characterization of **19**, and mono- or dibenzyl derivatives have been prepared and characterized from **20a,b**.[16]

These results show that the greater stability of ester relative to thiol ester is sufficient to dominate over ring size effects. In the most demanding 6- to 8-membered ring conversion **17** → **19**, the result is somewhat obscured by competing dimer formation, but the trends are clear. Differences in ring strain between thiol lactone and mercapto lactone isomers are only important in the reactions **17** → **19** and **16** → **18**. In larger rings, the lactone is favored by a clear margin. Synthetically useful conversions of hydroxyalkyl thiol lactones to mercapto lactones are expected in the absence of drastic changes in strain or transannular interactions.

Acknowledgment. This work was supported by the National Science Foundation (Grant CHE-8113026).

Registry No. 1a, 79815-79-5; **1b**, 79815-88-6; **3**, 81044-80-6; **3a**, 81044-81-7; **3b**, 81044-82-8; **4a**, 81044-83-9; **4b**, 81098-22-8; **5a**, 81044-84-0; **5b**, 81044-85-1; **7a**, 81044-86-2; **7b**, 81044-87-3; **8a**, 81044-88-4; **8b**, 81064-08-6; **9a**, 81044-89-5; **9b**, 81044-90-8; **10**, 81044-91-9; **11**, 61448-27-9; **13**, 81044-92-0; **14**, 81044-93-1; **15**, 81044-94-2; **16**, 81044-95-3; **17**, 81044-96-4; **18**, 81044-97-5; **19**, 81044-98-6; **20a**, 81044-99-7; **20b**, 81045-00-3; **21**, 81045-01-4; 2-diphenylphosphinyl-7-(dimethylbutyl)silyloxymethylthiepane, 81064-09-7; 2-diphenylphosphinyl-6-(2-hydroxy)ethyl-tetrahydrothiopyran, 81045-02-5.

(15) **21** (oil): NMR (270 MHz, $CDCl_3$) δ 7.3 (5 H, m), 4.3 (1 H, ddd, J = 11.4, 5.9, 4.0 Hz), 4.1 (1 H, ddd, J = 11.4, 5.5, 4.0 Hz), 3.7 (2 H, s), 2.57 (1 H, m), 2.15 (2 H, two overlapping dt, J = 15.4, 6.6 Hz and J = 15.4, 6.3 Hz), 1.8 (2 H, J_{AB} = 5.5 Hz), 1.67 (2 H, m), 1.48 (4 H, m); IR (neat) 1740 cm^{-1}.

(16) Satisfactory exact mass data have been obtained for all lactones and dilactones.

(17) A solution of 2-lithiothiepane *S*-oxide was added to excess dimethyl carbonate in THF (at 20 °C, 45% yield of 2-carbomethoxythiepane *S*-oxide). Reduction with $NaBH_4$ in ethanol–THF (1.5 h, 20 °C) gave **14** (82%).

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Suicidal Inactivation of Cytochrome P-450 by Cyclopropylamines. Evidence for Cation-Radical Intermediates

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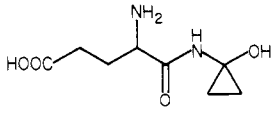
Cyclopropylamine derivatives are known to have interesting and sometimes useful properties as enzyme inhibitors. For example Coprine (**1**), a constituent of inky-cap mushrooms (*Coprinus* sp.),



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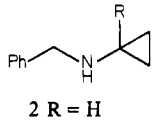
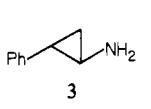


2 R = H
6 R = CH_3



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is hydrolyzed in vivo to 1-hydroxycyclopropylamine and cyclopropanone hydrate, which inhibit aldehyde dehydrogenase.[1,2] This in turn gives rise to a disulfiram-like reaction if these mushrooms are ingested with ethanol. *N*-Benzylcyclopropylamine (BCA, **2**)[3] and related arylalkyl cyclopropylamines[4] are inhibitors of mitochondrial monoamine oxidase (MAO, E.C. 1.4.3.4) and tranylcypromine (**3**) is a therapeutically useful MAO inhibitor. We recently reported that **2** and a number of its derivatives were potent inhibitors of cytochrome P-450 enzymes.[5] Several characteristics of the inhibition process suggested that it might involve suicide inactivation of the enzyme via a metabolite of the parent amine. Thus, loss of enzyme activity followed first-order kinetics, required oxygen and NADPH, and was inhibited by carbon monoxide but *not* by glutathione. In this communication we report further studies that firmly establish the suicidal nature of the enzyme inactivation process and suggest the involvement of a novel mechanism for the enzymatic activation of cyclopropylamines by cytochrome P-450.

