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Structure and Spectral Properties of β-Carbolines. 8.[1] Mechanism of the Pictet-Spengler Cyclization: An MNDO Approach

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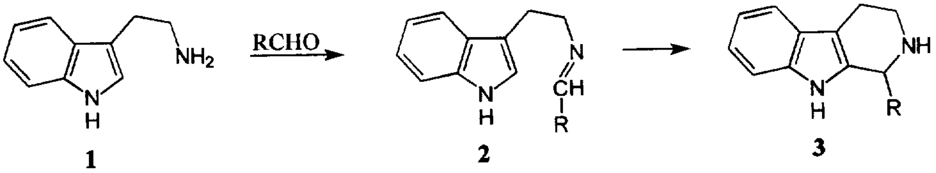
Abstract: Formation of 1,2,3,4-tetrahydro-β-carboline in the Pictet-Spengler reaction was studied using an MNDO approach. It was shown that the formation of the spiroindolenine intermediate **6** was a thermodynamically favourable process compared with a direct C-2 pathway (**5**). However, since the rearrangement of **6** into **5** involves a high energy transition state, the direct C-2 pathway seems to be a key step in the Pictet-Spengler cyclization.

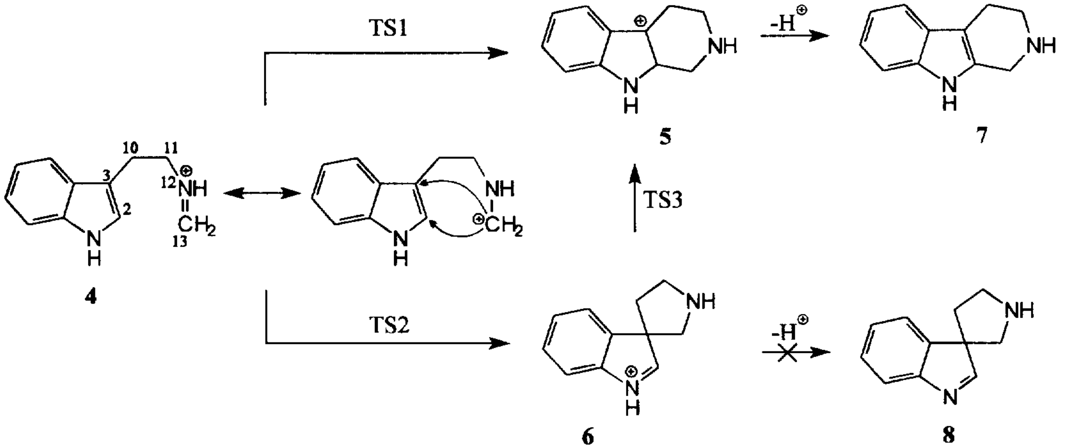
The Pictet-Spengler (P-S) reaction is the most general and efficient method of preparing 1,2,3,4-tetrahydro-β-carbolines.[1,2] It has been well established that the Schiff base (**2**) is a stable intermediate in the P-S cyclocondensation (Scheme 1).[1,2c,2d,3]



SCHEME 1

The Schiff base is protonated under reaction conditions to give the imminium form (**4**, Scheme 2). Then two likely pathways may be engaged in the cyclization process. An electrophilic attack of the methylene carbon atom C_{13} of **4** may proceed either directly at C-2 (**5**) or at C-3 to form spiroindolenine **6** which rearranges into **5**. The loss of a proton from **5** yields 1,2,3,4-tetrahydro-β-carboline 7 (Scheme 2).[2c-e,2g,2j,3a,3d,4] There gains ground a prevalent view that the spiroindolenine pathway is preferable with respect to the direct C-2 attack.[2e,3a,3d,4a,4b,5,6] However, a direct pathway cannot be excluded, as the electrophilic attack at position 2 of the indole ring system takes place under kinetic control conditions of the reaction.[3b,4c,4d,7]

Jackson *et al.*[3a,8] discussed two feasible pathways of the electrophilic attack on 3-substituted indoles. They concluded that disruption of the resonance energy of the benzene ring during the direct C-2 attack (**5**) should require more energy than formation of the corresponding indolenine (**6**). In our previous paper we discussed the P-S reaction pathways in terms of the most sensitive centres of the indole ring system towards the electrophilic attack.[1] We analysed net atomic charges (calculated by an MNDO method) of the intermediate of type **4**, and applied a charge sensitive analysis (CSA) including its basic concepts such as electronegativity, hardness/softness and the Fukui function index. The performed analysis supported some earlier concepts that the P-S reaction involves a spiroindolenine mechanism rather than a direct C-2 attack.[1]

