2. Scientific paper workshop

Summary

Outline of the exercise

In this exercise students analyse and discuss in groups a short, recently published research paper. They are presented with the paper in short sections on individual handouts; a number of questions follow each section, and are designed to check students' understanding and interpretation of what they have read and to elicit ideas about how to tackle specific practical problems. The exercise is an ideal introduction to handling scientific literature, and it aims to build students' confidence in reading and interpreting papers. The emphasis on effective team work throughout the exercise should also be noted.

This particular article is based on the following paper: "Direct Proof of the Involvement of a Spiro Intermediate in the Pictet-Spengler reaction", P.D. Bailey, *J. Chem. Res.*, 1987, 202–203. General guidance for the preparation of similar exercises based on other papers are provided in the tutor's guide.

Key aims

- to foster team working skills;
- to improve problem solving skills;
- to introduce information retrieval skills;
- to increase students' confidence in their ability to comprehend primary literature; and
- to plan and interpret (modest) research experiments.

Time requirements

- 2 hour workshop (tutor contact time)
- 1 hour private study

A proposed timetable for the exercise is given below, and is based on two 1 hour teaching slots. Groups need to be given the handout for section 3 at the end of the first workshop, so that they can spend approximately an hour studying and discussing it before Workshop 2.

Workshop 1		Workshop 2	
Introduction	10 mins	Section 3 (groups)	10 mins
Section 1 (groups)	10 mins	Section 3 (plenary)	5 mins
Section 1 (plenary)	5 mins	Section 4 (groups)	5 mins
Section 2 (groups)	10 mins	Section 4 (plenary)	5 mins
Section 2 (plenary)	15 mins*	Section 5 (groups)	10 mins
		Section 5 (plenary)	5 mins
(*Hand out Section 3 after workshop 1)		Section 6 (groups)	5 mins
		Section 6 (plenary)	5 mins
Total	50 mins		50 mins

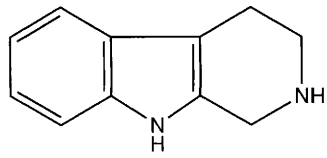
S2 Scientific paper workshop

Student handout 1

Investigating the Pathway taken by the Pictet-Spengler Reaction

This exercise is based on the following paper: P. D. Bailey, *J. Chem. Res.* (S), 1987, 202–203

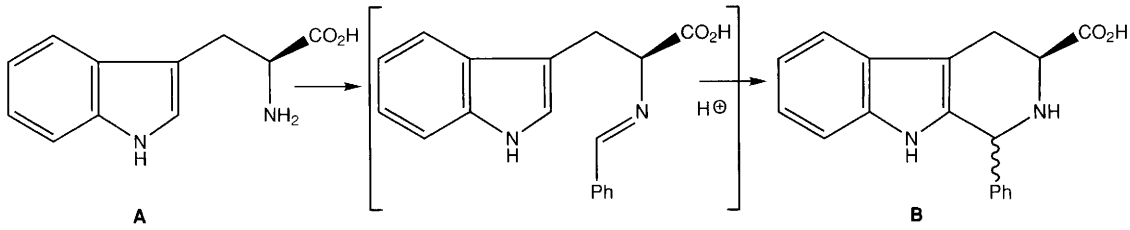
Background information



Many naturally occurring alkaloids contain the tetrahydro-β-carboline unit:

Such indolic natural products, and derivatives of them, can be synthesised in the laboratory by the Pictet-Spengler reaction, which involves condensation between an amine and an aldehyde, followed by ring closure. The reaction scheme below shows one example of a Pictet-Spengler reaction involving a familiar indolic reactant. The naturally occurring amino acid L-tryptophan, **A**, reacts to form a 1,3-disubstituted tetrahydro-β-carboline **B**; notice that **B** is formed as a mixture of *cis* and *trans* isomers.

This workshop is based on a short paper published in a chemical journal. The work described in the paper addressed an important and challenging chemical problem, but the answer to the problem required simple chemical procedures with which you are familiar. By the end of the exercise you will have had an opportunity to read, discuss and comment on the whole paper, and the work that it describes.



Introduction

■ Read the introduction to the paper. (The small numbers shown in superscript refer to published papers which justify the statements made by the authors.)

Direct Proof of the Involvement of a Spiro Intermediate in the Pictet-Spengler Reaction

Recent syntheses of several alkaloids have relied upon the stereospecific formation of tetrahydro-β-carbolines via the Pictet-Spengler reaction[1]: in particular, both *cis*- and *trans*-1,3-disubstituted derivatives have been used in asymmetric routes to a number of indolic natural products.[1a–c] If the stereochemical control possible using the Pictet-Spengler reaction is to be fully exploited, it is vital that the reaction pathway should be elucidated; we therefore undertook to carry out a detailed study on the mechanism of this reaction.

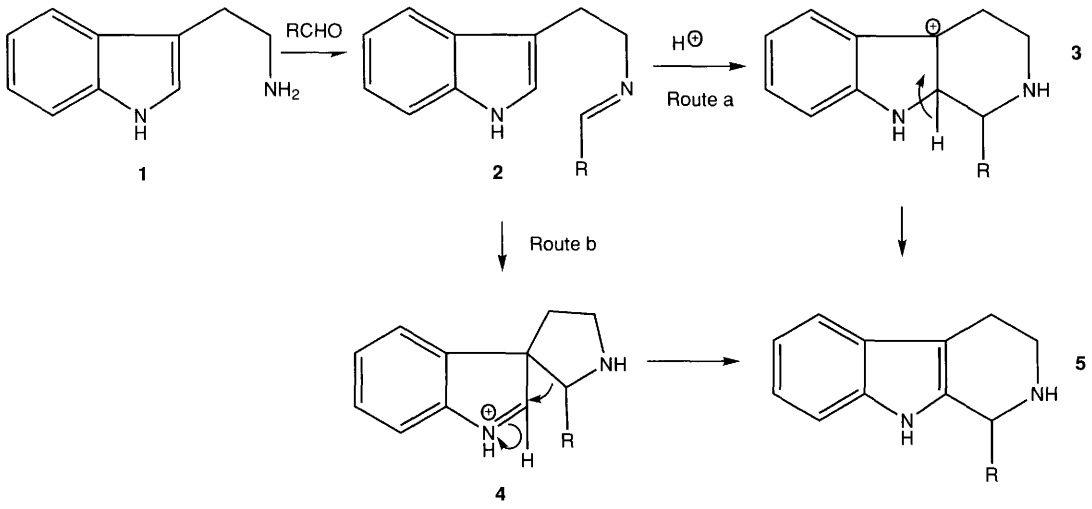
■ Now answer the questions below, which help you think about why the author was interested in this particular problem.

