against xenobiotic substances that elicit tissue injury by metabolism to highly reactive electrophilic or free-radical species. Studies on the protection by MTCA against other toxic xenobiotics and the evaluation in this regard of various other 2-substituted thiazolidine-4-carboxylic acids are in progress.

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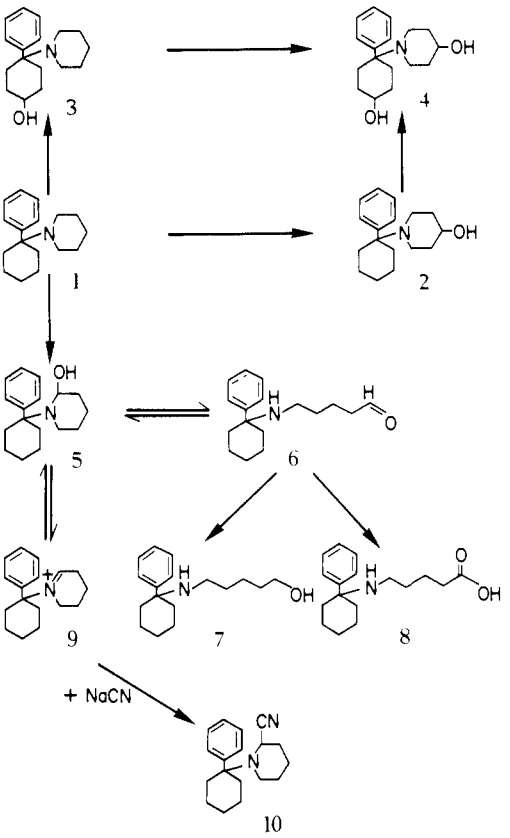
Metabolic Formation of Iminium Species: Metabolism of Phencyclidine

Sir:

Phencyclidine, 1-(1-phenylcyclohexyl)piperidine (1; Scheme I), is a commonly abused drug which displays both acute and long-term neurotoxic effects. Interest in the possibility that metabolites may contribute to the pharmacological and toxicological effects of phencyclidine has led to the identification of the ring-hydroxylated metabolites **2**–**4** in several species.[1] More recently, an amino alcohol (**7**)[2] and amino acid (**8**)[3] have been characterized as metabolites of phencyclidine. The formation of such ring-opened metabolites presumably proceeds via initial α-C-hydroxylation to yield the carbinolamine **5**, which ring opens to the corresponding amino aldehyde **6**, the intermediate leading to **7** and **8**. An unidentified metabolite of 1 has been shown to bind irreversibly to rat and rabbit liver and lung microsomal protein.[4]

Results from previous studies have established that metabolically generated carbinolamines, such as **5**, ionize to yield the corresponding iminium ions.[5,6] These electrophilic species are trapped with nucleophilic cyanide ion as the corresponding α-aminonitriles. With phencyclidine, this sequence would lead to iminium ion **9** and α-aminonitrile **10**. Given the potential reactivity of such an iminium species, it could contribute to the reported metabolically dependent covalent binding to proteins observed with radioactive phencyclidine.[4] Therefore, we were prompted to examine the metabolism of phencyclidine in an attempt to trap **9** as the corresponding α-aminonitrile **10**.

Scheme I



Rabbit liver microsomes were prepared as described previously.[7] Incubation mixtures consisted of 5–10 mg of microsomal protein in 5 mL of 0.1 M *N*-2-hydroxyethylpiperazine-*N'*-2-ethanesulfonic acid (Hepes) buffer, pH 7.6, which contained phencyclidine (1.0 mM), $Na^{14}CN$ (1.0 mM, specific activity 0.5 mCi/mmol), and an NADPH-generating system containing 0.5 mM $NADP^+$, 8 mM glucose 6-phosphate, 1 unit/mL glucose-6-phosphate dehydrogenase, and 4 mM $MgCl_2$. Incubations were carried out at 37 °C for 30 min, and cold 0.1 M $NaHCO_3$, pH 8.2, was added to quench the metabolic activity of the system. This mixture was passed through a Sep-Pak C-18 reverse-phase cartridge (Waters Associates, Inc.). The Sep-Pak was washed extensively with water, and the organic material was subsequently eluted with methanol. Acid–base partitioning led to the isolation of the organic base fraction, which was subjected to thin-layer chromatography on silica gel 60 (EtOAc–CH_3CN–concentrated NH_4OH, 175:20:1). The major radioactive zone detected was extracted and analyzed by chemical-ionization mass spectrometry (130 °C, isobutane/1.0 torr). A prominent ion of mass 242 was observed, consistent with the pseudomolecular ion (MH^+) of aminonitrile **10** minus 1 mol of HCN. Further analysis of the organic base fraction by gas chromatography–electron-impact mass spectrometry (temperature programmed 130–250 °C at 6 °C min^{-1} on a 21 m, 0.2% OV-1, 0.3 mm i.d., fused silica column, 70

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eV) resulted in a peak at 180–185 °C, which gave a fragmentation pattern consistent with **10**: *m/e* (relative intensity) 241 ([M – HCN]$^+$, 5%), 158 (100%), 143 (52%), 129 (80%), 115 (55%), 91 (59%), 83 (58%).