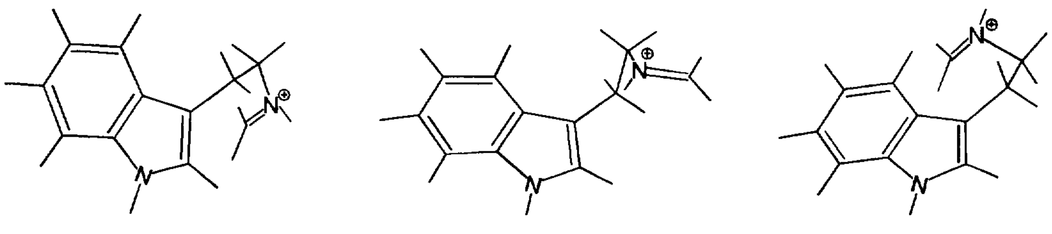


SCHEME 2

As a continuation of our studies, we now present a discussion about the energy of intermediates of the P-S reaction (**4**, **5** and **6**) and the transition states (TS) between them. The geometry and heat of formation of intermediates **4**-**6** and the respective transition states TS1, TS2, and TS3 were calculated by an MNDO method (Table).[9]

The chain at position 3 of the indole nucleus of intermediate **4** is highly flexible. Of the numerous feasible low-energy conformations of the chain, only some folded ones have been taken into consideration as the most important for the cyclization process. The folded conformation **4a** was related to the global energy minimum, whereas **4b** and **4c** formed two local minima (Fig. 1).

The calculated heat of formation of the spiroindolenine intermediate **6** ($\Delta H = 205.3$ kcal/mol) is by 1 kcal/mol lower than that of **5** ($\Delta H = 206.3$ kcal/mol), and either of them is thermodynamically favourable in relation to **4a**, as well as to **4b** and **4c**. Moreover, the distance $d_{C3\text{-}C13}$ for **4a** is significantly shorter than the distance $d_{C2\text{-}C13}$ (Table). Hence it may be anticipated that the formation of spiroindolenine **6** is somewhat more likely than the direct attack at C-2. Although rotation around the C_3-C_{10} bond of **4a** produces some conformations ($-30° \leq \tau_1 \leq 80°$) with $d_{C2\text{-}C13} \leq d_{C3\text{-}C13}$, their energies are by at least 2.6 kcal/mol higher compared with the global energy minimum ($\tau_1 = -90°$). In contrast, the $d_{C2\text{-}C13} > d_{C3\text{-}C13}$ relationship characterizes all low-energy conformations ($-100° \leq \tau_1 \leq -70°$ and $100° \leq \tau_1 \leq 130°$, Figs. 2A and 2C). A similar relationship ($d_{C2-C13} > d_{C3-C13}$) was observed in the whole range of rotations around the C_{10}-C_{11} bond (Figs. 2B and 2D).



4a **4b** **4c**

Figure 1. The calculated (MNDO) low-energy conformations of **4**; details are given in Table

Table. Results of MNDO Calculations: Geometry and Heat of Formation of **4a-c**, and Transition States TS1, TS2, and TS3.

No.	Torsion angle [°] [a]			d_{C2-C13} [Å]	d_{C3-C13} [Å]	ΔH [kcal/mol]
	τ_1	τ_2	τ_3			
4a	-86.0	-61.1	99.1	4.28	3.52	217.5
4b	-84.5	-56.5	-98.6	5.22	4.09	217.8
4c	-113.4	52.6	-101.5	4.05	3.50	218.0
TS1a [b]	-49.5	-16.7	67.4	2.21	2.77	237.3
TS2a [b]	-115.2	-13.2	42.8	2.90	2.22	233.6
TS1c [c]	-63.4	43.1	-60.6	2.21	2.70	234.1
TS2c [c]	-110.3	25.8	-47.2	2.86	2.22	233.7
TS3	-70.2	19.4	-37.8	1.97	1.99	249.1

[a] τ_1 (C_2-C_3-C_{10}-C_{11}), τ_2 (C_3-C_{10}-C_{11}-N_{12}), τ_3 (C_{10}-C_{11}-N_{12}-C_{13}); [b] **4a** was used as the starting geometry; [c] **4c** was used as the starting geometry.

It may be intuitively concluded that the shorter the distance between the reaction centres, the lower the Δ H of the transition states. We used conformers **4a** and **4c** as the starting geometry for calculation of TS1 and TS2. The geometry and heat of formation of the particular transition states are given in Table. The calculations indicate that TS2a has the heat of formation by 3.7 kcal/mol lower than TS1a, when conformation **4a** is set as the starting geometry. On the other hand, when conformer **4c** is used for the calculations, the ΔH of TS2c is only by 0.4 kcal/mol lower than that of TS1c. The observed differences Δ(ΔH) between the respective transition states come from the shortening of the distance d_{C2-C13} for **4c** compared with **4a** (Table). The above results strongly suggest that formation of the spiroindolenine intermediate (**6**) is thermodynamically favourable in comparison with **5**. It seems, however, that formation of intermediate **5** is thermodynamically permissible, hence a direct attack at position C-2 cannot be excluded.