1. What are alkaloids?
2. Why should anyone want to synthesise alkaloids?
3. What features of a synthesis would make it a 'good' synthesis?
4. Why might an understanding of the mechanism of the Pictet-Spengler reaction help to achieve a 'good' synthesis of an indolic alkaloid?

Student Handout 2
Methods for following reaction pathways

■ Read the second paragraph of the paper, which gives information about the state of knowledge of possible reaction pathways at the time this work was started.

There are two main pathways (Scheme 1) by which the ring closure could take place, involving either direct attack at the indole 2-position (route a), or attack at the 3-position followed by migration (route b).[2]



Experiments on related systems have suggested that a spiroindolenine intermediate (**4**) is probably involved (route b);[3,4] however, electrophilic attack at the indole 2-position is known to compete (in acyclic systems) with attack at the 3-position,[5] and it has been noted that certain stereochemical features of the Pictet-Spengler reaction are consistent with either mechanism;[6] moreover, attack at the indole 3-position would presumably involve the 'disfavoured' 5-*endo-trig* ring-closure, whereas direct attack at the 2-position would proceed through the 'favoured' 6-*endo-trig* pathway.[7]

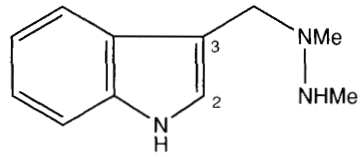
1. Does the author give you the impression that route a is more likely than route b, or vice versa, or that either route is equally likely, or that both routes occur simultaneously? From the way the author has presented the case, suggest likely odds from a bookmaker for the Pictet-Spengler reaction proceeding via route a or route b.

2. Many different methods have been used to study reaction pathways – list as many as you can (general methods and specific techniques). Decide whether these techniques could be used to investigate which of the two suggested routes for the Pictet-Spengler reaction is correct.

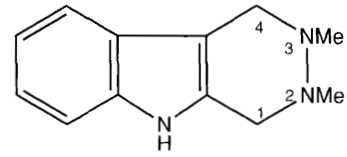
Student Handout 3
Examining the author's strategy

■ Read the following summary of the author's plans.

> In an attempt to clarify the mechanism, we studied the formation of 2,3-dimethyl-1,2,3,4-tetrahydro-3-aza-β-carboline (**7**) by the condensation of the indolic hydrazine (**6**) with formaldehyde, so that any spiro intermediate would possess a plane of symmetry. On repeating the experiment using isotopically labelled formaldehyde, we expected that the label would have been localised on C(1) if direct attack had occurred at the indole 2-position (route a), but would have been distributed between C(1) and C(4) if migration from the indole 3-position had occurred (route b).



6
reactant



7
product

1. What general technique did the author actually use?
2. Draw structures of the intermediates you would expect to obtain in the formation of 2,3-dimethyl-1,2,3,4-tetrahydro-3-aza-β-carboline (**7**) if the reaction proceeds via:

   (i) Route a (*ie* the 3-aza-analogue of **3**);

   (ii) Route b (*ie* the 3-aza-analogue of **4**).

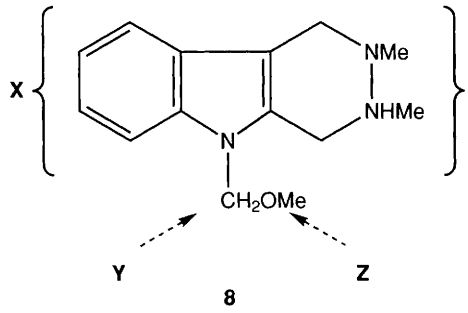
   There is something special about the intermediate from (ii), which might allow the pathways to be distinguished – what is it? (Note: you might find this much easier to see if you make a simple molecular model of the intermediate).
3. Hence, explain why the author expected to be able to clarify the mechanism by carrying out the reaction using labelled methanal, and then studying the distribution of the isotopic label in the final product.
4. Formaldehyde could be labelled with ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{17}O, or ^{18}O. No labelled formaldehyde was commercially available at the time this experiment was done, so the author had to make some. Consider each of the isotopes and decide how you would determine their positions in the final product. Which isotope do you think would most easily provide an answer?

Student Handout 4
The synthesis of products

■ Read what the author did next.

> The indolic hydrazine (**6**) was prepared by the reaction of gramine methosulphate[8] with 1,2-dimethylhydrazine in the presence of aqueous NaOH;[9] reaction of (**6**) with aqueous formaldehyde in methanolic HCl gave the expected Pictet-Spengler adduct (**7**) (26%) and its N^{in}-methoxymethyl derivative (**8**) (50%), after purification by flash chromatography.[10] [$^2H_2$]Formaldehyde was generated by oxidising methanol with pyridinium chlorochromate (PCC),[11] and the CD_2O was swept by nitrogen into a solution of the hydrazine (**6**) in CD_3OD–HCl–D_2O. The condensation reaction proceeded as expected, the tetrahydro-3-aza-β-carboline being isolated as before: its isotopic composition was investigated.

1. Which isotope did the author opt for? Why do you think this isotope was chosen?
2. Why do you think the author initially carried out the synthesis in the absence of an isotope?
3. What is the origin of compound **8** which was found in 50% yield? (In other words, what are the sources of the tricycle (**X**), the CH_2 (**Y**) and the MeO (**Z**) in structure **8**?)



8

4. The author is apparently satisfied with a yield of the desired product (**7**) of only 26%. Why?
5. Decide which technique(s) you would use to investigate the isotopic composition of compound **7** and give reasons for your choice.

Student Handout 5
Analysis of results

■ Here is how the authors studied the isotopically labelled product 7:

> The condensation reaction proceeded as expected, the tetrahydro-3-aza-β-carboline being isolated as before: its isotopic composition was investigated using ^{1}H NMR spectroscopy and mass spectrometry.

