientalis*. Similarly support for the predicted secologanin stereochemistry (1) of the monoterpenoid glucoside moiety was obtained by feeding [O-methyl-³H] loganin (0.3% incorporation).

The next stage required the determination of the C-3stereochemistry and here use was made of the established 5α -configuration. Methoxide-catalysed epimerisation[†] of 5α -methoxycarbonylstrictosidine penta-acetate (13), m.p. 200°, gave a separable mixture of monoacetates (14) and (15), which were shown to equilibrate under the reaction conditions. The predominant isomer (15), afforded a new penta-acetate (16) on acetylation. Similar treatment of 5α -dihydromethoxycarbonylstrictosidine penta-acetate (17) gave an even greater preponderance of the 5β -derivative (18). Examination of this series of C-5-epimers by n.m.r. spectroscopy revealed the presence of a low-field proton signal τ 3·9—4·1 (C₆D₆) in the 5 α -series only.

In order to study this distinguishing feature, methyl esters (19), m.p. 68° , $[\alpha]_{\rm D} - 92$ (MeOH), and (20), m.p. 153° , $[\alpha]_{\rm D} + 15^{\circ}$ (MeOH) were prepared by condensation of L-tryptophan (3) with acetaldehyde⁶ followed by esterification with methanolic hydrogen chloride. Acid-catalysed equilibrations demonstrated that the major isomer (19) was the thermodynamically more stable, suggesting its $3\alpha,5\alpha$ stereochemistry and in agreement, the n.m.r. spectrum revealed a characteristic ABX pattern for the 5-H-6-H ($J_{\rm AB}$ 15, $J_{\rm AX}$ 4.5, $J_{\rm BX}$ 10.8 Hz). The n.m.r. spectrum of the minor isomer (20) further supported the stereochemical assignment.

сно

(1)

(5) $R^1 = H$

(6) $R^1 = H$

 $(7) R^{1} = H$

(8) $R^1 = CO_2 H R^2 = Me$

(9) $R^1 = CO_2 H R^2 = H$

(10) $R^1 = CO_2 H R^2 = Me$

(11) $R^1 = CO_2 Me R^2 = Me$

(27) $R^1 = CO_2 H R^2 = Me$

ÇO₂Me

ŌGlu

18

 $R^2 = Me$

 $R^2 = Me$

 $R^2 = H$

ŌGlu

3α

зβ

3α

3α,5α

3α,5α

3β,5α

3α,5α

3α,5**β**

[‡] All methoxycarbonylamides subjected to C-5 equilibration are in the Table.

On acetylation (19) produced the amide (21), m.p. 195°, $[\alpha]_{\tt D}$ +192° (MeOH) whose n.m.r. spectrum possessed the characteristic low-field proton signal [τ 3.9 (CDCl₃)] which was absent from the epimeric amide (22) m.p. 209° $[\alpha]_n$ $+13^{\circ}$ (MeOH). Owing to restricted rotation about the NCOCH₃ linkage each spectrum was composed of contributions from the two possible rotamers which aided their interpretation. Double irradiations strongly supported the $3\alpha, 5\alpha$ assignment for the major amide (21) which was interpretable in terms of rotamers (21X) and (21Y).

In contrast to the behaviour of 5-methoxycarbonylstrictosidine derivatives, on methoxide-catalysed equilibration the enantiomers (21) and (23), possessing the lowfield terms of rotamer population and τ values for 3-H and 5-H.

All the evidence now favoured the assignment of the 3α configuration to 5a-methoxycarbonylstrictosidine pentaacetate (13). Final proof was obtained when secologanin (1),^{7,10,11} (fresh R. orientalis leaves) became available. Condensation of (1) with L-tryptophan (3) gave predominantly the *cis*-isomer 5α -carboxystrictosidine (8) and 5α carboxyvincoside (10). A similar condensation starting with D-tryptophan (4) yielded the cis-isomer, 5 β -carboxyvincoside (26), and 5β -carboxystrictosidine (27). Methylation followed by acetylation produced the corresponding penta-acetates which were interrelated by methoxidecatalysed equilibrations $(13) \rightleftharpoons (16)$, $(28) \rightleftharpoons (29)$.

Structure (A) $R^1 = Ac R^2 =$		(I)	3α,5α (II)	(III)	(I)	3α,5α (II)	(III)	(I)	3β,5α (II)	(III)	(I)	3β,5β (II)	(III)
I G	•••	(13) (14)	-50 -25	32 32	(16) (15)	-40 - 16	68 68	(29)	-86	55	(28)	-178	4 5
J Me	••	(17)	-51	25	(18)	-62	75	(22)	+ 19	9	(32)	101	07
Bui	•••	(21)	+192 + 28	30 30	(24)	-14 + 45	70	(22)	-47	70	(23)	-191 -27	97 30
PhCH ₂ Pri	••		+107	$\frac{25}{2}$		-41	75 98		$+40_{8}$	75			25

Methoxycarbonyl-amides subjected to methoxide catalysed C-5 equilibrations

(I) Compound No.; (II) [a]²⁵_D (MeOH) except I, G, and J. (CHCl₃); (III) % on C-5 equilibration.

^a Prepared from (DL)tryptophan.



(19) $R^1 = H_{\chi}$ R² = Me 30,50 $G_1 R = H$ (20) $R^1 = H_1$ R²= Me 3β,5α $I_1 R = Ac$ (25) $R^1 = Ac$, $R^2 = CH_2OAc$ 30,50 J: R = Ac vinyl reduced

signal, proved to be much more stable than their transisomers (22) and (24). This was attributed to the greater steric requirements encountered in rotamers (X) and (Y) when the methyl group was further substituted. Accordingly a range of such substituents was studied (Table).

In each case esterification of the condensation products gave a preponderance of the cis-isomer possessing the characteristic ABX pattern. Acetylation produced the corresponding amides whose n.m.r. spectra and thermodynamic stabilities substantiated the steric rationalisation. The cis-stereochemistry of the major condensation product was finally proved by utilising glycolic aldehyde and L-tryptophan which afforded the lactone (31), m.p. 232°, $[\alpha]_{\mathbf{D}}$ +70° (MeOH) convertible into acetoxy-ester (25), m.p. 124°, whose n.m.r. spectrum paralleled that of (21) in

 5α -Carboxyvincoside (10) undergoes simple lactamisation vielding, after methylation and acetylation, 5x-methoxycarbonylvincoside lactam tetra-acetate (30) [5-H, τ 4.0 (CDCl₃)]. In conformational terms this observation is in complete agreement with the predicted stabilities of the C/D ring systems, for only in the 5 α -carboxyvincoside series are all the steric interactions, dipoles, and orbitaloverlap requirements of the alkoxyacrylic lactam function, favourable. This rationalisation when applied to the ease of lactamisation¹ in the corresponding tryptamine-derived compounds strictosidine (5) and vincoside (6) offers a further vindication of the previous chemical correlation^{8,9} which proposed the 3α -configuration for strictosidine (5).

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