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STEREOSPECIFICITY IN THE PICTET-SPENGLER REACTION KINETIC VS THERMODYNAMIC CONTROL

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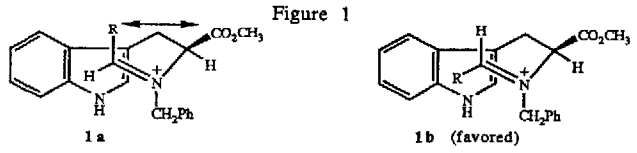
Summary: *The Pictet-Spengler reaction of N_b-benzyl tryptophan methyl ester **4** with **5** in refluxing benzene yielded a mixture of cis and trans tetrahydro β-carbolines in a ratio of **7a**(23)/**7b**(77), whereas the analogous reaction of isopropyl ester **10** with **5** provided increased trans stereoselectivity [cis(13):trans(87)]. The implications in regard to the role of intermediates **1-3** in this condensation are described. Moreover, Pictet-Spengler reaction of **4** or **10** with aldehydes (Ph,Δ) led to kinetic trapping of the cis/trans diastereomers, whereas reaction in TFA/CH_2Cl_2(25 °C) provided tetrahydro β-carbolines via thermodynamic control and increased trans diastereoselectivity in most cases.*

The Pictet-Spengler reaction has occupied a central role in the synthesis of indole alkaloids for some time.[1] More recently, it has been employed as the key reaction in the preparation of β-carboline-3-carboxylic acid esters which are active at the benzodiazepine receptor.[2,3] For example, the ethyl and methyl esters of β-carboline-3-carboxylic acid have been shown to elicit activity *in vivo* opposite (anxiogenic, somnolytic, convulsant and proconvulsant)[4] to that of the benzodiazepines and are central to the determination of the mechanism/function of this important binding site in the CNS.[5] In 1987 in this journal, Bailey[6] published a paper on stereospecificity in the Pictet-Spengler reaction which was essentially a recapitulation of work reported in detail by Ungemach *et al.* in 1981.[7] Ungemach had proposed that in the condensation of aldehydes with N_b-benzyl tryptophan methyl ester *via* imminium ions **1a** and **1b**, that **1b** was favored due to steric interactions present in **1a**.[7] Moreover, he had proposed that if R were a bulky group (R=phenyl or C_6H_{11}) that **1b** would be even more favored than **1a** and that attack of the indole double bond on imminium ion **1b** (see **2b**, Scheme I) should occur preferentially from the face opposite the ester group to generate the *trans* diastereomer **3b**.

In keeping with our interest in chiral control in the Pictet-Spengler reaction for the stereospecific, enantiospecific synthesis of indole alkaloids[8] we wish to report new results with regard to intermediate **1b** which strongly suggest that attack on the imminium ion does occur as in **2b**. Moreover, new evidence with **4** suggests that the ratio of *cis* to *trans* diastereomers (**3a/3b**) obtained in refluxing benzene is the result of kinetic trapping,[9] whereas ratios obtained in acidic solution (TFA)[10] more accurately reflect the products of thermodynamic control. Experiments are based on kinetic trapping of the *cis/trans* diastereomers (**3a/3b**) in refluxing benzene,[9] followed by

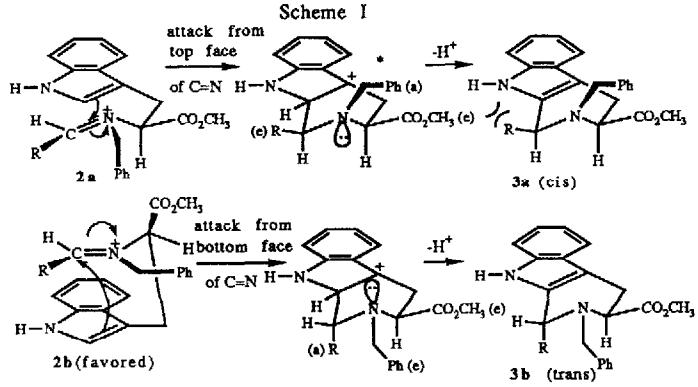
conversion into the thermodynamic ratio on treatment of the mixture of **3a/3b** at room temperature with trifluoroacetic acid in methylene chloride.[10]

Figure 1



1a **1b** (favored)

Scheme I

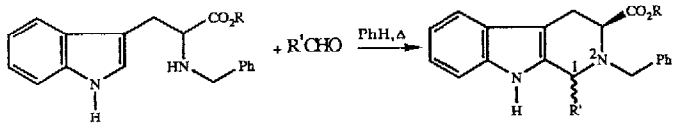


* $A^{1,2}$-strain is less in this carbocation than in **3a**

In all cases previously reported (see references 7-11) the N_b-benzyl group promoted formation of the *trans* diastereomer with high diastereoselectivity;[7] however, no evidence for involvement of the ester group (see **2b**) has appeared. As illustrated in Scheme II, reaction of acetaldehyde **5a** with methyl ester **4** (sealed tube) at 78°C gave a mixture of the *cis/trans* diastereomers **6a/6b** in a ratio of 26:74. When this sequence was repeated with the bulky isopropyl ester **10**, essentially no increase in *trans* stereoselectivity (**11a/11b** 23:77) was observed within experimental error. This is not surprising, for *trans* stereoselectivity decreases with smaller aldehydes since both Z and E isomers **1a** and **1b** are more likely involved in the cyclization in agreement with earlier findings.[7,11-13] However, as illustrated in Scheme II, reaction of **4** with butyraldehyde **5b** (PhH,Δ) gave **7a/7b** in a ratio of 23(*cis*):77(*trans*), but when the analogous condensation was performed with the isopropyl ester **10**, the *trans* stereoselectivity was significantly increased to provide **12a/12b** in a ratio of 13(*cis*):87(*trans*). When cyclohexylcarboxaldehyde **5d** was employed in the process both esters **4** and **10** gave the *trans* diastereomer (**9b** or **13b**, respectively) in stereospecific fashion.