■ Read the extracts that describe the results, and answer the questions below which help you to interpret them.

The NMR spectrum

The N-methyl groups, present as two sharp singlets in the ^{1}H NMR spectrum of the non-deuterated compound, were each resolved into four singlets of roughly equal intensity in the deuterated product. (Figure 1).

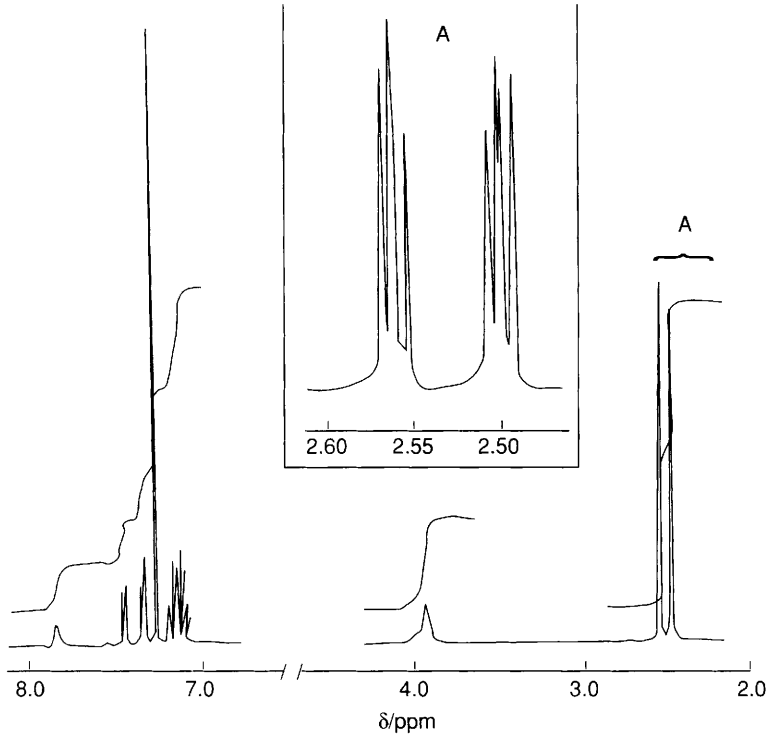


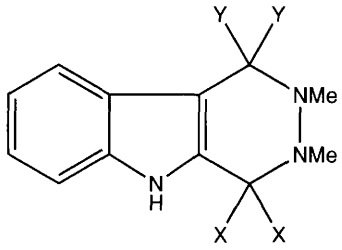
Figure 1 360 MHz ^{1}H NMR spectrum of the deuterated Pictet-Spengler adduct

The C(1) and C(4) hydrogens would be expected to resonate at approximately δ4 in unlabelled **7**.

1. Explain how you might expect to be able to use ^{1}H NMR to tell whether the product had deuterium atoms at positions C(1) and/or C(4)? (In other words what *specific* change in the NMR of the labelled product *vs* the unlabelled product should allow the pathway to be elucidated?)
2. The C(1) and C(4) protons are broad and poorly resolved in the ^{1}H NMR spectrum of the undeuterated adduct. Why can these signals not be used to determine the location of deuterium in the deuterated adduct?
3. The N-methyl hydrogens resonate in the region around δ2.5. Explain why the two methyl groups give signals at slightly different chemical shifts, and why both signals were present as sharp singlets in the undeuterated adduct.

4. Do you agree that there are four signals in the ^{1}H NMR for each of the N-methyl groups?

5. The deuterated compound gave rise to a spectrum containing 'four singlets of roughly equal intensity in the region of δ2.5'. Look at the structure below representing the deuterated product, and decide what arrangement of hydrogen and deuterium in the positions X and Y could give rise to this observation. (Note that the CH_2/CD_2 groups remain intact; isotopes cause slight changes in chemical shifts).



The mass spectrum

Moreover, the mass spectrum revealed parent ions not only at the expected *m/z* of 203, but also at 201 and 205 (Figure 2).

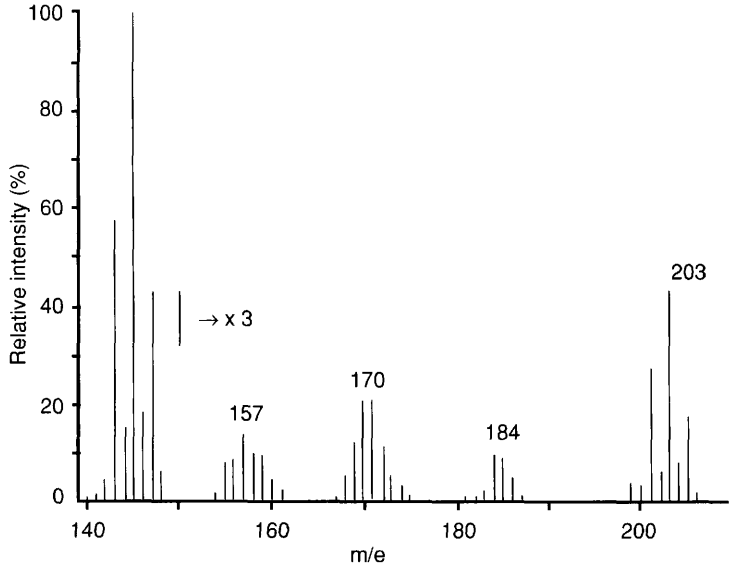


Figure 2 Mass spectrum (E.I.) of the deuterated Pictet-Spengler adduct. Relative ratio of peaks at 201:203:205 = 30:48:22

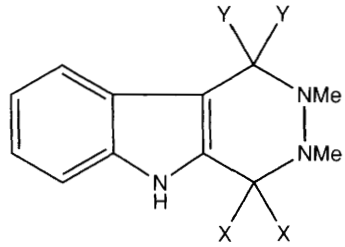
6. Suggest the identities of the molecules which give rise to the parent ions which appear at m/z 201, 203 and 205 in the spectrum.

7. Does your interpretation of the mass spectrum support your ideas about the identity of the deuterated product that you formulated from the NMR spectrum?

