# 5α-Carboxystrictosidine†

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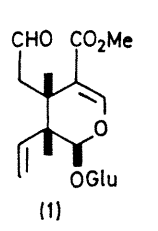
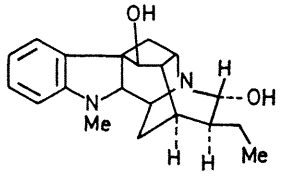
*Summary* The isolation, structural elucidation, biosynthesis, and partial synthesis of 5α-carboxystrictosidine and related compounds are described.

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 Tamelen[2] 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 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.



(1)



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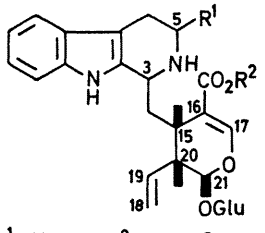
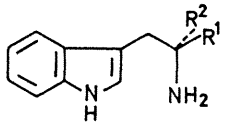
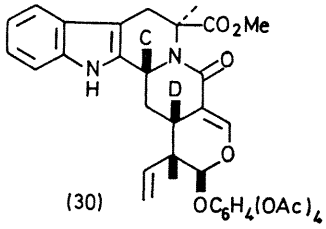


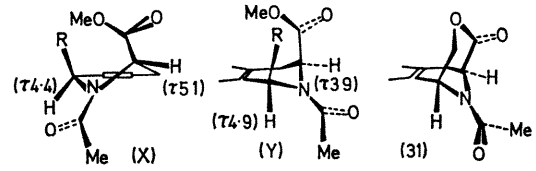

(2) $R^1 = R^2 = H$
(3) $R^1 = CO_2H$, $R^2 = H$
(4) $R^1 = H$, $R^2 = CO_2H$

| | | | |
|---|---|---|---|
| (5) | $R^1 = H$ | $R^2 = Me$ | 3α |
| (6) | $R^1 = H$ | $R^2 = Me$ | 3β |
| (7) | $R^1 = H$ | $R^2 = H$ | 3α |
| (8) | $R^1 = CO_2H$ | $R^2 = Me$ | 3α,5α |
| (9) | $R^1 = CO_2H$ | $R^2 = H$ | 3α,5α |
| (10) | $R^1 = CO_2H$ | $R^2 = Me$ | 3β,5α |
| (11) | $R^1 = CO_2Me$ | $R^2 = Me$ | 3α,5α |
| (27) | $R^1 = CO_2H$ | $R^2 = Me$ | 3α,5β |
| (26) | $R^1 = CO_2H$ | $R^2 = Me$ | 3β,5β |



(30)

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



τ-values for (21) R=Me

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. spectroscopy[5] 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 [$^3$H]-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*-$^3$H] loganin (0·3% incorporation).

The next stage required the determination of the C-3-stereochemistry 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 ($C_6D_6$) in the 5α-series only.

In order to study this distinguishing feature, methyl esters (**19**), m.p. 68°, $[\alpha]_D$ −92 (MeOH), and (**20**), m.p. 153°, $[\alpha]_D$ +15° (MeOH) were prepared by condensation of L-tryptophan (**3**) with acetaldehyde[6] followed by esterification with methanolic hydrogen chloride. Acid-catalysed equilibrations demonstrated that the major isomer (**19**) was the thermodynamically more stable, suggesting its 3α,5α stereochemistry and in agreement, the n.m.r. spectrum revealed a characteristic ABX pattern for the 5-H–6-H ($J_{AB}$ 15, $J_{AX}$ 4·5, $J_{BX}$ 10·8 Hz). The n.m.r. spectrum of the minor isomer (**20**) further supported the stereochemical assignment.

† For indole alkaloid numbering see preceding communication.
‡ All methoxycarbonylamides subjected to C-5 equilibration are in the Table.

On acetylation (**19**) produced the amide (**21**), m.p. 195°, $[\alpha]_D$ +192° (MeOH) whose n.m.r. spectrum possessed the characteristic low-field proton signal [$\tau$ 3·9 ($CDCl_3$)] which was absent from the epimeric amide (**22**) m.p. 209° $[\alpha]_D$ +13° (MeOH). Owing to restricted rotation about the $NCOCH_3$ linkage each spectrum was composed of contributions from the two possible rotamers which aided their interpretation. Double irradiations strongly supported the 3α,5α 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 $\tau$ values for 3-H and 5-H.

All the evidence now favoured the assignment of the 3α-configuration to 5α-methoxycarbonylstrictosidine penta-acetate (**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, 5β-carboxyvincoside (**26**), and 5β-carboxystrictosidine (**27**). Methylation followed by acetylation produced the corresponding penta-acetates which were interrelated by methoxide-catalysed equilibrations (**13**) ⇌ (**16**), (**28**) ⇌ (**29**).

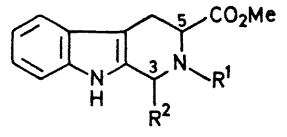
*Methoxycarbonyl-amides subjected to methoxide catalysed* C-5 *equilibrations*

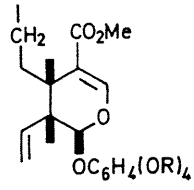
| Structure (A) | | 3α,5α | | | 3α,5α | | | 3β,5α | | | 3β,5β | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $R^1$ = Ac $R^2$ = | | (I) | (II) | (III) | (I) | (II) | (III) | (I) | (II) | (III) | (I) | (II) | (III) |
| I .. | .. | (**13**) | − 50 | 32 | (**16**) | −40 | 68 | (**29**) | −86 | 55 | (**28**) | −178 | 45 |
| G .. | .. | (**14**) | − 25 | 32 | (**15**) | −16 | 68 | | | | | | |
| J .. | .. | (**17**) | −51 | 25 | (**18**) | −62 | 75 | | | | | | |
| Me | .. | (**21**) | +192 | 98 | (**24**) | −14 | 2 | (**22**) | +13 | 3 | (**23**) | −191 | 97 |
| Bu$^i$ | .. | | + 28 | 30 | | +45 | 70 | | −47 | 70 | | − 27 | 30 |
| $PhCH_2$ | .. | | +107 | 25 | | −41 | 75 | | +40 | 75 | | −103 | 25 |
| Pr$^i$ | .. | | | 2 | | | 98 | | [a] | | | [a] | |

(I) Compound No.; (II) $[\alpha]_D^{25}$ (MeOH) except I, G, and J. ($CHCl_3$); (III) % on C-5 equilibration.

[a] Prepared from (DL)tryptophan.

(A)




(**19**) $R^1$ = H, $R^2$ = Me 3α,5α G; R = H

(**20**) $R^1$ = H, $R^2$ = Me 3β,5α I; R = Ac

(**25**) $R^1$ = Ac, $R^2$ = $CH_2OAc$ 3α,5α J; R = Ac vinyl reduced

signal, proved to be much more stable than their *trans*-isomers (**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°, $[\alpha]_D$ +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 yielding, after methylation and acetylation, 5α-methoxycarbonylvincoside lactam tetra-acetate (**30**) [5-H, $\tau$ 4·0 ($CDCl_3$)]. In conformational terms this observation is in complete agreement with the predicted stabilities of the C/D ring systems, for only in the 5α-carboxyvincoside series are all the steric interactions, dipoles, and orbital-overlap requirements of the alkoxyacrylic lactam function, favourable. This rationalisation when applied to the ease of lactamisation[1] 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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