Observations on the Pictet-Spengler Synthesis of 1,2,3,4-Tetrahydro-β-carbolines

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The Pictet-Spengler cyclisation of the benzylideneimine of tryptophan methyl ester in xylene, contrary to literature reports, occurs extremely slowly, if at all, in the absence of acids. The cyclisation is Bronsted acid catalysed and the rate of cyclisation is related to the pK_a of the Bronsted acid and its concentration. All the acid catalysts studied give essentially the same stereoisomeric mixture of tetrahydro-β-carbolines (*cis* : *trans*, *ca.* 1.2 : 1). The benzylideneimine of tryptamine smoothly cyclises under the same conditions.

Cook *et al.*[1,2] have described, in a series of papers, the cyclisation of tryptophan imines (1) in benzene to tetrahydro-β-carbolines (2). The imines (1) were generated *in situ* from tryptophan methyl ester and the appropriate aldehyde. The current interest in the Pictet-Spengler reaction [3-5] prompts us to correct the assertion [1,2] that the cyclisation (1) ⟶ (2) occurs in benzene in the absence of acids.

The cyclisation (1) ⟶ (2) is generally considered to proceed *via* a transient spiro-imine (3).[6] This cyclisation (1) ⟶ (3) formally constitutes an example of a disfavoured 5-*endo-trig* process.[7]

Hence the direct, geometrically favoured, 6-*endo-trig* cyclisation (1) ⟶ (2) might seem more probable for the Pictet-Spengler cyclisation producing tetrahydro-β-carbolines. However, there are a growing number of formal 5-*endo-trig* processes [8,9] especially in nitrogen-containing systems. Unfortunately, in most cases, there is insufficient evidence to rule out alternative mechanisms involving geometrically favoured processes. Thus the isolation of the spiroindoline (4),[10] from a Pictet-Spengler cyclisation in the presence of Raney nickel, is not necessarily significant support for a spiro-intermediate in tetrahydrocarboline formation. The immonium ion precursor of (4) could participate in ring-chain equilibration without leading to tetrahydrocarboline. Similarly the recently reported [5] stereospecific Pictet-Spengler cyclisation (5) ⟶ (6) provides strong evidence for an *exo-tet* process involving (7). However (5) ⟶ (6) does not distinguish between a 5-*exo-tet* process, studied in detail in indoles by Jackson and his co-workers,[11] and a 6-*exo-tet* process, nor does it establish unequivocally that (6) is the kinetically controlled product.

Our interest in 5-*endo-trig* cyclisations [8] prompted us to re-examine the Pictet-Spengler cyclisation (1a) ⟶ (2a,b) in aprotic solvents reported earlier by Cook *et al.*[1,2] The cyclisation of the pre-formed imine (1a) in benzene at 80 °C essentially fails to proceed. Even at 110 °C in [$^2H_{10}$]-*o*-xylene the half-life of (1a) is *ca.* 151 h (Table). A repeat of Cook's original work (tryptophan methyl ester, benzaldehyde, benzene, 80 °C, 48 h), *i.e.* generating the Schiffs base *in situ*, gave only the Schiffs base (1a) and no β-carboline (2a,b). Less than 50% conversion into β-carbolines (2a,b) occurred when tryptophan methyl ester was heated (48 h) in boiling benzene with benzaldehyde containing 2% (w/w) of benzoic acid. A repeat of the reaction with benzaldehyde containing 10% (w/w) benzoic acid gave a mixture of Schiffs base (1a) (*ca.* 37%) and β-carbolines (2a,b) (*ca.* 63%). In both cases the ratio of *cis* to *trans* β-carbolines (2a : 2b) was *ca.* 1.3 : 1. This is the reverse of that reported by Cook *et al.*[12] We thus conclude that the cyclisation (1a) ⟶ (2a,b) under Cook's conditions [1] is due to acidic impurities.