Student handout 6
The author's conclusions

The author concluded that the 4 NMR signals for each methyl group at δ2.5 were due, not to coupling, but to the presence of four separate compounds which were very similar indeed:

It was therefore concluded that the labelled product consisted of roughly equal proportions of (**9**), (**10**), (**11**) and (**12**).



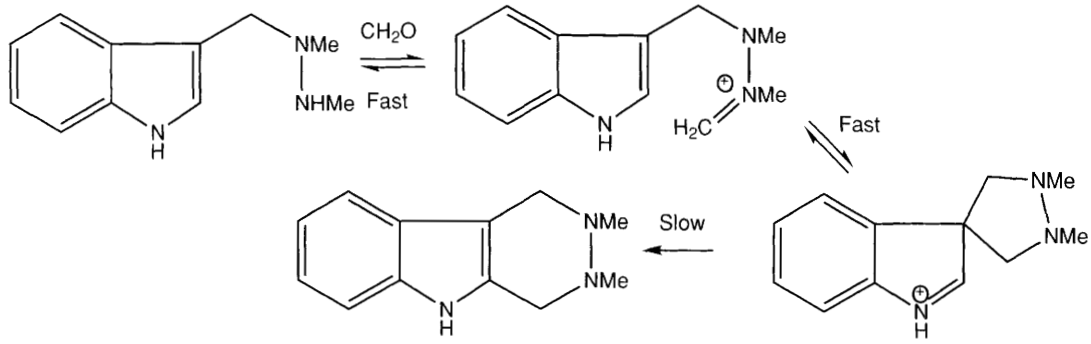
(9) X=Y=H
(10) X=D, Y=H
(11) X=H, Y=D
(12) X=Y=D

1. Did you reach the same conclusion as the author?(If not, who is right?)
2. Are these results consistent with pathway a, or pathway b, or neither?

■ Now read the author's conclusions about the pathway taken by the Pictet-Spengler reaction.

This statistical mixing of the deuterium label is consistent with the series of equilibria shown in Scheme 2, involving a spiro intermediate and reversible imine formation-hydrolysis; subsequent cyclisation to the tetrahydro-3-aza-β-carboline (**7**) must have been slow with respect to these processes.

Therefore, we have provided unambiguous evidence that this Pictet-Spengler reaction involves the rapid reversible formation of a spiro intermediate, and thus it seems likely that tetrahydro-β-carbolines are formed by a migratory pathway. We believe that the findings described herein could lead to a better understanding of the stereochemical features of the Pictet-Spengler reaction.



Scheme 2. Proposed mechanism for the Pictet-Spengler reaction

3. The most unexpected observation was the formation of a product containing four deuterium atoms – convince yourself that Scheme 2 would allow this to occur, and hence that all of the products **9–12** could have been formed if the mechanism in Scheme 2 were operating.

■ Summarise, in your own words, what the author claims to have discovered about the pathway taken by the Pictet-Spengler reaction.

Your summary of the conclusion from the work (maximum 50 words):

The author wrote a fifty-word abstract as the first paragraph of the paper – have a look at that summary. Do you think it is clear and accurate?

Some interesting observations... and what happened later

a) There seems to be little doubt that the author would have used ^{13}C as the label of choice, but presumably selected deuterium on the grounds of cost. He almost certainly expected the loss of ^{1}H signals in the ^{1}H NMR to be used to identify the pathway, and was disappointed to find that it could not be used reliably. But he probably did not expect the isotope effect to be sufficient to yield the necessary data. The mass spectrometry was very important, in order to back up the interpretation. If the isotope effect had not distinguished the methyl groups in the ^{1}H NMR, he could have resorted to the use of a ^{13}C label, although there are other ways to determined the location of the deuterium atoms (how?).

b) The model reactions were carried out in aqueous solution, because (unlabelled) methanal comes as an aqueous solution (formalin; CH_2O is a gas that readily polymerises). With the conditions sorted out, the labelled reaction was also carried out under these conditions. Because imine formation is reversible *in the presence of water*, it became clear that formation of the spiro intermediate was reversible (see c). If water had not been present (and Pictet-Spengler reactions are usually conducted under anhydrous conditions), the involvement of the spiro intermediate would have been proven, but there would have been no evidence that its formation was reversible (**10** and **11** would be formed in equal amounts, whether it was reversible or not).

c) Because the formation of the spiro intermediate was fast and reversible, it was concluded that six-membered ring formation (*via* route a or route b – we cannot tell which) must be the slow, rate determining step, and that factors controlling the stereochemistry of six-membered ring formation should operate. The research group was able to show a few years later that this conclusion was correct[1] – the stereochemistry of the Pictet-Spengler reaction can be controlled by careful choice of substituents and conditions, exactly as predicted by the pathway in Scheme 2. In particular, reference 1 provides a general method of making *cis*-1,3-disubstituted tetrahydro-β-carbolines, which has now been used to synthesise indole alkaloids such as suaveoline[2].

[1] P. D. Bailey *et al.*, *J. Chem. Soc., Perkin Trans. 1*, 1993, 431–9.

[2] P. D. Bailey and K. M. Morgan, *J. Chem. Soc., Chem. Commun.*, 1996, 1479–80.

Student handout 7

202 J. CHEM. RESEARCH (S), 1987

Direct Proof of the Involvement of a Spiro Intermediate in the Pictet–Spengler Reaction†

J. Chem. Research (S), 1987, 202–203†

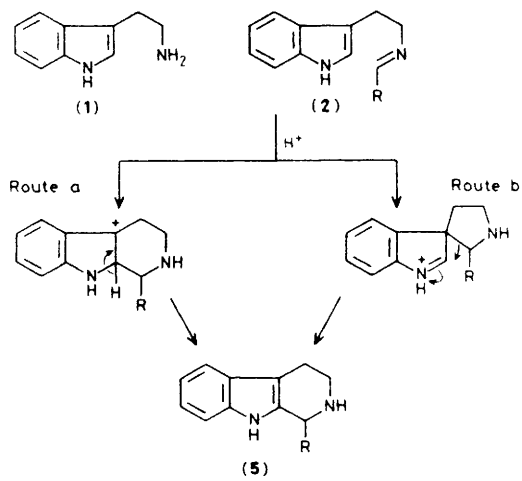
Patrick D. Bailey

Department of Chemistry, University of York, Heslington, York YO1 5DD, U.K.

