New Evidence for the Presence of a Spiroindolenine Intermediate in Pictet–Spengler Reaction of N^b-Hydroxytryptamine[1]

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The Pictet–Spengler reaction between N^b-hydroxytryptamine and cysteinals in the presence of trifluoroacetic acid gave, in addition to the normal products, β-carbolines (**12**)—(**17**), the unexpected tetracyclic compounds (**4**)—(**9**), providing new evidence for a spiroindolenine intermediate.

Previously[2] we developed a synthetic approach to the eudistomins (**1**),[3] involving a ring transformation of 1-(4-thiazolidinyl)-β-carboline to yield an optically active 1-amino-3-thiaindoloquinolizidine, a possible precursor for the eudistomin ring system. As an alternative synthetic approach to (**1**), we now report the Pictet–Spengler (P–S) reaction between N^b-hydroxytryptamines (**2**) and cysteinals (**3**), see Scheme 1 and Table 1.

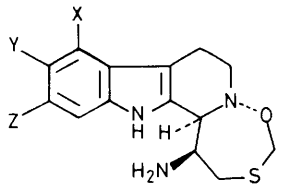
When (**2a**) was treated with (**3a**), prepared from an L-cysteine derivative, and trifluoroacetic acid (TFA) (1 mol. equiv.)† an unexpected tetracyclic compound (**4**) was obtained as a single isomer, in addition to the 2-hydroxy-1,2,3,4-tetrahydro-β-carbolines (**12a**) and (**12b**) as a mixture of diastereoisomers. Similar results were obtained when (**2a**) was treated with a series of protected cysteinals, runs 1—6 in Table 1. In the case of N^a-protected N^b-hydroxytryptamines, such as (**2b**) and (**2c**), the tetracyclic compounds (**10**)—(**11**)

Table 1. P–S reaction of N^b-hydroxytryptamines (**2**) and cysteinals (**3**).

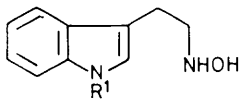
Run	(2)	(3)	Tetracyclic compounds (%)		β-Carbolines (%; a : b)
1	**a**	**a**	(**4**)	(39)	(**12**) (51; 1 : 4)[a]
2	**a**	**b**	(**5**)	(76)	(**13**) (18; 1 : 8)[a]
3	**a**	**c**	(**6**)	(21)	(**14**) (62; 1 : 4)[b]
4	**a**	**d**	(**7**)	(47)	(**15**) (34; 1 : 5)[b]
5	**a**	**e**	(**8**)	(33)	(**16**) (56; 1 : 6)[b]
6	**a**	**f**	(**9**)	(75)	(**17**) (24; 1 : 8)[a]
7	**b**	**f**	(**10**)	(80)	
8	**c**	**g**	(**11**)	(88)	

[a] Ratio by isolation. [b] Ratio by ^{1}H n.m.r.

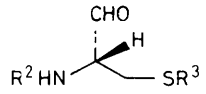
† When the reaction of (**2a**) with (**3a**) was carried out without TFA, the nitrone produced was isolated and readily converted into (**4**), (**12a**), and (**12b**) by addition of TFA.



(1) **a**; X = H, Y = OH, Z = Br
b; X = Br, Y = OH, Z = H
c; X = Y = H, Z = Br
d; X = Z = H, Y = Br



(2) **a**; R^1 = H
b; R^1 = MOM
c; R^1 = Me



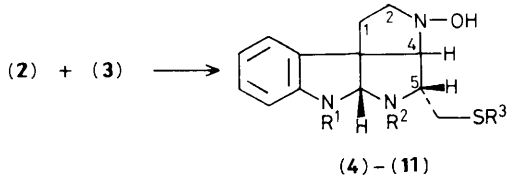
(3) **a**; R^2 = Boc, R^3 = CO_2Me
b; R^2 = Boc, R^3 = Me
c; R^2 = Troc, R^3 = CO_2Me
d; R^2 = CO_2Me, R^3 = Boc
e; R^2 = CO_2Me, R^3 = Troc
f; R^2 = CO_2Me, R^3 = Me
g; R^2 = CO_2Me, R^3 = MEM

MOM = Methoxymethyl, MEM = $MeOCH_2CH_2OCH_2$, Troc = 2,2,2-trichloroethoxycarbonyl, Boc = benzyloxycarbonyl

(runs 7—8) were the only products obtained and no β-carboline derivatives were detected.