The *cis/trans* ratio (26:74) of **6a/6b** in refluxing benzene was intriguing for it had recently been shown[11] that reaction of **4** with acetaldehyde dimethyl acetal in TFA/CH_2Cl_2 at 25°C, analogous to the conditions of Massiot[10] and Ottenheim,[13] gave **6a/6b** in a ratio of 16:84. Moreover, a *cis/trans* mixture (28:72) of N_a-methyl, N_b-benzyl-1-alkyl-3-methoxycarbonyl-1,2,3,4-tetrahydro β-carboline had been converted

Scheme II



				Cis/trans ratio (kinetic)* (benzene, Δ)		*Cis/trans* ratio*** (TFA/CH_2Cl_2, 25°C)	
4,	$R=CH_3$	**5a**,	$R'=CH_3$	**6a/6b**	26:74	**6a/6b**	12:88**
	$R=CH_3$	**5b**,	$R'=CH_2CH_2CH_3$	**7a/7b**	23:77	**7a/7b**	11:89
	$R=CH_3$	**5c**,	$R'=CH(CH_3)_2$	**8a/8b**	5:95	**8a/8b**	3:97
	$R=CH_3$	**5d**,	$R'=C_6H_{11}$	**9a/9b**	0:100	**9a/9b**	0:100
10,	$R=CH(CH_3)_2$	**5a**,	$R'=CH_3$	**11a/11b**	23:77	**11a/11b**	13:87
	$R=CH(CH_3)_2$	**5b**,	$R'=CH_2CH_2CH_3$	**12a/12b**	13:87	**12a/12b**	12:88
	$R=CH(CH_3)_2$	**5d**,	$R'=C_6H_{11}$	**13a/13b**	0:100	**13a/13b**	5:95

* Under the conditions of Massiot *et al.* and Ottenheim the ratio of **6a/6b** was *cis(16)/trans(84)*.
** The ratios were determined by integration of the proton NMR (250 mHz) spectra of the mixture and are accurate to within ±3%.
*** Thermodynamic control

(MeOH/HCl, 68°C) entirely into the thermodynamically more stable *trans* diastereomer in optically pure form. This isomerization was shown to occur *via* cleavage across the C(1)-N(2) bond followed by bond rotation and recyclization.[9] In order to determine if these results were general, the mixture of the *cis/trans* isomers (**6-13**) were stirred for 72 hours at 25°C in a mixture of TFA and CH_2Cl_2. As illustrated in Scheme II, the amount of *trans* diastereomer in **6,7** and **11** increased from a *cis/trans* ratio of 25:75 to 11:89 in TFA. Moreover, the ratio of **13a/13b** decreased to 11:89 in the case of the 1-cyclohexyl THβC. It appears that the *trans* diastereoselection in TFA is the result of thermodynamic control presumably *via* scission across the C(1)-N(2) carbon-nitrogen bond followed by recyclization.[9]

From the intermediates in Figure 1 and Scheme I it is easy to rationalize the *trans* diastereoselectivity in refluxing benzene for scission across the C(1)-N(2) bond can not occur. The reaction is irreversible. Attack predominantly occurs on **1b** from the side opposite the ester function to provide high *trans* diastereoselectivity. This analysis is consistent with the loss of stereoselectivity in the N_b-alkoxy substituted tryptophan methyl esters[11] which has recently been confirmed by Ottenheim *et al.*[13]

The origin of the *cis/trans* isomers in trifluoroacetic acid is much more complex. The effect of $A^{1,2}$-strain and 1,3-diaxial interactions between substituents at positions-1 and -3 in the twist chair conformation are complicated by the interaction of the benzyl group with the substituents at positions-1 and -3 as well as an axial hydrogen atom at C(4). Moreover, in acidic media scission across the C(1)-N(2) bond may occur to provide a ratio based on thermodynamic stability. Based on the data available (see also references 6,7,9,11), it appears that interaction with the indole N_a-H function ($A^{1,2}$ strain) in the transition state is minimized during the kinetic trapping in refluxing

benzene; however, once the indole double bond has reformed (see **2a**—>**3a**, Scheme I), the $A^{1,2}$ strain is increased and favors further conversion into the *trans* diastereomer. This is supported by the increase in *trans* stereoselectivity observed when the mixture of *cis/trans* isomers (Scheme II) from kinetic trapping (PhH,Δ) were stirred in trifluoroacetic acid. Moreover, the increased *trans* diastereoselectivity in the 1-phenyl-3-methoxycarbonyl-1,2,3,4-THBC series ascribed to temperature by Bailey (TFA, CH_2Cl_2, 40°C)[15] may be due to this same phenomenon; acid-catalyzed scission of the C(1)-N(2) bond followed by recyclization to provide the products of thermodynamic control.

The results depicted here indicate that high *trans* stereoselectivity in the Pictet-Spengler reaction with **4** can be obtained in refluxing benzene with the use of bulky aldehydes, as reported.[7] This can be improved upon by use of the isopropyl ester **10**[16] in place of methyl ester **4**. More importantly, the increased thermodynamic stability of the *trans* diastereomer can be employed to advantage by simply stirring the acid-stable aldehyde and **4** (or **10**) in TFA/CH_2Cl_2 at room temperature.[10]

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