The formation of 2,3-dimethyl-1,2,3,4-tetrahydro-3-aza-β-carboline (**7**)‡ by the Pictet–Spengler reaction is shown herein to involve the rapid reversible formation of a spiroindolenine intermediate, giving direct proof of the involvement of such a species in this reaction.

Recent syntheses of several alkaloids have relied upon the stereospecific formation of tetrahydro-β-carbolines *via* the Pictet–Spengler reaction:[1] in particular, both *cis*- and *trans*-1,3-disubstituted derivatives have been used in asymmetric routes to a number of indolic natural products.[1a–c] If the stereochemical control possible using the Pictet–Spengler reaction is to be fully exploited, it is vital that the reaction pathway should be elucidated; we therefore undertook to carry out a detailed study on the mechanism of this reaction.

There are two main pathways (Scheme 1) by which the ring closure could take place, involving either direct attack at the indole 2-position (route a), or attack at the 3-position

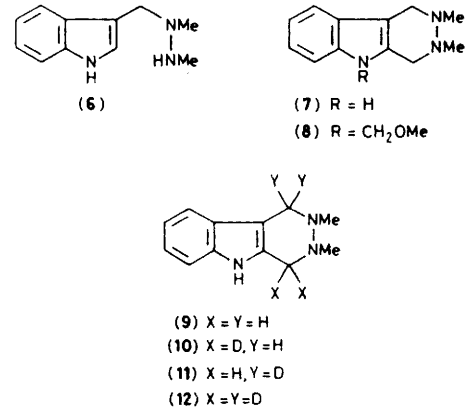


Scheme 1 Possible pathways for the Pictet–Spengler reaction

followed by migration (route b).[2] Experiments on related systems have suggested that a spiroindolenine intermediate (**4**) is probably involved (route b);[3,4] however, electrophilic attack at the indole 2-position is known to compete (in acyclic systems) with attack at the 3-position,[5] and it has been noted that certain stereochemical features of the Pictet–Spengler reaction are consistent with either mechanism;[6] moreover, attack at the indole 3-position would presumably involve 'disfavoured' 5-*endo-trig* ring-closure, whereas direct attack at the 2-position could proceed through the 'favoured' 6-*endo-trig* pathway.[7]

In an attempt to clarify the mechanism, we studied the formation of 2,3-dimethyl-1,2,3,4-tetrahydro-3-aza-β-carboline (**7**) by the condensation of the indolic hydrazine (**6**) with formaldehyde, so that any spiro intermediate would possess a plane of symmetry. On repeating the experiment using isotopically labelled formaldehyde, we expected that the label would have been localised on C(1) if direct attack had occurred at the indole 2-position (route a), but would have been distributed between C(1) and C(4) if migration from the indole 3-position had occurred (route b).

The indolic hydrazine (**6**) was prepared by the reaction of gramine methosulphate[8] with 1,2-dimethylhydrazine in the presence of aqueous NaOH;[9] reaction of (**6**) with aqueous formaldehyde in methanolic HCl gave the expected Pictet–Spengler adduct (**7**) (26%) and its N^{in}-methoxymethyl derivative (**8**) (50%), after purification by flash chromatography.[10] [$^2H_2$]Formaldehyde was generated by oxidising methanol with pyridinium chlorochromate (PCC),[11] and the CD_2O was swept by nitrogen into a solution of the hydrazine (**6**) in CD_3OD–HCl–D_2O. The condensation reaction proceeded as expected, the tetrahydro-3-aza-β-carboline being isolated as before: its isotopic composition was investigated by n.m.r. spectroscopy and mass spectrometry.



It was immediately apparent that the spectra did not correspond to either of the expected results. The *N*-methyl groups, present as two sharp singlets in the ^1H n.m.r. spectrum of the non-deuterated compound, were each resolved into four singlets of roughly equal intensity in the deuterated product (Figure 1). Moreover, the mass spectrum revealed parent ions not only at the expected *m/z* of 203, but also at 201 and

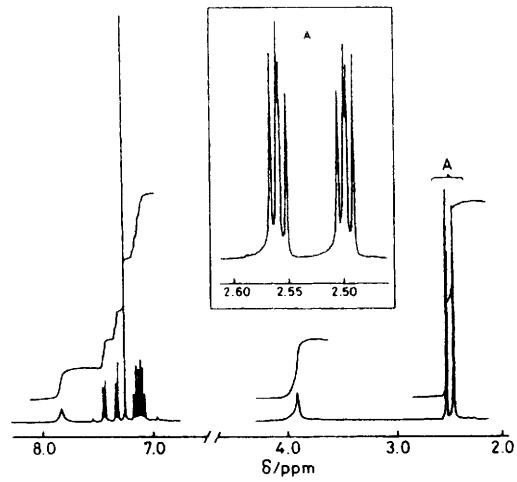


Figure 1 360 MHz ^1H N.m.r. spectrum of the deuterated Pictet–Spengler adduct

†This is a Short Paper as defined in the Instructions for Authors [*J. Chem. Research (S)*, 1987, Issue 1, p. ii]; there is therefore no corresponding material in *J. Chem. Research (M)*.

‡To facilitate the discussion and comparison with previous work on β-carbolines, the term '3-aza-β-carboline' is used for a β-carboline in which the CH at position 3 has been replaced by N. The systematic name for compound (**7**) is given in the Experimental section.

