added and the reaction mixture was left at 0 °C for 12 h. The crystalline (+)-Ipc_2BH was isolated, washed with EE (3 × 30 mL), and dried at 25 °C at 12 mmHg: 51.5 g, 72% yield. The (−)-α-pinene obtained by displacement exhibited $[\alpha]^{23}_D$ −51.1° (neat), 99% ee.

Reaction of (−)-IpcBH$_2$ with (+)-α-Pinene of 91.6% ee in THF. A 50-mL centrifuge vial fitted with a rubber septum and a magnetic stirring bar was charged with 14.3 mL of (−)-$IpcBH_2$ (100% ee) in EE (10 mmol).[16] The solvent EE was evaporated at 25 °C under reduced pressure (12 mmHg). The neat (−)-$IpcBH_2$ was dissolved in 12.3 mL of THF to give a 0.7 M solution and cooled to 0 °C. (+)-α-Pinene of 91.6% ee (1.59 mL, 10 mmol) was added dropwise with stirring. After the addition of α-pinene was complete, the stirring was stopped and the centrifuge vial was stored at 0 °C for 12 h. The crystalline (−)-Ipc_2BH was collected as outlined previously: 2.3 g, 8.03 mmol, 80% yield. The (+)-α-pinene isolated exhibited $[\alpha]^{23}_D$ +51.55° (neat), ≥99.9% ee.

Reaction of (−)-IpcBH$_2$ with (+)-α-Pinene of 84% ee in THF. The experiment was carried out as described above. (+)-α-Pinene of 84% ee was used for the preparation of crystalline (−)-Ipc_2BH: 2.2 g, 7.7 mmol, 77% yield. The (+)-α-pinene isolated exhibited $[\alpha]^{23}_D$ +51.55° (neat), ≥99.9% ee.

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Registry No. (+)-1, 7785-70-8; (−)-1, 7785-26-4; (+)-2, 16997-72-1; (−)-2, 88764-06-1; BMS, 13292-87-0; TMED·$2BH_2$(Ipc), 67826-92-0; (−)-$IpcBH_2$, 74112-25-7.

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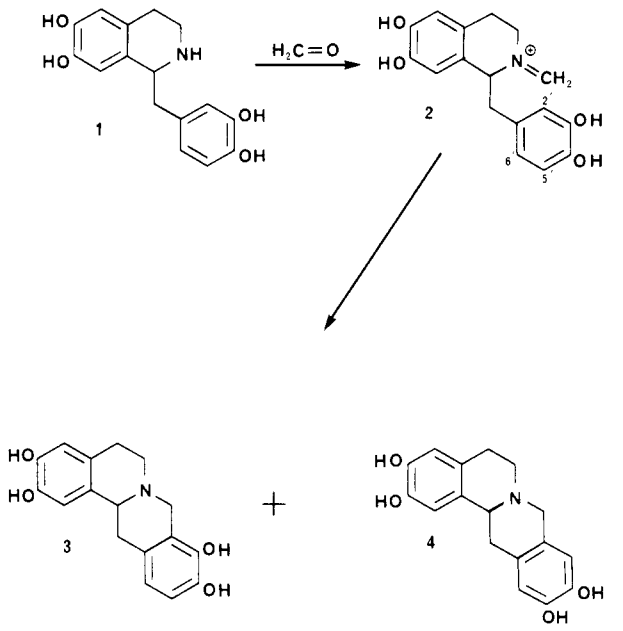
Communications

Kinetics and Product Distribution in Pictet–Spengler Cyclization of Tetrahydropapaveroline to Tetrahydroprotoberberine Alkaloids

Summary: The rate of Pictet–Spengler condensation of tetrahydropapaveroline (THP), a pharmacologically active 1-benzyltetrahydroisoquinoline alkaloid, with formaldehyde in aqueous buffer at 37.5 °C and pH 7.4 is very rapid (k_{obsd} = 30.1 M^{-1} s^{-1}), and this reaction appears to be a viable candidate for the nonenzymatic production of tetrahydroprotoberberine alkaloids in mammalian systems.

Sir: The chemistry of tetrahydropapaveroline (THP; norlaudanosoline; 1-(3,4-dihydroxybenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline; **1**, Scheme I) is of interest for several reasons. The compound occupies the position of apparent central progenitor of many alkaloids found in plants.[1] Futhermore, it has been suggested that **1** may play a role in the development of some of the pharmacological manifestations of alcohol.[2] An integral part of this theory is the postulate that THP, once formed in mammals, may be converted to other pharmacologically active alkaloids, such as the tetrahydroprotoberberines. Publication of this hypothesis stimulated research focused on demonstrating the presence of THP or its metabolites in mammalian systems. THP was reported to be present in the brains of rats given L-dihydroxyphenylalanine (L-Dopa) orally.[3] The alkaloid has also been found in the urine of human patients receiving large amounts of L-Dopa during treatment for Parkinson's disease.[4] Additionally, several tetrahydroprotoberberine derivatives of **1** were demonstrated to be present in the urine of patients with Parkinson's disease receiving L-Dopa therapy and in the urine of rats receiving THP through intraperitoneal injection.[5] The first link between THP and alcohol-related

