"Pictet-Spengler-like" Synthesis of Tetrahydro-β-carbolines under Hydrolytic Conditions. Direct Use of Azalactones as Phenylacetaldehyde Equivalents

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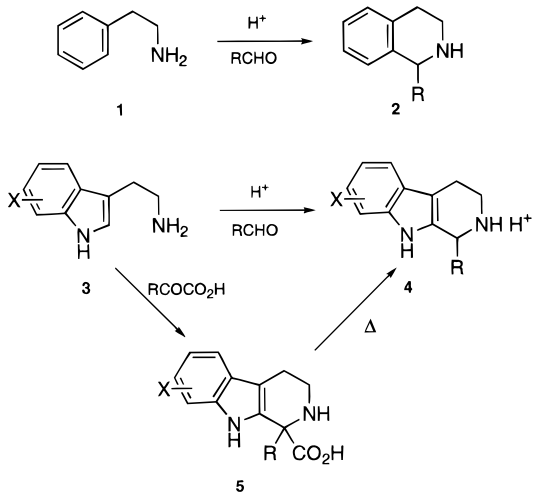
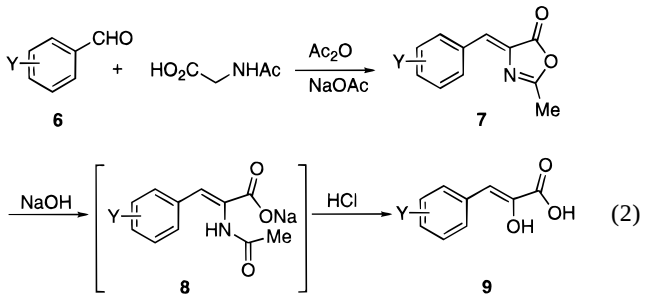
The Pictet−Spengler reaction has been employed routinely to provide access to a variety of isoquinolines (**2**) and tetrahydro-β-carbolines (**4**).[1] While traditional protocols call for the condensation of tryptamines and phenethylamines with aldehydes and reactive ketones, variants have emerged that employ alternative electrophilic components such acetals,[2] α-keto acids,[3] and activated alkynes,[4] further broadening the scope of targets accessible with this methodology.



(1)

In the course of our investigation of the structure−activity relationship (SAR) of a series of serotonin 2B receptor antagonists,[5] we required a robust and general synthesis of tetrahydro-β-carbolines possessing CH_2-aryl substituents at C-1. While the Pictet−Spengler reaction of tryptamines with phenylacetaldehyde itself is well-behaved, the variety of readily available substituted phenylacetaldehydes is quite limited.[6] In our exploration of alternatives, we came upon a solution to this problem first identified more than a century ago.[7] We recognized the conversion of benzaldehydes to phenylpyruvic acids (**9**) via their azalactones (**7**) as a source of considerable structural diversity in "phenylacetaldehyde equivalents", which could then be utilized in a Pictet−Spengler tetrahydro-β-carboline synthesis to drive our SAR studies.[3,6]



(2)

As anticipated, the azalactone syntheses were straightforward, with unoptimized yields typically 50−70% of material isolated by simple filtration.[8] However, in our hands, the two-stage (base followed by acid) hydrolysis to the phenylpyruvic acids was problematic and low-yielding, primarily due to difficulties with product isolation and the necessity for both acid and base stability of accompanying functionality. To further complicate issues, the subsequent Pictet−Spengler reaction with tryptamines (typically carried out in alcoholic solvent) was accompanied by the production of varying amounts of the esterified analog of acid **5**, thereby precluding decarboxylation, making final product isolation tedious and necessitating chromatographic purification.[3] Our observation that a single-stage acidic hydrolysis of the azalactones was feasible[10] suggested to us a short-circuit approach and prompted us to attempt an *in situ* acidic hydrolysis of the azalactone in the presence of the tryptamine, thereby avoiding issues of α-keto acid stability and isolation. Further, the use of aqueous medium for the reaction would preclude the possibility for esterification prior (or subsequent) to cyclization. In the event, admixture of the tryptamine HCl salt and a slight excess of the azalactone in 1 N HCl and heating to reflux for 12−72 h allowed for complete conversion to the tetrahydro-β-carboline (Table 1). Reaction progress could be monitored by TLC or by visual observation of cessation of CO_2 evolution. Product typically could be isolated in pure form (as its HCl salt) in useful yields directly from the reaction mixture by filtration, in many cases avoiding the necessity for chromatographic purification (method A for direct isolation, method B for neutralization, extraction, and chromatography).[11] Although the phenylpyruvic acid **9** could be detected in solution, the direct involvement of enamide **8** (or protonated **7**) in imine formation cannot be excluded.