205 (Figure 2). It was therefore concluded that the labelled product consisted of roughly equal proportions of (**9**), (**10**), (**11**), and (**12**). This statistical mixing of the deuterium label is consistent with the series of equilibria shown in Scheme 2, involving a spiro intermediate and reversible imine formation–hydrolysis; subsequent cyclisation to the tetrahydro-3-

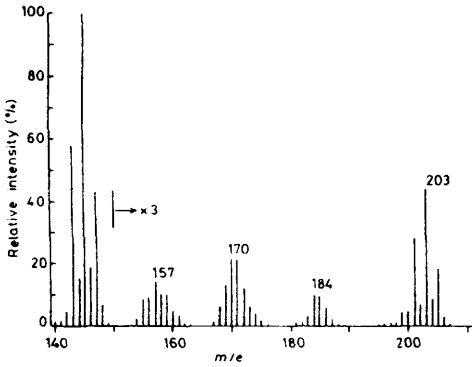
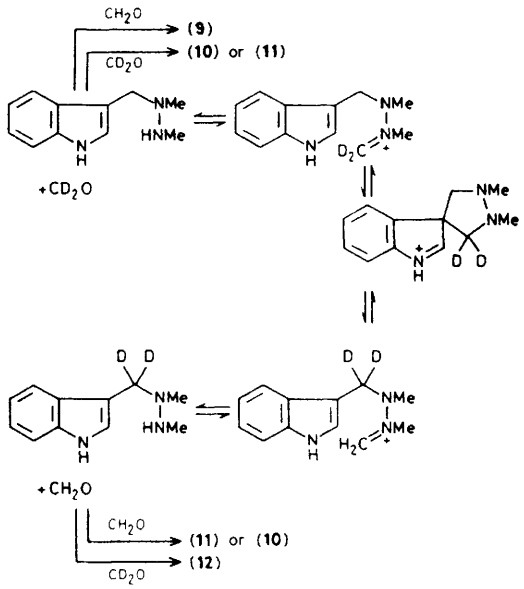


Figure 2 Mass spectrum (e.i.) of the deuterated Pictet–Spengler adduct. Relative ratio of peaks at 201:203:205 = 30:48:22



Scheme 2 Proposed reversible step for the Pictet–Spengler reaction

aza-β-carboline (**7**) must have been slow with respect to these processes.

Therefore, we have provided unambiguous evidence that this Pictet–Spengler reaction involves the rapid reversible formation of a spiro intermediate, and thus it seems likely that tetrahydro-β-carbolines are formed by a migratory pathway. However, it is worth noting that the results of the labelling experiments do not preclude the possibility that isotopic scrambling occurs during the initial reversible step, but that the formation of the six-membered ring occurs by direct attack at the indole 2-position. Nevertheless, we believe that the findings described herein could lead to a better understanding of the stereochemical features of the Pictet–Spengler reaction.

Experimental

M.p.s were determined on a Reichert microscope hot-stage apparatus. N.m.r. spectra were recorded on a JEOL FX90Q spectrometer at 90 MHz (^{1}H) or 22.5 MHz (^{13}C), and chemical shifts are quoted in ppm downfield from Me_4Si as internal standard. Mass spectra were obtained by electron impact at 70 eV on an A.E.I. MS3074 spectrometer. All solvents were purified and dried by standard methods. Flash chromatography[10] was carried out using silica as the stationary phase.

1-(Indol-3-ylmethyl)-1,2-dimethylhydrazine (**6**).—Gramine methosulphate[8] (12.0 g, 40.0 mmol) and 1,2-dimethylhydrazine dihydrochloride (5.32 g, 40.0 mmol) were dissolved in 30% aqueous MeOH (30 ml) at 0 °C and 2 M aqueous NaOH (80 ml) was added. After stirring for 0.5 h at 0 °C, and 1.75 h at room temperature, the mixture was extracted into CH_2Cl_2 (200 ml total). After removal of the solvent, the product was purified by flash chromatography (MeOH–$CHCl_3$; 1:4 v/v), giving a golden oil (4.98 g, 66%); δ_H ($CDCl_3$) 2.41 (3 H, s), 2.60 (3 H, s), 3.02 (1 H, br s), 3.96 (2 H, s), 6.91–7.74 (5 H, m), and 9.49 (1 H, br s); δ_C ($CDCl_3$) 34.83 (q), 43.29 (q), 52.28 (t), 109.43 (s), 111.33 (d), 119.08 (d), 119.35 (d), 121.68 (d), 124.76 (d), 127.96 (s), and 136.30 (s); *m/z* 189 (M^+), 130, and 60 (Found: M^+, 189.1265. $C_{11}H_{15}N_3$ requires *M*, 189.1266).

2,3-Dimethyl-2,3,4,5-tetrahydro-1H-pyridazino[4,5-b]indole (**7**). —The indolic hydrazine (**6**) (95 mg, 0.50 mmol) in a mixture of MeOH (10 ml) and 2 M HCl (0.25 ml) was reacted with 40% w/v aqueous CH_2O (0.1 ml, 1.2 mmol) at 50 °C under N_2 for 3 h. After removal of the methanol *in vacuo*, the product was taken up in CH_2Cl_2, washed with 1 M aqueous NaOH, and evaporated to dryness. Preparative t.l.c. (Chromatotron) in MeOH–$CHCl_3$ (1:9 v/v) eluted *5-methoxymethyl-2,3-dimethyl-2,3,4,5-tetrahydro-1H-pyridazino[4,5-b]indole* (**8**) (62 mg, 50%) as the higher R_f component; δ_H ($CDCl_3$) 2.52 (3 H, s), 2.55 (3 H, s), 3.19 (3 H, s), 3.92 (2 H, br s), 3.98 (2 H, br s), 5.34 (2 H, s), and 7.09–7.49 (4 H, m); δ_C ($CDCl_3$) 35.70 (q), 37.87 (q), 46.48 (t), 47.73 (t), 55.64 (q), 73.95 (q), 106.99 (s), 109.38 (d), 117.99 (d), 120.00 (d), 121.68 (d), 126.33 (s), 130.99 (s), and 137.33 (s); *m/z* 245 (M^+), 187, 157, and 45. (Found: M^+ 245.1530. $C_{14}H_{19}N_3O$ requires *M*, 245.1528). The desired product (**7**) was a component of lower R_f and was obtained as a golden oil (26 mg, 26%), which could be crystallized from CH_2Cl_2 giving colourless *crystals*, m.p. 163.5–164.5 °C; δ_H ($CDCl_3$) 2.40 (3 H, s), 2.53 (3 H, s), 3.71 (2 H, br s), 3.91 (2 H, br s), 7.03–7.47 (4 H, m), and 8.68 (1 H, br s); δ_C ($CDCl_3$) 35.33 (q), 37.83 (q), 46.60 (t), 48.44 (t), 105.49 (s), 111.12 (d), 117.62 (d), 119.30 (d), 121.31 (d), 125.91 (s), 129.49 (s), and 136.20 (s); *m/z* 201 (M^+), 143, and 43 (Found: M^+, 201.1271. $C_{12}H_{15}N_3$ requires *M*, 201.1266).