A more systematic study of the cyclisation of (1a) was undertaken and the reactions were conveniently run in [$^2H_{10}$]-*o*-xylene and followed by n.m.r. spectroscopy (Table). The cyclisation (1a) ⟶ (2a,b) was found to be catalysed by a range of acids. The rate of cyclisation is directly related to the pK_a of the added acid catalyst and its concentration (Table). The strongest acid (CF_3CO_2H, $pK_a = 0$) studied gave the fastest rate of cyclisation and the weakest (*p*-nitrophenol, $pK_a = 7.14$) gave the slowest rate of cyclisation. The rate of

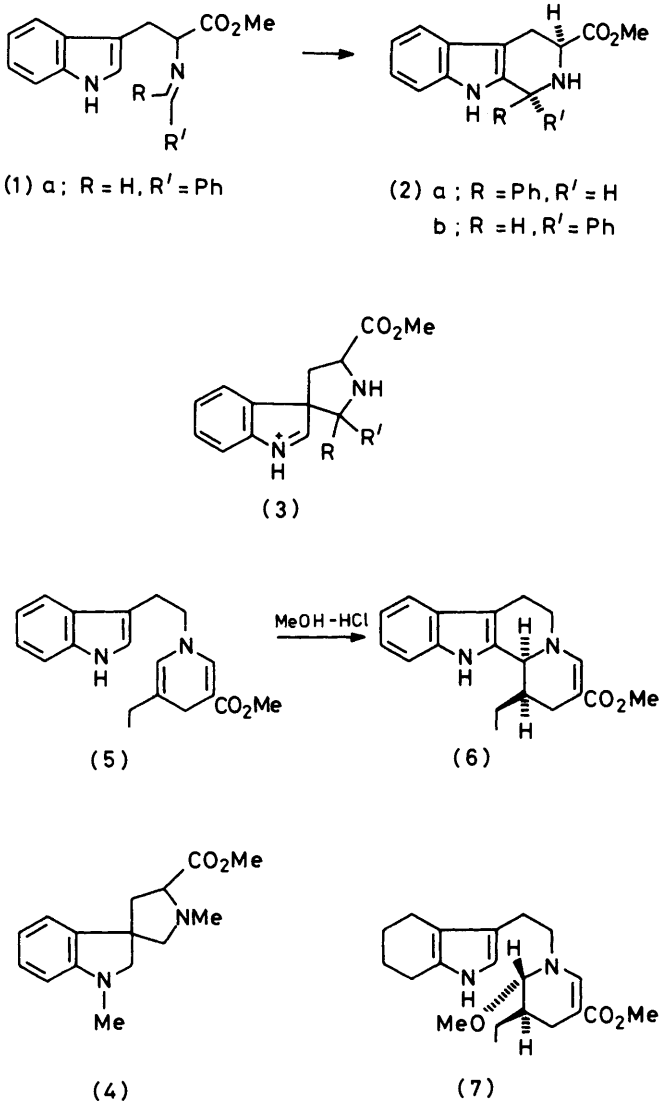
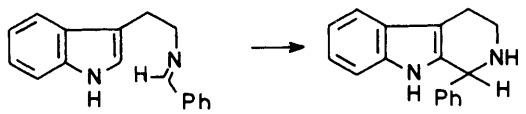


Table.[a] Effect of pK_a of acid catalyst on rate of cyclisation of (1a) (0.2M solution in [$^2H_{10}$]-*o*-xylene)

Acid (M)	pK_a of acid	T/°C [b]	(2a) : (2b) [c]	Pseudo-first-order rate constant ($\times 10^{-5}$) (s^{-1}) [c]	$t_{\frac{1}{2}}$/min [c]	Yield (%) [d]
—	—	110	1.21 ± 0.03	—	9 060 ± 30	—
Benzoic acid (0.05)	4.2	110	1.17 ± 0.01	3.16 ± 0.06	366 ± 7	—
Benzoic acid (0.10)	4.2	110	1.20 ± 0.01	11.4 ± 0.10	101.3 ± 0.9	92
Benzoic acid (0.15)	4.2	110	1.20 ± 0.01	14.2 ± 0.10	81.3 ± 0.5	—
Benzoic acid (0.20)	4.2	110	1.23 ± 0.03	27.6 ± 0.50	41.8 ± 0.7	—
p-Nitrophenol (0.10)	7.14	110	1.36 ± 0.02	1.02 ± 0.03	1 132 ± 32	96
Formic acid (0.10)	3.7	60	1.20 ± 0.06	1.56 ± 0.13	740 ± 57	—
o-Nitrobenzoic acid (0.10)	2.17	60	1.23 ± 0.04	—	—	—
Dichloroacetic acid (0.10)	1.3	60	1.21 ± 0.05	34.9 ± 0.27	33 ± 3.7	—
Trifluoroacetic acid (0.10)	0	60	1.31 ± 0.04	48.8 ± 2.8	23.7 ± 1.3	94

[a] Kinetics were measured in the probe of a Brucker WH90 spectrometer, spectral width 1 000 Hz, 4K data points. [b] Temperature accurate to ±0.5 °C. [c] Errors refer to statistical errors. [d] Yields calculated from the n.m.r. spectra using an internal standard.