The structures of the tetracyclic compounds (**4**)—(**11**) and β-carbolines (**12**)—(**17**) were determined from their spectral data. The stereochemistry of these compounds was confirmed by *X*-ray analysis of (**4**) and (**17b**).‡ Thus, the tetracyclic compound (**4**) has a *trans* relationship between C-4 and C-5. Further treatment of (**5**) with TFA (6 mol. equiv.) (CH_2Cl_2, room temp., 6 h) afforded the corresponding β-carbolines (**13a**) (9%) and (**13b**) (72%).§ Most surprisingly, the major β-carboline product (**13b**) has the opposite configuration at its C-1 position compared with the corresponding carbon (C-4) of (**5**), although a mechanism which rationalizes this result is not clear at present. However, the isolation of these tetracyclic compounds implies the existence of the spiroindolenine intermediate (**18**).[5]

However, as the tetracyclic compounds are aniline derivatives, it was expected that a selective electrophilic substitution



(**4**)–(**11**)

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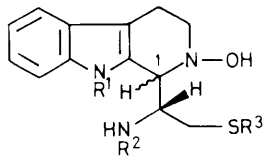
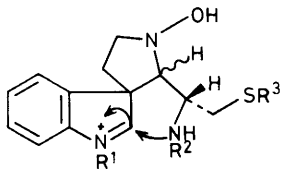
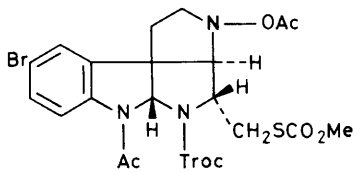


(**12**)–(**17**) **a**; C-1 = α-H
b; C-1 = β-H

Scheme 1. *Reagents and conditions:* i, TFA (1 equiv.), CH_2Cl_2, room temp., 5 min.



(**18**)



(**19**)

could occur *para* to the benzene ring nitrogen of the tetracyclic compounds. Thus, treatment of the diacetyl derivative obtained from acetylation of (**6**) with *N*-bromo succinimide (NBS) (1.2 mol. equiv.) (AcOH, room temp., 3.5 h) gave the 5-bromo derivative (**19**) (90%) which can be considered a key precursor to eudistomin L (**1d**).

Financial support from The Ministry of Education, Science and Culture of Japan, in the form of a Grant-in-Aid for Scientific Research, is greatly appreciated.

Received, 12th November 1987; Com. 1654

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‡ *Crystal data* for (**4**): $C_{23}H_{25}N_3O_5S$, monoclinic, space group $P2_1/N$, a = 11.548(3), b = 21.544(3), c = 9.896(2) Å, β = 112.89°, U = 2267.62 Å^3, Z = 4, D_c = 1.33 g cm^{-3}.

For (**17b**): $C_{16}H_{21}N_3O_3S$, triclinic, space group $P1$, a = 10.295(5), b = 8.293(4), c = 11.730(4) Å, α = 108.32, β = 114.62, γ = 82.44°, U = 864.32 Å^3, Z = 2, D_c = 1.29 g cm^{-3}.

Lattice constants and intensity data were measured using graphite monochromated Cu-K_α radiation on a Rigaku AFC-5 diffractometer. A total of 3065 unique reflections for compound (**4**) and 2470 for compound (**17b**) with $F_0 > 3\sigma(F_0)$ were obtained using the $\omega < 30° < \omega - 2\theta$ scanning method with a 2θ scan speed of 4° min^{-1} to 2θ = 120°. The structure was solved by the UNICS-III system MULTAN 80 (Library of Computer Center of Tokyo University, T. Sakurai and K. Kobayashi, *Rep. Inst. Phys. and Chem. Res.*, 1979, **55**, 69) based on direct methods, and refined to final R values of 0.051 for (**4**) and 0.044 for (**17b**).

Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1, 1988.

§ Similarly, (**4**) and (**6**)—(**9**) were converted into the corresponding β-carbolines while (**10**) and (**11**) were stable under these conditions and were recovered unchanged.