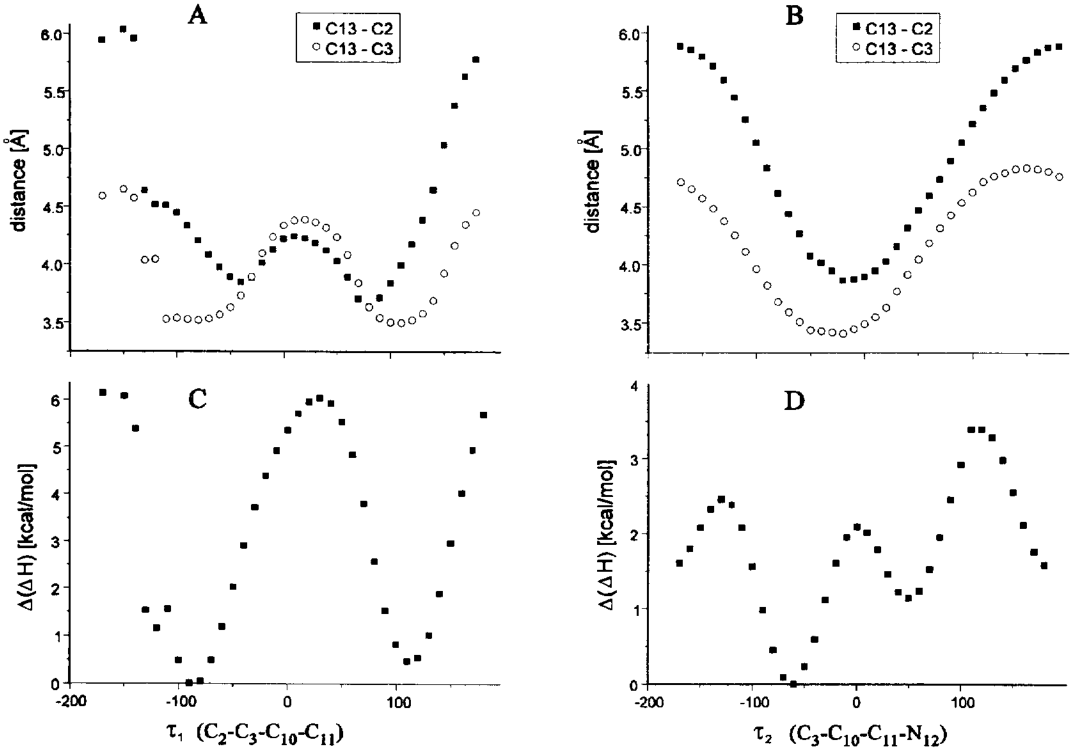
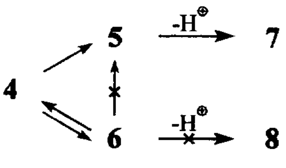


Figure 2. The distances d_{C2-C13} and d_{C3-C13} , and the conformation energy profiles upon rotation about the C_3-C_{10} bond (A and C) and about the C_{10}-C_{11} bond (B and D) calculated by the MNDO method.[10]

The most unexpected results were obtained from an analysis of the rearrangement process of **6** into **5**. An energy of the transition state TS3 was very high (Table), and the energy barrier of the process **6** → **5** equalled 43.8 kcal/mol [ΔH(TS3) - ΔH(**6**)]. Hence it may be anticipated that a direct conversion of **6** → **5** would proceed extremely slowly, and alternative reactions would predominate. If this is the case, the formation of intermediate **5** may proceed only *via* the C_3-C_{13} ring cleavage of spiroindolenine **6** to the protonated Schiff base **4** and its further C_2-C_{13} cyclization. It is also noteworthy that the calculated heat of formation of 1,2,3,4-tetrahydro-β-carboline (**7**) is significantly lower than that spiroindolenine (**8**) (ΔH = 36.8 and 47.8 kcal/mol, respectively).



SCHEME 3

The present results permit us to conclude that **6** is a thermodynamically preferable intermediate in the Pictet-Spengler reaction. However, as shown in Scheme 3, the spiroindolenine intermediate (**6**) is not directly involved in formation of the final 1,2,3,4-tetrahydro-β-carboline (**7**). Therefore it may also be inferred that the direct electrophilic attack at position 2 of the indole nucleus is a key step in the Pictet-Spengler cyclization.

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9. Starting geometries were generated by molecular mechanics optimization of structures built with the molecular modelling package SYBYL 6.0 (Tripos Associates, Inc.), installed on an ESV 10/33 workstation. The MNDO calculations (full geometry optimization, gradient norm < 0.1 kcal/mol/Å) were conducted using an MOPAC 6.0 (QCPE) program. Transition states were calculated using a

SADDLE subroutine. An NLLSQ procedure was used for gradient optimization (< 0.1 kcal/mol/Å). Calculations were performed until at least one negative Hessian value was obtained.

10. To investigate the rotational energy barriers, thirty-six conformations were a generated by step-wise rotation of 10^o around τ_1 or τ_2. Next, each of these conformations was optimized using an MNDO method over all internal coordinates except the one which defines the relative orientation of the chain (gradient norm < 0.1 kcal/mol/Å).

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