(8) (9)

cyclisation of (1a) in the presence of *o*-nitrobenzoic acid (pK_a 2.17) was too fast to measure at 110 °C, whilst at 60 °C the acid was only partially soluble. The tetrahydrocarboline from (1a) is always obtained as a mixture of stereoisomers (2a,b) in these cyclisations. The major product is always the *cis*-isomer, the *cis* : *trans* ratio being *ca.* 1.2 : 1 in all cases. This contrasts with Cook's work which reports the *trans*-isomer as the major product.[12] In all cases the cyclisation occurred cleanly and in high yield (Table; estimated by n.m.r. spectroscopy). We cannot explain the discrepancy between Cook's work [11] and our own with regard to the isomer ratio of the product. Our ratios were estimated directly from the n.m.r. spectra of the crude reaction mixture and confirmed by comparison with spectra of the pure isomers obtained by t.l.c. separation. (*cis*, m.p. 201—202 °C, *trans*, m.p. 176 °C; lit.,[11] *cis*, m.p. 201—203 °C, *trans*, m.p. 175—176 °C).

Finally, it was of interest to compare the rate of cyclisation of (1a) with that of (8) ⟶ (9) in view of the assertion [1] that tryptamine and benzaldehyde do not cyclise to (9) in boiling benzene. This assertion is based on the preparation of (8) by Jackson and Smith [13] under conditions (tryptamine, freshly distilled benzaldehyde, benzene, 80 °C, 30 min) which clearly minimise catalysis by adventitious benzoic acid.

We find that the rate of cyclisation of (8) (0.2M in [$^2H_{10}$]-*o*-xylene) to (9) (64% isolated yield) in the presence of benzoic acid (0.1M) is approximately half as fast (pseudo-first-order rate constant = 5.74×10^{-5} s^{-1}) * as the cyclisation (1a) ⟶ (2a,b) (Table).

Experimental

N.m.r. experiments were performed in sealed tubes previously flushed with argon.

Reaction of Tryptophan Methyl Ester with Benzaldehyde.—(a) Tryptophan methyl ester (2.2 g, 0.01 mol) and benzaldehyde (1.0 g, 0.01 mol) were dissolved in dry benzene (50 ml) and the mixture boiled under reflux for 48 h. Evaporation of the solvent gave a pale yellow residue whose n.m.r. spectrum showed it to be *N*-benzylidenetryptophan methyl ester. The solid was crystallised from methanol to give (1a) (2.38 g, 78%) as colourless prisms, m.p. 128—129 °C (lit.,[1] m.p. 120 °C).

(b) The above experiment was repeated on half scale with the addition of benzoic acid (10 mg). An aliquot was removed after 48 h, the solvent evaporated, and the residue dissolved in [$^2H_6$]dimethyl sulphoxide. The ^1H n.m.r. spectrum of the sample showed it comprised *N*-benzylidenetryptophan methyl ester (1a) (56.25%) and the tetrahydro-β-carbolines (2a,b) (43.75%). The ratio of *cis*-(2a) to *trans*-carboline (2b) was 1.33 : 1. All product ratios were estimated from the ^1H n.m.r. spectrum by comparing the imine proton signal at δ 8.17 with the C(1)-H signals for *cis*-carboline (2a) (δ 5.22) and *trans*-carboline (2b) (δ 5.34).

(c) Experiment (a) was repeated on half-scale with the addition of benzoic acid (50 mg). Work-up of an aliquot as described above gave a mixture of (1a) (37.5%) and (2a,b) (62.5%). The ratio of *cis*-(2a) to *trans*-carboline (2b) was 1.31 : 1.

1-Phenyl-1,2,3,4-tetrahydro-β-carboline.—*N*-Benzylidenetryptamine (25 mg, 10^{-4} mol) and benzoic acid (6.1 mg, 5×10^{-5} mol) were dissolved in *o*-xylene (0.5 ml) and heated at 110 °C for 24 h. On cooling the product crystallised (16 mg, 64%) and was separated by filtration, m.p. 168 °C (lit.,[14] 168 °C).

Acknowledgements

We thank the S.E.R.C. and Queen's University for support.

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* Product precipitation interfered with later data collection, so the value is an approximate one based on *ca.* 40% reaction.

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Received 21*st June* 1982; *Paper* 2/1029