Table I. Covalent Binding of Radioactivity to Microsomal Proteins[a]

incubation conditions	time, min	nmol bound ^3H	nmol bound ^{14}C
expt A, [7-^{3}H,7-^{14}C]-**2**			
standard	10	2.49 ± 0.09	2.03 ± 0.50
−NADPH	10	0.20 ± 0.05	0.10 ± 0.05
standard	60	6.63 ± 1.24	6.54 ± 0.89
−NADPH	60	0.16 ± 0.03	0.22 ± 0.04
expt B, [7-^{3}H,7-^{14}C]-**2**			
standard	60	3.74 ± 0.27	3.86 ± 0.40
+glutathione (1 mM)	60	0.92 ± 0.05	1.11 ± 0.17
+semicarbazide (0.1%)	60	2.56 ± 0.13	2.60 ± 0.14
expt C, [7-^{3}H]-**6**			
standard	60	0.88	
+glutathione (1 mM)	60	0.48	

[a] Standard conditions were as described in ref 6. Each experiment used a different preparation of microsomes, but these results are typical of several such experiments. At the indicated times aliquots of incubation mixture were withdrawn and covalently bound radioactivity was measured by using method A (ref 9). Results are net binding after correction for a small zero-time background and are expressed as the mean ±SD (n = 3) or averages of duplicates.

Under standard conditions,[6] incubation of **2** with rat liver microsomes leads to a first-order loss of aminopyrine demethylase activity with a half-life of 14.9 min,[7] as shown in Figure 1a. So that it could be determined whether the inactivation of P-450 by **2** involved covalent modification of the enzyme, [7-^{3}H]-**2** was prepared[8] and incubated with microsomes under the standard

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(6) Liver microsomes were prepared from male rats (200–300 g) and washed by resuspension in 1.15% KCl and recentrifugation at 105000*g*. Incubations contained 100 mg of microsomes (ca. 8 mg of protein)/mL in 0.1 M NaK phosphate buffer (pH 7.6) containing 1 mM EDTA, 7 mM $MgCl_2$, 6.6 mM glucose-6-phosphate, 0.65 mM NADP, and 1–2 IU of glucose 6-phosphate ddehydrogenase/mL. Incubations were carried out at 33 °C under air. Aminopyrine was added at 3.5 mM (along with 0.1% semicarbazide) and incubated for 5 min; formaldehyde was measured by the Nash procedure. Cyclopropylamines **2** and **6** were added to incubations to a concentration of 1 mM.

(7) It is probable that the total inhibition observed at a given time includes a reversible component as well as that due to enzyme inactivation by **2** or **6** and that significant inactivation of cytochrome P-450 by **2** or **6** occurs even during the 5-min assay with aminopyrine. Hence the exact amount of enzyme remaining at a given time is somewhat ambiguous, and inactivation plots tend to be shifted to the right of the covalent binding plots. However, neither of these eventualities interfere with measurement of the *rate of change* in enzyme activity with time and the associated half-life for inactivation under standard conditions.

(8) Amines **2** and **6**, tritiated on the benzylic carbon, were prepared by reduction of the corresponding benzylidene Schiff bases in absolute ethanol with [^{3}H]$NaBH_4$. For incubations they were diluted with cold carrier to final specific activities of 2–6 Ci/mol. Carbon-14 labeled **2** was prepared from [*carboxyl*-^{14}C]benzoic acid by successive treatment with oxalyl chloride in benzene, excess cyclopropylamine in ether, and excess BH_3-tetrahydrofuran at 25 °C for 24 h. For incubations [^{14}C]-**2** was used at a specific activity of 0.7 Ci/mol.

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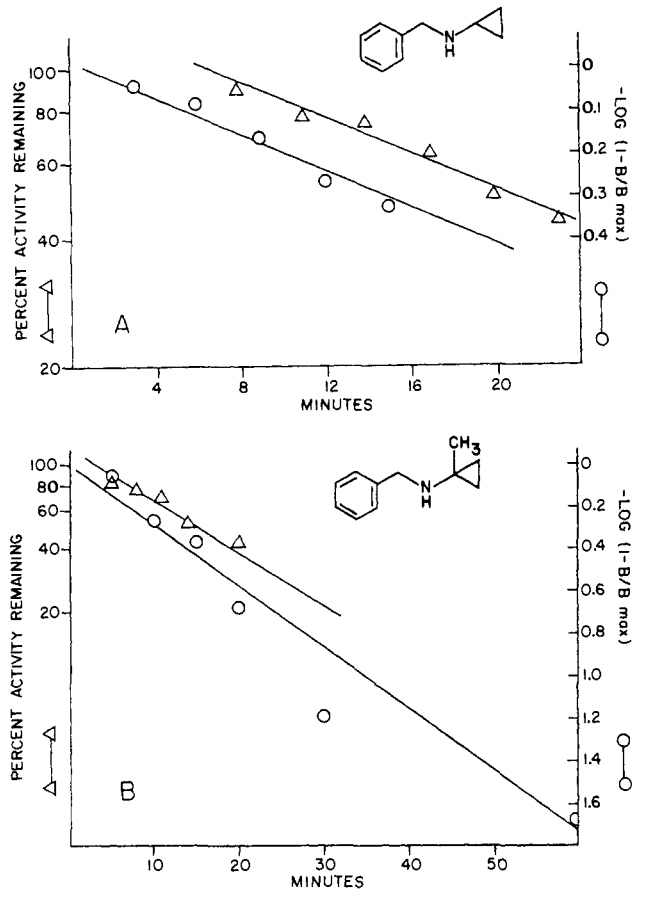
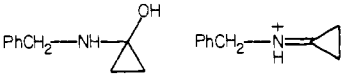