For control samples incubated in the absence of NADP$^+$, less than 0.5% of the initial radioactivity was found in the organic base containing fraction following Sep-Pak chromatography and acid–base partitioning. This compared with 18% for the incubates with NADP$^+$. With subsequent thin-layer chromatography, no zone of radioactivity was detectable. These results confirm that formation of the ^{14}C-labeled organic material is dependent on enzymatic processes utilizing NADPH.

Confirmation of the structure of this product was approached by synthesis of aminonitrile **10**. Following the descriptions given by Leonard and Cook,[8] phencyclidine (3.04 g, 12.5 mmol) was oxidized to the corresponding iminium ion **9** by the addition of the tertiary amine to a solution of mercuric acetate (15.9 g, 50 mmol) in 65 mL of 5% acetic acid which previously had been warmed to 90 °C. After stirring for 2 h at this temperature, the cooled reaction mixture was filtered, and the filtrate was treated with H_2S to precipitate any mercury ions remaining in solution. The filtrate was treated with concentrated $KHCO_3$ until the pH reached 5.5, and then NaCN (3.1 g, 63 mmol) was added. The resulting reaction mixture was stirred overnight at room temperature, and the white precipitate which had separated (2.1 g, 62%) was collected and recrystallized from 2-propanol to yield pure 1-(1-phenylcyclohexyl)-2-cyanopiperidine: mp 85–86 °C; 360-MHz NMR ($CDCl_3$) 2.45–3.45 (m, ring CH_2 protons, 16 H), 3.68 (N-CH, t, J = 7 Hz, 1 H), 4.33 (N-CH, m, 1 H), 5.04 (N-CHCN, m, 1 H), 7.20 (s, Ar H, 5 H) ppm; CIMS (130 °C, isobutane/1.0 torr) *m/e* 242 (MH$^+$ – HCN); GC/EIMS (conditions same as above) *m/e* (relative intensity) 241 ([M – HCN]$^+$, 5%), 158 (100%), 143 (56), 129 (82%), 115 (56%), 91 (54%), 83 (55%); IR (m.o. mull) 2218 (CN) cm^{-1}. Anal. ($C_{18}H_{24}N_2$) C, H, N.

Synthetic **10** cochromatographed with the metabolically derived radioactive adduct of phencyclidine. Isotope dilution analysis (recrystallization to constant specific activity) further confirmed the common identity of the metabolically derived product and synthetic **10**.

Identification of the cyano adduct formed from the coincubation of phencyclidine and NaCN provides indirect evidence for the metabolic formation of iminium ion **9**. We have examined the metabolically dependent covalent binding of 0.1 mM [^{3}H]phencyclidine to rabbit liver microsomal protein as previously described.[4] Under the above incubation conditions, 6 to 8% of the radiolabeled substrate was found covalently bound to protein after 30 min. In the presence of 0.1 mM NaCN, this binding was inhibited by 75%. Concentrations of CN$^-$ as high as 1 mM did not significantly inhibit phencyclidine metabolism by hepatic microsomes. The relative insensitivity of cytochrome P-450 mediated reactions to CN$^-$ has been reported previously.[6] These results lead us to suggest the iminium ion **9** may be undergoing covalent binding to microsomal macromolecules.

Additional studies are in progress to more fully characterize the properties of the iminium ion **9**. Preliminary estimates indicate that 15 to 20% of the initial substrate is trapped as **10**, suggesting that α-C-hydroxylation is a major pathway for phencyclidine metabolism.

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Prostaglandins and Congeners. 29.[1] (16*RS*)-(±)-15-Deoxy-16-hydroxy-16-vinylprostaglandin E_2, an Orally and Transdermally Active Hypotensive Agent of Prolonged Duration

Sir:

The hypotensive action of the 9-ketoprostaglandins has been recognized from the early days of prostaglandin research.[2] However, inasmuch as this effect was no more than transient and obtained only on intravenous administration, it lacked practical application and remained a matter of laboratory interest, albeit an interest enhanced by its favorable mechanism of action and the possibility that clinical hypertension indeed might be a reflection, at least in part, of prostaglandin imbalance.[3] The prospect for the practical exploitation of this property by the development of a prostaglandin analogue with a prolonged hypotensive effect, administrable by a route satisfactory for extended use, and free of significant side-effects has continued as an elusive goal, which to our knowledge has not even been closely approached.[4] In this paper we wish to report substantial progress toward the achievement of this end.

For some time we have been investigating the synthesis and biology of the 15-deoxy-16-hydroxyprostaglandins and have reported the interesting gastric acid secretion inhibitory properties and bronchodilator properties of certain members of this series.[5] In the course of our further exploration of this important prostaglandin class, we had occasion to prepare the 16-vinyl member, which in addition to blocking metabolic inactivation of the transpositioned 16-hydroxy group would also restore allylic character to this function. This compound was prepared by the conjugate addition procedure as illustrated in Scheme I.

The β-chain (C_{13}–C_{20}) precursor **5** was obtained without difficulty from commercial 1-hepten-3-ol (**1**) via oxidation with pyridinium chlorochromate[6] to 1-hepten-3-one (**2**)

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