Thus, the protocol met our criteria for simplicity and generality and has provided us with a vehicle for preparation of a diverse set of compounds for SAR evaluation.

(1) Pictet, A., Spengler, T. *Ber.* **1922**, *44*, 2030. Whaley, W.; Govindochari, T. *Organic Reactions*; John Wiley & Sons, Inc.: New York, 1951; Vol. VI, p 74. Whaley, W.; Govindochari, T. *Organic Reactions*; John Wiley & Sons, Inc.: New York, 1951; Vol. VI, p 151. Sundberg, R. *The Chemistry of Indoles*; Academic Press: New York, 1970; p 236. Abramovitch, R.; Spencer, I. *Advances in Heterocyclic Chemistry*; Academic Press: New York, 1964; Vol. 3, p 79. Ungemach, F.; Cook, J. M. *Heterocycles* **1978**, *9*, 1089.

(2) Valls, N.; Segarra, V. M.; Bosch, J. *Heterocycles* **1986**, *24*, 943.

(3) Knabe, J.; Suggau, R. *Arch. Pharmaz.* **1973**, *306*, 500. Hudlicky, T.; Kutchan, T. M.; Shen, G.; Sutliff, V. E.; Coscia, C. J. *J. Org. Chem.* **1981**, *46*, 1738.

(4) Vercauteren, J.; Lavaud, C.; Levy, J.; Massiot, G. *J. Org. Chem.* **1984**, *49*, 2278.

(5) Audia, J. E.; Evrard, D. A.; Murdoch, G. R.; Droste, J. J.; Nissen, J. S.; Schenck, K. S.; Fludzinski, P.; Cohen, M. L. *J. Med. Chem.* **1996**, *39*, 2773.

(6) ACD database searching indicated commercial availability of only the parent phenylacetaldehyde. Conversely, a similar ACD database search indicated commercial availability of >500 benzaldehyde derivatives.

(7) Plöchl, E. *Ber.* **1883**, *16*, 2815.

(8) We note the exception of 2,6-disubstituted benzaldehydes in which azalactone formation fails, presumably due to steric factors.

(9) Snyder, H. R.; Buck, J. S.; Ide, W. S. *Organic Syntheses*; Blatt, A. H., Ed.; John S. Wiley & Sons: New York, 1943; Collect. Vol. II, p 333.

(10) Our observation was that single stage hydrolysis was an effective, albeit slow, means of preparation of the phenylpyruvic acids. See: MacDonald, S. F. *J. Chem. Soc.* **1948**, 376.

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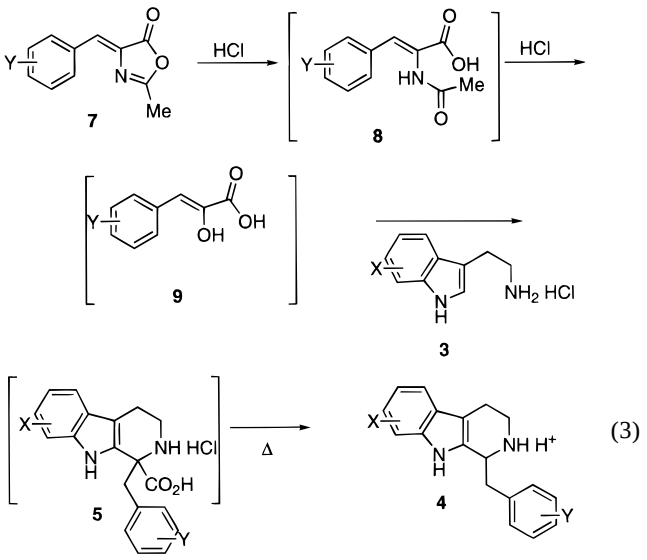


(3)

In addition, the direct isolation of products in pure form without further purification makes this procedure amenable for efficient scaleup.

