Tetrahedron Letters,Vol.28,No.43,pp 5181-5184,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

ON THE STEREOCHEMISTRY OF THE PICTET-SPENGLER REACTION

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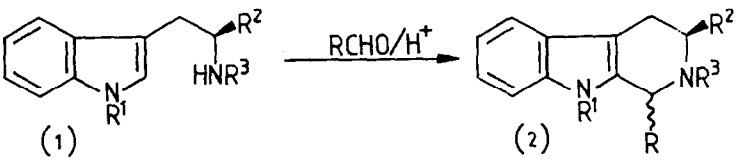
Summary. A pathway for the Pictet-Spengler reaction is proposed herein, which is consistent with all of the known mechanistic and sterochemical observations concerning the formation of tetrahydro-β-carbolines by this method.

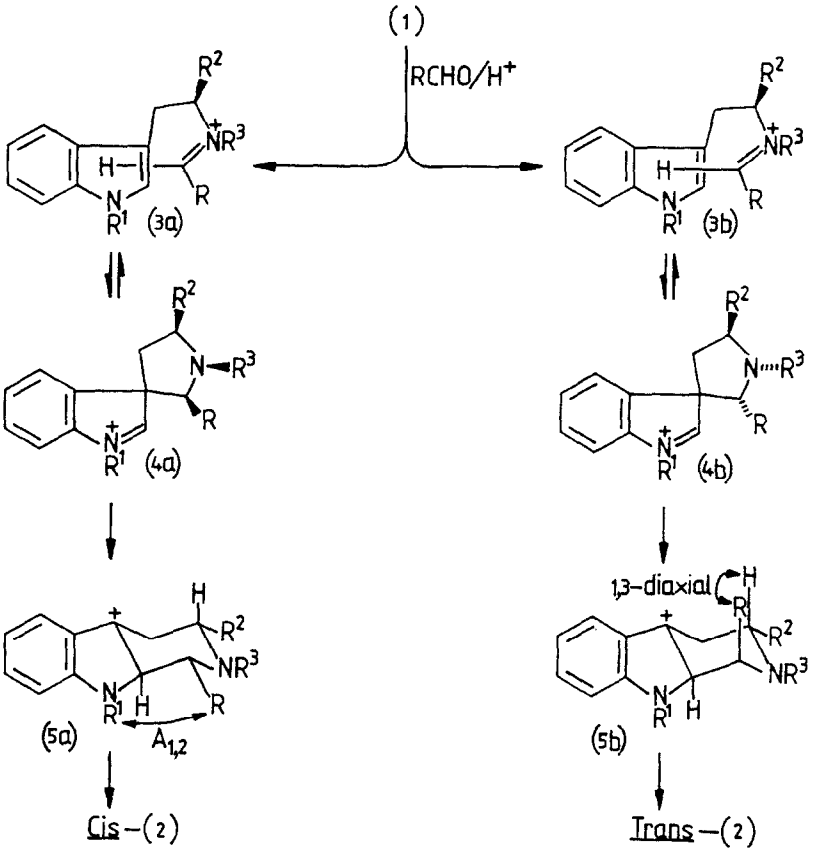
The tetrahydro-β-carboline moiety is a central feature of many indole alkaloids, and the Pictet-Spengler reaction (Scheme 1) continues to be the most widely used method of synthesising the crucial tricyclic ring-system.[1] With emphasis now resting on the enantiospecific synthesis of natural products, the importance of stereochemical control in the Pictet-Spengler reaction is greater than ever.[2] An indication of the ease of stereochemical control was demonstrated in the previous paper, in which it was shown that low reaction temperatures induce cis selectivity in the formation of simple 1,3-disubstituted tetrahydro-β-carbolines.[3] Nevertheless, no single mechanism has been proposed which is consistent with all of the known stereochemical features of the Pictet-Spengler reaction.



Scheme 1

There is now overwhelming evidence that the Pictet-Spengler reaction proceeds through a spiro-intermediate,[4] the stereochemistry of which is presumably retained during the subsequent migration step. However, recent isotopic labelling experiments suggest that the formation of such spiroindolenines is both rapid and reversible.[5] The sequence outlined in Scheme 2 is consistent, therefore, with the known mechanistic features of the reaction; moreover, this pathway

offers the first full explanation for the stereochemical observations concerning the formation of tetrahydro-β-carbolines by this method.



Scheme 2

Thus, starting from the L-tryptophan derivative (1), condensation with an aldehyde R-CHO presumably generates mainly the E-iminium cation (3a/b), in which the bulkiest groups display a trans relationship.[6] Nucleophilic attack on this iminium ion can take place with the C=N group either below or above the plane of the indole ring, giving rise to spiroindolenines (4a) or (4b) respectively;[7] the stereochemistry of these intermediates is governed by the observations of Deslongchamps,[8] who noted that such additions can take place trans with respect to the nucleophile and the developing lone pair of electrons.

By invoking the single assumption that the migration step involves a "late" transition state,[9] formation of the protonated cis-1,3-disubstituted tetrahydro-β-carboline (5a) (R^3 = H) would be favoured by conditions of kinetic control (e.g. low temperature); this is because the ring substituents would be able to adopt the preferred equatorial positions in the resulting piperidine "chair" structure. However, the initial equilibrium [(4a) ⇌ (3a) = (3b) ⇌ (4b)] would favour the trans-1,3-disubstituted pyrrolidine spiro-intermediate (4b); therefore, whilst less stereo-selectivity would (obviously) be shown at higher temperatures, the trans-1,3-disubstituted tetrahydro-β-carboline might predominate slightly via the thermodynamically preferred spiro-intermediate (4b). This is precisely the observation noted in the previous paper.[3] Moreover, if the indole nitrogen were substituted (i.e. $R^1 \neq H$), then the observed reduction in cis selectivity[10] would again be expected, due to an increase in $A_{1,2}$ ring strain.[11]

For N^{α}-benzyl derivatives of tryptophan (i.e. $R^3 = CH_2Ph$), reaction would again proceed via the E-iminium cation (3a/b), but formation of (4a) would be effectively prohibited because the stereochemistry of this 1,2,3-trisubstituted spiro-intermediate would be all-cis; rearrangement of spiroindolenine (4b) would thus lead to the observed trans relationship of the 1,3-substituents in the final tetrahydro-β-carbolines.[12] However, if the aldehyde side-chain (R) were small, then significant amounts of the Z-iminium cation would be formed; this could yield either the cis or trans 1,3-disubstituted products, thereby accounting for the reduced trans selectivity with small aldehydes.[13].

The pathway outlined in Scheme 2 is consistent, therefore, with all of the known mechanistic and stereochemical features of the Pictet-Spengler reaction. Application of these ideas to the preparation of key tetrahydro-β-carbolines is already leading to more precise stereochemical control in the synthesis of indole alkaloids.

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6 Inversion/rotation of the imine is expected (see M. Pankratz and R.F. Childs, J. Org. Chem., 1985, 50, 4553, and references therein), but the E/Z ratio would still be governed by the thermodynamic stability of the isomeric imines.

7 Inversion of stereochemistry at nitrogen could readily take place after formation of the spiroindolenine. If this intermediate proceeds to give the tetrahydro-β-carboline, then the 1,3-stereochemistry must be retained; if it re-equilibrates to the imine, then thermodynamic factors should regain the imine E/Z ratio (see Note 6).

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(Received in UK 21 August 1987)