Scheme I



behavior was furnished by Myers and Melchior[6] who reported that chronic infusion of minute amounts of this compound into the cerebral ventricles of rats evoked marked and long-lasting increases in voluntary consumption of alcohol. This pharmacological action of THP was later confirmed by Duncan and Deitrich.[7]

Although the excessive voluntary selection of alcohol is reported to persist long after cessation of THP infusion,[6,7] it is also noted that brain levels of infused **1** are rapidly decreased.[8] THP, therefore, appears to be readily me-

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Table I. Observed Second-Order Rate Constants and Product Distribution of the Conversion of 1 to 3 and 4 at 37.5 °C and Selected Reaction pH Values

pH	k_{obsd},[a] M^{-1} s^{-1}	3[b]	4[b]
2.0	0.00304	7	93
4.0	0.224	10	90
6.0	9.08	22	78
7.4	30.1	35	65
8.0	36.8	40	60
10.0	40.7	48	52

[a] Each value is the mean of five determinations. [b] Expressed as percent of product mixture.

tabolized in brain of the intact animal. Details of one possible pathway of THP metabolism, i.e., methylation by catechol-O-methyltransferase, have been described.[9] Another metabolic possibility involves condensation of THP with formaldehyde to form 2,3,9,10- and 2,3,10,11-tetrahydroxyberbine (THB) alkaloids (**3** and **4**, Scheme I). Although conversion of **1** to a mixture of **3** and **4** has long been known,[10,11] the kinetics involved have not been described.[12] Such data would be helpful in assessing the potential for nonenzymatic conversion of THP to THB alkaloids in vivo. Accordingly, kinetics and product distribution of the reaction under physiological conditions were determined.

Authentic **1**, **3**, and **4** were prepared by demethylating tetrahydropapaverine,[13] tetrahydropalmatine,[14] and xylopinine,[15] respectively, in refluxing constant-boiling HBr or in concentration HCl at 160 °C in a sealed tube. Demethylations proceeded for 2 h and provided the materials in analytical purity (within 0.3% of calculated values) in 90–95% yields.[16]

Reactions were monitored by high-performance liquid chromatography.[17] Reactions for kinetic measurements were initiated by injecting thermally equilibrated formaldehyde into amine–buffer solutions contained in 3-mL vials equipped with Teflon-faced septa. Reactions with half-times greater than approximately 10 min were analyzed by injecting aliquots directly onto the chromatography column. More rapid reactions were quenched by 1:1 dilution with cold 0.1 M phosphoric acid prior to analysis. Kinetics were determined under pseudo-first-order conditions with formaldehyde in at least 10-fold molar excess by plots of ln THP concentration vs. time, or under second-order conditions with equal concentrations of alkaloid and aldehyde (1 mM) by plotting 1/THP concentration with time.[18]

The rate of condensation of **1** with formaldehyde is strongly base catalyzed. At pH 8 the second-order rate constant is 10^4 times greater than the rate constant at pH 2 (Table I). However, above pH 8 further increases in hydroxyl ion concentration have little effect on the rate constant.

The product distribution of the reaction is also strongly dependent on pH. At pH 2 the reaction produces mainly **4**, while under basic conditions cyclization proceeds to give nearly equivalent amounts of **3** and **4** (Table I).

The generally accepted mechanism of the Pictet–Spengler reaction (Scheme I) involves preliminary formation of a cationic imine, following by nucleophilic attack by the electron-rich 2′ or 6′ carbon.[10] The data presented appear to be consistent with this mechanism. High pH should facilitate cyclization of the intermediate by increasing electron density at the positions ortho and para to the 3′-hydroxyl group. The reaction should be relatively pH insensitive above the p*Ka* of the 3′-hydroxyl group. Product distribution should be approximately 1:1 if electron density at the condensing carbons of the benzylic group is sufficient to insure reaction each time close proximity is achieved. It should be emphasized that the mechanism depicted in Scheme I represents extreme simplification. Many factors that might potentially contribute to the reaction (e.g., equilibria, general acid–base catalysis) are not represented.

The data presented, however, indicate that nonenzymatic Pictet–Spengler condensation of THP (**1**) with formaldehyde under physiological conditions is a rapid process that appears to be sufficiently facile to maintain the reaction as a possible candidate for production of tetrahydroprotoberberine alkaloids in vivo.

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Synthesis of a Chiral Steroid CD-Ring Synthon from D-Leucine by means of Diastereotopic Face-Selection

Summary: Synthesis of (−)-(1*R*,7a*R*)-7a-methyl-7,7a-dihydro-1-[3(*R*)-hydroxy-5-methyl-1(*Z*)-hexenyl]-5(6*H*)-indanone (**11**) by highly stereoselective double Michael addition and determination of its optical purity and absolute configuration by ^{19}F NMR of the PIPA ester and CD spectra, respectively, are presented.

Sir: The discovery of interesting steroids with novel side chains has stimulated the research on the two major problems in steroid synthesis: (1) the stereoselective in-

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