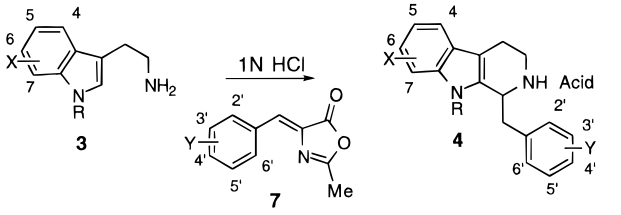
Experimental Section

General Procedures. Solvents and reagents were obtained from commercial suppliers and were used without further purification except as noted. Benzaldehydes were purified by recrystallization from suitable solvents (hexanes, diethyl ether) or by distillation prior to use. The tryptamines employed were obtained from commercial suppliers or were prepared by literature methods. Melting points were determined in open capillary tubes on a Gallencamp melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR were determined at 300 and 75.4 MHz, respectively, in $CDCl_3$ or DMSO-d_6 and chemical shifts reported downfield of TMS. Coupling constants are reported in Hz. Elemental analyses were performed by the Physical Chemistry Department of Eli Lilly and Co. TLC analysis was conducted on silica gel plates visualized with UV at 254 nM and/or staining with *p*-anisaldehyde solution and heating. Preparative chromatography was carried out using modified flash chromatography on 230−400 mesh silica gel, eluting with methanol- or 2-propanol/chloroform mixures in the presence of 0.1% ammonium hydroxide solution.

Procedure for Preparation of Azalactone (7a). 2-Bromo-3,4-dimethoxybenzaldehyde (39.2 g, 0.16 mol) was dissolved in 147 mL of acetic anhydride. *N*-Acetylglycine (19.0 g, 0.16 mol) was added followed by sodium acetate (13.1 g, 0.16 mol), and the mixture was heated to 100 °C in an oil bath for 4 h. The flask containing the reaction mixture was allowed to remain in the oil bath under continued stirring during a slow overnight cooling. During this time, the azalactone precipitated as an orange/red granular solid and was isolated by filtration. Washing with 100 mL of cold diethyl ether and drying under reduced pressure afforded 34.4 g (66%) of azalactone of suitable purity for use in subsequent synthetic operations.

Hydrolytic Condensation of Azalactones with Tryptamines. Procedure A: Preparation of 6-Methyl-1,2,3,4-tetrahydro-1-[(2-bromo-3,4-dimethoxyphenyl)methyl]-9*H*-pyrido[3,4-*b*]indole Hydrochloride (4a). To 60 mL of a 1.0 N solution of hydrochloric acid was introduced 3.0 g (14.26 mmol) of 5-methyltryptamine hydrochloride followed by 5.58 g (17.1 mmol, 1.2 equiv) of azalactone **7a**. Stirring was initiated, and the mixture was heated to reflux for 48 h under an atmosphere of nitrogen. The reaction was allowed to cool to room temperature, and the resulting precipitate was collected through filtration. The solid was washed with water, 2-propanol, and diethyl ether and dried in a vacuum oven. The product tetrahydro-*β*-carboline was obtained as its hydrochloride salt of acceptable purity for biological evaluation without further purification (5.09 g, 79%): mp = 254−256 °C; ^{1}H NMR (DMSO, 300 MHz) δ 2.38 (s, 3H), 2.84 (d, 1H), 3.08 (m, 1H), 3.23 (m, 3H), 3.53 (m, 1H), 3.79 (s, 3H), 3.84 (s, 3H), 4.85 (bs, 1H), 6.95 (d, 1H), 7.13 (d, 1H), 7.29 (m, 2H), 7.43 (d, 1H), 9.05 (bs, 1H), 10.05 (bs, 1H), 11.22 (s, 1H); ^{13}C NMR (DMSO, 75.4 MHz) δ 17.9, 21.1, 37.1, 38.6, 41.5, 52.0, 56.0, 59.8, 105.8, 111.1, 112.0, 117.6, 119.7, 123.3, 126.0, 126.7, 127.4, 129.1, 134.7, 152.7. Anal. Calcd for $C_{21}H_{24}N_2O_2ClBr$: C, 55.83; H, 5.35; N, 6.20. Found: C, 55.57; H, 5.36; N, 6.09.

Table 1. Preparation of Tetrahydro-*β*-carbolines by Direct Condensation of Tryptamines with Azalactones in 1 N HCl