Deuterated Pictet–Spengler Reaction.—The CD_2O was generated by the reaction of PCC[11] (2 g) in CH_2Cl_2 with CD_3OD (2 ml) under reflux; the CD_2O was flushed into the reaction vessel by a continuous stream of N_2. The indolic hydrazine (**6**) (51 mg, 0.27 mmol) was dissolved in a mixture of D_2O (6 ml), 12 M HCl (0.25 ml), and CD_3OD (5 ml), and was then allowed to react with the CD_2O during 3 h at 80 °C under N_2. After removal of the solvents *in vacuo*, the deuterated Pictet–Spengler adducts (**9**)–(**12**) were isolated by flash chromatography (MeOH–$CHCl_3$; 1:9 v/v) as a colourless oil (4.8 mg, 8.8%), which was identical with the non-deuterated parent (**7**) by t.l.c., and which gave the ^{1}H n.m.r. and mass spectra shown in Figures 1 and 2 respectively (Found for M^+ at 205: 205.1514. $C_{12}H_{11}D_4N_3$ requires *M*, 205.1517. Found for M^+ at 203: 203.1394. $C_{12}H_{13}D_2N_3$ requires *M*, 203.1392).

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References

1 (a) G. Massiot and T. Mulamba, *J. Chem. Soc., Chem. Commun.*, 1983, 1147; 1984, 715; (b) P. Flecker and E. Winterfeldt, *Tetrahedron*, 1984, **40**, 4853; (c) M. Shimizu, M. Ishikawa, Y. Komoda, T. Nakajima, K. Yamaguchi, and S. Sakai, *Chem. Pharm. Bull.*, 1984, **32**, 1313; (d) T. Suzuki, E. Sato, K. Unno, and T. Kametani, *Heterocycles*, 1985, **23**, 835, 839; (e) S. Takano, S. Sato, E. Goto, and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, 1986, 156.
2 F. Ungemach and J. M. Cook, *Heterocycles*, 1978, **9**, 1089.
3 A. H. Jackson, B. Naidoo, and P. Smith, *Tetrahedron*, 1968, **24**, 6119.
4 J. R. Frost, B. R. P. Gaudilliere, and A. E. Wick, *J. Chem. Soc., Chem. Commun.*, 1985, 895.
5 G. Casnati, A. Dossena, and A. Pochini, *Tetrahedron Lett.*, 1972, **13**, 5277.
6 F. Ungemach, M. DiPierro, R. Weber, and J. M. Cook, *J. Org. Chem.*, 1981, **46**, 164.
7 J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 1976, 734.
8 C. Schopf and J. Thesing, *Angew. Chem.*, 1951, **63**, 377 (*Chem. Abstr.*, 1954, **48**, 4509e).
9 *cf.* J. Thesing, *Chem. Ber.*, 1954, **87**, 507 (*Chem. Abstr.*, 1955, **49** 9616f).
10 W. C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.
11 E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 1975, **16**, 2647.

T2 Scientific paper workshop

The aim of this exercise is for students to look at a recently published scientific paper, use their chemistry knowledge to anticipate the steps the researcher might take, and to come up with solutions to problems the author encountered. It is important to demonstrate that the results presented in a paper are the final outcome of numerous ideas, and that undergraduate students are capable of coming up with good, viable solutions to research problems, even though the paper only reports one approach to the particular problem.

Reasonable answers to the questions in the student handouts are provided in Appendix A.

The exercise works best if no preparatory work is expected of the students – it loses some impact if the students have read a lot of background information. Some background information should be given on the first student handout in order to set the scene and outline the task.

Approximately two hours of total contact time are required to run this exercise, although a variety of slots can be used; for example, a single two hour workshop, three fifty minute sessions (each one tackling two sections of the exercise with slightly more discussion possible), or two fifty minute slots with some private study in between. The timing can be manipulated either to extend the exercise, by encouraging more discussion, or to shorten the exercise, by bringing the plenary sessions to a rapid conclusion.

The workshop is not restricted to groups (students could work as individuals or in pairs), although the discussion sessions seem to work particularly well with this arrangement.

This exercise is quite labour intensive on the part of the tutor, who will need to:

- introduce the paper;
- ensure the exercise keeps to time;
- circulate, to ensure discussions are progressing well [additional tutor(s) might help here];
- prompt students for answers in plenary sessions; and
- summarise conclusions at the end of the plenary sessions.

Some ideas for papers to use in this exercise are given below. A number have been broken down in the suggested manner, and in one case questions and answers are also provided for the tutor.

Designing similar exercises

The following notes are given to guide the development of a new exercise. Suggested sources are letters, communications, or short papers, which can be split into sections which are discussed sequentially. The guidelines below assume that the students do not see the complete paper until the end of the exercise.

Most papers can be split into the following sections:

- Introduction
- Experimental section
- Results
- Conclusions

The content of the paper should be divided into several parts and provided on separate handouts. It can also be edited to reduce the amount of information the students have to deal with. Each of these sections can then be studied in turn, and the students' understanding/interpretation confirmed with questions.

Introduction
From the introduction the students should understand why the work described was important. In some instances background information may also be required in order to explain unfamiliar concepts and place the paper's contents in context. If a key statement is made in the introduction, the students could be asked to discuss this. Questions could be structured in a way that guides students to the key points. They could also discuss the choice of any measurement techniques or experimental methods, perhaps suggesting alternatives.

Experimental Section
If possible, students should be asked to draw on their experience in the laboratory when considering the experiments in the paper, and they should decide how they would have planned a similar study. Potential hazards or difficulties and how they should be dealt with could also be covered.

Results
The results section often needs to be split into several sub-sections, so that students are supplied with the 'raw' data if possible, and are asked to consider how it should be interpreted; for example, if spectral data are included, the structure of the sample could be determined. In the case of physical chemistry, the students could be prompted to draw out key features in the data, calculate constants and explain trends. Methods used to present data, such as tables, graphs or spectra, could be discussed and which is most appropriate for a particular situation decided. Students might then discuss the authors' interpretation of the results.

