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CARBOXYL-MEDIATED PICTET-SPENGLER REACTION. DIRECT SYNTHESIS OF 1,2,3,4-TETRAHYDRO β-CARBOLINES FROM TRYPTAMINE-2-CARBOXYLIC ACIDS.[1]

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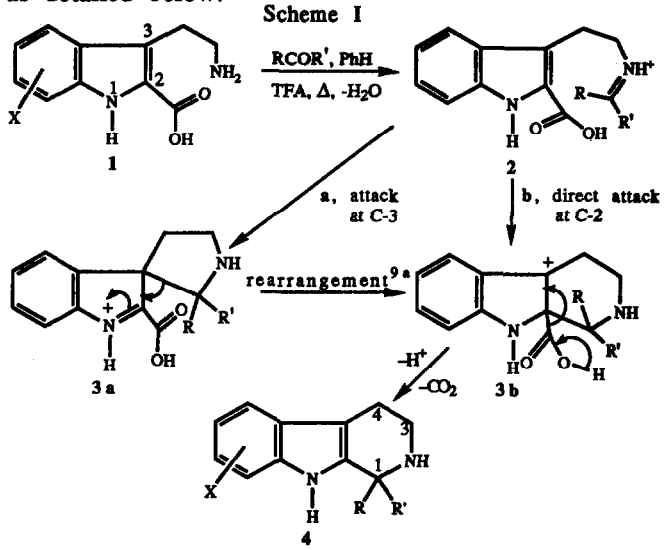
Summary: The Pictet-Spengler condensation of various tryptamine-2-carboxylic acids **1** with carbonyl compounds in benzene/dioxane/trifluoroacetic acid (Table) with simultaneous loss of carbon dioxide, afforded directly the corresponding 1,2,3,4-tetrahydro β-carbolines **4** in good to excellent yields.

The alkaloids 1-methoxycanthine-6-one, 1,11-dimethoxycanthine-6-one and their congeners have been shown to exhibit cytotoxic, antileukemic activity via their inhibitory effects on DNA synthesis in GPK epithelial cells.[2,3,4] Oxygenation of the canthine-6-one skeleton either at position-1 (C-4 in the β-carboline numbering system) and/or in ring A greatly enhances the cytotoxic, antileukemic activity of these bases.

Although 1-methoxycanthine-6-one has recently been prepared in our laboratory,[5] current efforts have centered on the synthesis of "unnatural products" such as 1,8,10-trimethoxycanthine-6-one to investigate the mode of action *in vivo* of these unique oxygenated canthine-6-ones.[2-4] The synthetic approach to these bases requires a simple route to substituted tryptamines, the most straightforward of which was reported earlier by Abramovitch and Shapiro.[7] This process suffers, however, because the decarboxylation of the tryptamine-2-carboxylic acid to provide the substituted tryptamine sometimes occurs in only moderate yields and occasionally fails completely to provide the desired tryptamine. This is due to the nature of the substituents on the indole ring.[6] Since the Abramovitch-Shapiro method is perhaps the best route to substituted tryptamine-2-carboxylic acids, the mechanism of the Pictet-Spengler reaction[7a-c] was reviewed in regard to this problem. As outlined in Scheme I, if the tryptamine-2-carboxylic acid **1** could be encouraged to form the Schiff base **2**, and is then heated, this might provide the spiroindolenine intermediate **3a** (C-3) or the carbocation **3b** [path b (C-2) or from **3a**].[9a,b] Loss of both the proton and the elements of CO_2 from **3b** to satisfy the positive charge would provide

the desired 1,2,3,4-tetrahydro β-carboline **4**. We wish to report the realization of this objective, as detailed below.

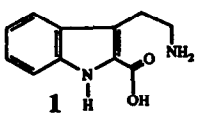
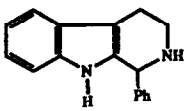
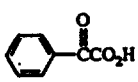
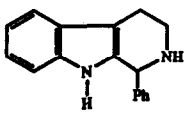
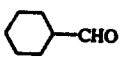
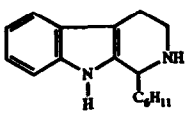
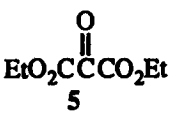
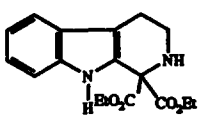
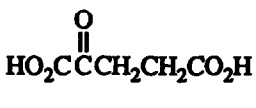
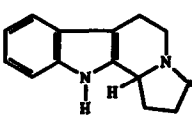
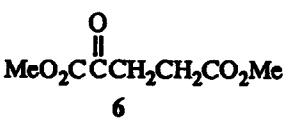
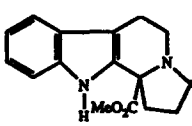
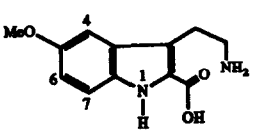
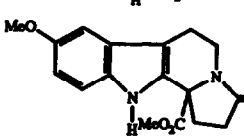
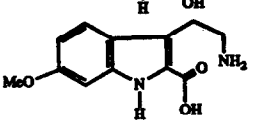
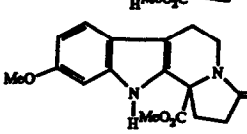
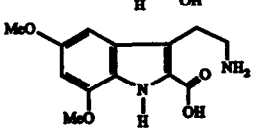
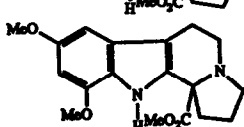
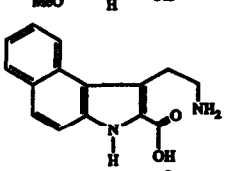
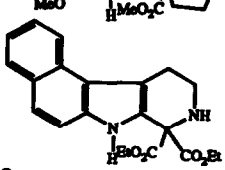
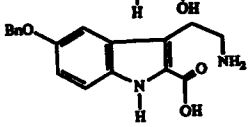
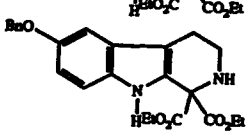
Scheme I