entry	R	X[a]	Y	yield,[b] %	method of prep, salt form
4a	H	5-Me	2′Br, 3′,4′-OMe	79	A, HCl
4b	H	5-Me	3′-OH, 4′-OMe	36	A, HCl
4c	H	5-Me	3′-NO_2, 4′5′-OMe	86	A, HCl
4d	H	5-Me	2′Cl, 3′,4′-OMe	62	A, HCl
4e	H	5-Me	2′Cl, 3′-OH, 4′-OMe	57	A, HCl
4f	H	5-Me	3-CF_3	42	A, HCl
4g	H	5-Me	3′,4′-Me	59	A, HCl
4h	H	4-F,5-Me	2′Cl, 3′,4′-OMe	43	A, HCl
4i	Me	5-Me	2′,3′-benzo	42	A, HCl
4j	H	5-Me	3′,4′,5′-OMe	62	A, HCl
4k	H	7-Br	3′,4′-OMe	55	A, HCl
4l	H	5-Me	3′-OMe	67	A, HCl
4m	H	5-Me	4′-OMe	58	A, HCl
4n	H	5-Me	2′,3′-benzo, 4′-OMe	48	A, HCl
4o	H	5-Me	2′,3′-Me, 4′-OMe	39	A, HCl
4p	H	4,6-Me	2′,3′,4′-OMe	59	A, HCl
4q	H	6-Me,7-Br	2′,3′,4′-OMe	43	A, HCl
4r	H	6-Me,7-Cl	3′,4′-OMe	82	A, HCl
4s	H	5-Br	3′,4′-OMe	42	B, maleate
4t	H	5-Me	3′,4′-F	52	B, maleate
4u	Me	5-Me	3′,4′-OMe	31	B, HCl
4v	H	5,7-Br	3′,4′-OMe	35	B, maleate

[a] Tryptamine numbering employed throughout. [b] Values reported are not optimized and reflect isolated yields of material for which satisfactory NMR, MS, and elemental analysis was obtained.

Procedure B. Preparation of 6-Bromo-1,2,3,4-tetrahydro-1-[(3,4-dimethoxyphenyl)methyl]-9*H*-pyrido[3,4-*b*]indole Maleate (4s). To 20 mL of a 1.0 N solution of hydrochloric acid was introduced 775 mg (3.68 mmol) of 5-methyltryptamine hydrochloride followed by 1.36 g (5.52 mmol) of azalactone (**7k**) (prepared as above, starting with 3,4-dimethoxybenzaldehyde). Stirring was initiated, and the mixture was heated to reflux for 36 h under an atmosphere of nitrogen. The reaction mixture was allowed to cool to room temperature, was diluted with 5% 2-propanol/chloroform, and was made basic by addition of saturated sodium carbonate solution. The layers were separated, and the aqueous layer was back-extracted with 2 volumes of 5% 2-propanol/chloroform. The combined organic phases were dried over sodium sulfate and concentrated under reduced pressure. The residue was subjected to flash chromatography on silica, eluting with 5% 2-propanol/chloroform solution (with 0.1% ammonium hydroxide). Fractions containing product were

(11) Yields reported are unoptimized and in many cases represent a single experiment. Our experience has been that the isolated yields are a reflection of crystallization efficiency, rather than reactivity. This is supported in some cases by examination of the mother liquors, which revealed the presence of additional product. This protocol has also been employed utilizing unpurified tryptamines. Often in these cases, direct product isolation (method A) by filtration was unsuccessful. Alternatively, neutralization of the reaction mixture and extraction with chloroform/IPA afforded crude product (method B). In these cases the yields were significantly lowered, and subsequent purification of the product tetrahydro-*β*-carbolines by silica chromatography was necessitated.

pooled and concentrated under reduced pressure. The product (free base) was dissolved in diethyl ether/methanol and treated with 180 mg (1.56 mmol) of maleic acid with stirring. The resulting salt was isolated by filtration, washed with 2-propanol followed by diethyl ether, and dried under reduced pressure (800 mg, 42%): mp = 184−188 °C; ^{1}H NMR (DMSO, 300 MHz) δ 2.92 (m, 3H), 3.28 (m, 3H), 3.42 (m, 1H), 3.59 (m, 1H), 3.72 (s, 3H), 4.97 (d, 1H), 6.03 (s, 2H), 6.92 (m, 3H), 7.26 (d, 1H), 7.41 (d, 1H), 7.73 (s, 1H), 8.93 (bs, 2H), 11.43 (s, 1H); ^{13}C NMR (DMSO, 75.4 MHz) δ 18.0, 36.9, 41.3, 53.8, 55.3, 55.5, 103.3, 106.1, 111.6, 113.4, 120.6, 121.6, 124.4, 127.7, 127.6, 131.3, 134.9, 135.7. Anal. Calcd for $C_{24}H_{25}N_2O_6Br$: C, 55.72; H, 4.87; N, 5.41. Found: C, 55.51; H, 5.09; N, 5.36.

Acknowledgment. We are grateful to the Physical Chemistry Laboratories of Eli Lilly & Co. for generating the physical data for compound characterization and to Dr. Michael E. Flaugh for his helpful discussions.

Supporting Information Available: ^{1}H NMR, ^{13}C NMR, and elemental (C,H,N) analysis for compounds **4b**−**r** and **4t**−**v** (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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