Conclusion
Students could be asked to provide their own conclusions based on the introduction to the paper, and the discussion of results, which could be compared to those of the authors. They could also consider further research that could be undertaken as a result of the paper, or suggest how the results might be of use in 'real life'.

Other suitable papers

The following papers from *Journal of the Chemical Society, Chemical Communications* between 1995–97, exemplify a range of suitable articles. Three of these articles have been further divided into sections and expanded.

1. A saccharide sponge. Synthesis and properties of dendritic boronic acid. T. D. James, H. Shinmori, M. Takeuchi & S. Shinkai, *J. Chem. Soc., Chem. Commun.*, 1996, 705

This paper describes how dendrimers that selectively bind to saccharides via boronic acid groups can be prepared.

i Background

Why might the detection of saccharides be useful? How might you detect them? What are dendrimers? Why might they be useful as sensors?

ii Background experiments

What features of **2** are crucial to its use as a sensor? From Figure 2, what is the binding constant for D-fructuose to **2**?

iii Experimental Section (Part A)

Why did the authors not simply use anthracenylmethyl bromide in the first step of Scheme 1? What are the likely practical problems in making a dendrimer?

iv Experimental Section (Part B)

What is the binding constant for D-fructose to dendrimer **1**? Are there likely to be any complications with the binding? Is this reflected in the binding data?

v Conclusions

What conclusions do you draw? Is the dendrimer useful?

2. New sensor for dissolved dioxygen: a gold electrode modified with a condensation polymer film of β-cylcodextrin hosting cobalt tetraphenylporphyrin. F. D'Souza, Y.-Y. Hsieh, H. Wickman & W. Kutner, *J. Chem. Soc., Chem. Commun.*, 1997, 1191–1192.

i Background

Why might a sensor by useful? How might you detect $[O_2]$ in solution? What is a cyclodextrin?

ii Introduction

Explain how the porphyrin, cyclodextrin, polymer and gold film are all intended to link together to form a sensor. What advantages might the sensor in the paper have over other methods for analysing $[O_2]$?

iii Preparation

Suggest how you might practically carry out the preparation of the new sensor. Did the authors use your method?

iv Results

Is the peak current linearly correlated with the $[O_2]$? At what potential would you monitor in order to get the most accurate measurement of $[O_2]$?

v Conclusions

Do you think the system could be used as a sensor for dioxygen? What problems might there be with it, compared with other oxygen sensors that are available?

3. First example of a copper(I)-water bond. Synthesis and structure of polymeric poly-μ-2,3-diphenylquinoxaline-(aqua)copper(I) cation. J. P. Naskar, S. Hati, D. Dutta & D. A. Tocher, *J. Chem. Soc., Chem. Commun.*, 1997, 1319.

i Background

Why is Cu(I) unstable in water? From the K value, how long would it take for the $[Cu^+]$ to halve in aqueous solution? How might you try and prepare a stable Cu(I)-water complex?

ii Background experiments

How would you prepare ligands L^1, L^2, and L^3?

iii Predictions

What characteristics would you predict for **1** concerning (a) its magnetic properties; (b) its colour; and (c) its stability to oxidation?

iv Results

From Figure 1(a) where are the Cu(1) and H_2O moieties? How much of the π-system in L^3 is planar?

v Conclusions

Does the close up of the X-ray structure confirm your initial interpretation? Why might the preparation of a Cu(I)-water complex be useful or interesting?

- **Formation of HNCO during catalytic reduction of NO_x with olefins over Cu/ZSM-5. F. Radthe, R. A. Koeppel & A. Barker, *J. Chem. Soc., Chem. Commun.*, 1995, 427–428.**
- **Facile formation of a *cis*-platin-nonapeptide complex of human DNA polymerase-α origin. R. N. Bose, D. Li, M. Kennedy & S. Basu, *J. Chem. Soc., Chem. Commun.*, 1995, 1731–1732.**
- **An electrostatic investigation: how polar are ionic surfactant hydrocarbon tails? S. R. Gadre & S. S. Pingale, *J. Chem. Soc., Chem. Commun.*, 1996, 595–596.**
- **It's on lithium! An answer to the recent communication which asked the question: 'if the cyano ligand is not on copper, then where is it?' S. H. Bertz, G. Miao & M. Eriksson, *J. Chem. Soc., Chem. Commun.*, 1996, 815–816.**
- **Reversible dissolution/deposition of gold in iodine-iodine-acetonitrile systems. Y. Nakao & K. Sone, *J. Chem. Soc., Chem. Commun.*, 1996, 897–898.**
- **Hypervalent iodine-induced oxidative nucleophilic additions to alkenes: a novel acetoxy thiocyanation reaction in 1,1,1,3,3,3-hexafluoropropan-2-ol. A. De Mico, R. Margarita, A. Mariani & G. Piancatelli, *J. Chem. Soc., Chem. Commun.*, 1997, 1237–1238.**
- ***In situ* probing of surface sites on supported molybdenum nitride catalyst by CO adsorption. S. Yang, C. Li, J. Xu & Q. Xin, *J. Chem. Soc., Chem. Commun.*, 1997, 1247–1248.**
- **A pH cleavable linker for zone diffusion assays and single bead solution screens in combinatorial chemistry. B. Atrash & M. Bradley, *J. Chem. Soc., Chem. Commun.*, 1997, 1397–1398.**

- **Probing peristatic chirality of alkaline cations: NMR study of alkaline borocryptates. E. Graff, R. Graff, M. Wais Hasseini, C. Huguenard & F. Taulelle, *J. Chem. Soc., Chem. Commun.*, 1997, 1459–1460.**
- **Self-replication in a Diels-Alder reaction. B. Wang & I. O. Sutherland, *J. Chem. Soc., Chem. Commun.*, 1997, 1495–1496.**
- **Immobilization and cleavage of DNA at cationic, self-assembled monolayers containing C_{60} on gold. N. Higashi, T. Inoue & M. Niwa, *J. Chem. Soc., Chem. Commun.*, 1997, 1507–1508.**

Assessment

The fifty-word abstract required in Section 6 of this exercise, submitted by groups or individuals, can be assessed. Alternative assessment exercises include asking students to:

- referee the paper using guidelines from a journal;
- describe an alternative means of studying the same research problem;
- outline a research proposal that might follow on from the results of the paper; or
- describe a potential application of the results.