Simply heating the substituted tryptamine-2-carboxylic acid **1** with the carbonyl compound in a solution of benzene/dioxane/trifluoroacetic acid at reflux[8] with water removal (Dean-Stark trap[9]) furnished the desired 1,2,3,4-tetrahydro β-carboline. The results of the condensation reaction between various tryptamine-2-carboxylic acids and a carbonyl component are summarized in the Table. The process appears to be quite general for simple aldehydes such as benzaldehyde and cyclohexanecarboxaldehyde (entries 1 and 3) can be employed, as well as more reactive electrophiles including α-ketoacids and α-ketoesters (entries 2, 4-11). The loss of CO_2 occurs during the Pictet-Spengler reaction, as shown in Scheme I. When tryptamine-2-carboxylic acid, 5-benzyloxytryptamine-2-carboxylic acid, or 5,7-dimethoxytryptamine-2-carboxylic acid were heated under the reaction conditions in the absence of a carbonyl component, no evidence for the formation of the parent tryptamines was observed, respectively.

The higher yield of THβC from 6-methoxytryptamine-2-carboxylic acid (entry 8, 80%) *vs* the 5-methoxy analog (entry 7, 60%) is noteworthy for this implies that cyclization has occured directly at C-2[7c] rather than by the normal mode of cyclization (C-3).[7a,b] Formation of the α-ketocarbonium ion intermediate **3a** is presumably too high in energy in comparison to **3b** (C-2).

Table 1. Synthesis of 1,2,3,4-Tetrahydro-β-carbolines from Tryptamine-2-carboxylic Acids.

Entry	Tryptamine-2-acid	Carbonyl component	Product (% yield)
1.	 1	PhCHO	 (75)
2.	1		 (62)
3.	1		 (65)
4.	1	 5	 (65)
5.	1		 (58)
6.	1	 6	 (55)
7.		6	 (60)
8.		6	 (80)
9.		6	 (65)
10.		5	 (60)
11.		5	 (75)

The significance of the above findings has far reaching implications in the indole area. In regard to the previous technology,[6] it is no longer necessary to remove the 2-carboxylic acid function from tryptamine-2-carboxylic acids prior to the execution of the Pictet-Spengler reaction. This further enhances the use of the Abramovitch-Shapiro method for the synthesis of substituted β-carbolines, as well as the Fischer, Reissert and Moody routes to such indoles.

References and Notes

1. Cook, J. M. A portion of this work was presented at the Mona Symposium, University of the West Indies, Mona, Jamaica, January 8-12, **1990**.
2. For a list of structures of these alkaloids see Hagen, T. J. Ph.D. Thesis, University of Wisconsin-Milwaukee, Milwaukee, WI, p164 (**1988**) and references cited therein.
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7. a) Jackson, A. H.; Naidoo, B.; Smith, P. *Tetrahedron*, **1968,** *24*, 6119.
   b) Ungemach, F.; Cook, J. M. *Heterocycles*, **1978,** *9*, 1089.
   c) Casnati, G.; Dossena, A.; Pochini, A. *Tetrahedron Lett.*, **1972,** 5277.
8. In a typical experiment, the tryptamine-2-carboxylic acid (1 mmole) and the carbonyl compound (1 to 1.5 mmol) were placed in a mixture of benzene/dioxane (2:1, 45 mL) and trifluoroacetic acid (0.5 mL) was added. The reaction mixture was heated to reflux with water removal (Dean-Stark trap) and monitored by tlc. After the reaction was complete, the solvents were removed under reduced pressure and the oil which resulted was partitioned between ethyl acetate and aq. sodium bicarbonate. The 1,2,3,4-tetrahydro β-carbolines were isolated either as hydrochloride salts or precipitated from the ethyl acetate layer on addition of ether. In the case of aldehydes, it is important to use only one equivalent of the carbonyl compound, since excess aldehyde results in the formation of byproducts from overoxidation of the tetrahydro β-carboline.
9. Soerens, D.; Sandrin, J.; Ungemach, F.; Mokry, P.; Wu, G. S.; Yamanaka, E.; Hutchins, L.; DiPierro, M.; Cook, J. M. *J. Org. Chem.*, **1979,** *44*, 535.

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