Figure 1. Inactivation of P-450 (△) and covalent modification of microsomal protein ((○) B = dpm/mg protein) by *N*-benzylcyclopropylamine (part A) and *N*-benzyl-1-methylcyclopropylamine (part B). The incubation and assay conditions are given in ref 6 and 9.

conditions for the inactivation reaction. As shown in Figure 1a, tritium became covalently bound[9] to heme-free microsomal protein, also with first-order kinetics and a half-life of 14.9 min, suggesting that both binding and enzyme inactivation involve a common enzymatically generated reactive intermediate.[11] So that the possible involvement of benzylic activation in the covalent binding process could be ruled out, [7-^{14}C,7-^{3}H]-**2** was prepared[8] and incubated with microsomes. As shown in Table I, the $^{3}H/^{14}C$ ratio in the bound material was the same as that of the starting material. Addition of glutathione (GSH) was found to depress the total amount of covalent binding, but it did not affect the $^{3}H/^{14}C$ ratio of the bound material. In contrast, GSH had no effect on either the rate of extent of loss of enzyme activity. This result suggests that covalent incorporation of **2** specifically involves the cyclopropyl–nitrogen moiety, a structural feature known to be an absolute requirement for enzyme inactivation.[5,12,13] It also suggests that the reactive species generated by the enzyme can diffuse from the active site and react either with glutathione or other protein groups in reactions that do *not* lead to enzyme inactivation. Presumably, therefore, enzyme inactivation results from the covalent binding of a reactive metabolite of **2** to parts of the enzyme *active site*.

In the case of compound **2** the usual α-hydroxylation mechanism for N-dealkylation of amines by cytochrome P-450 would lead to carbinolamine **4**. Such adducts of cyclopropanone readily



4 **5**

exchange ligands at C-1 via intermediates such as **5** or related isoelectronic structures in which O or S replaces the nitrogen atom,[14] and **5** has been proposed[3] as the active metabolite responsible for the suicide inactivation of MAO by **2**. According to this view, *N*-benzyl-1-methylcyclopropylamine (**6**), which cannot form a cyclopropylidene Schiff base analogous to **5**, should not be an inactivator of cytochrome P-450. We were thus surprised to find that **6** is indeed a very effective inactivator of cytochrome P-450. The inactivation process requires oxygen and NADPH (data not shown) and under standard conditions[6] follows first-order kinetics with a half-life of 12.1 min (Figure 1b). Furthermore, as with **2**, tritium from [7-^{3}H]-**6** is covalently incorporated into microsomal protein as the inactivation proceeds ($t_{1/2}$ = 10.7 min), and only a portion of this incorporation can be blocked by glutathione (Table I). For comparison, *N*-benzyl-*tert*-butylamine (**7**) was tested and found to be a very weak time-independent inhibitor of cytochrome P-450, much like *N*-benzylisopropylamine.[5] Thus, although **6** may not be capable of forming a cyclopropylidene Schiff base (e.g., **5**), it is clearly a suicide substrate for cytochrome P-450 and its activity also is associated with the cyclopropyl–nitrogen moiety.

An intriguing aspect of cytochrome P-450 action is its ability to utilize organic peroxides rather than NADPH and oxygen to carry out the oxidation of many of its substrates. Although the intermediates involved and the extent of similarity in mechanism between the P-450 peroxidase and mixed-function oxygenase processes are not clear, the fact that cytochrome P-450 catalyzes the cumene hydroperoxide dependent N-demethylation of aminopyrine via an aminium cation-radical intermediate[15,16] suggests a plausible mechanism for the activation of **6** (and possibly of **2**). Thus, one-electron oxidation of **6** to an aminium ion such as **8b** could activate the adjacent and already cyclopropyl ring for covalent reaction with the enzyme. Several modes of reaction are conceivable, as suggested in Scheme I. Path a would involve ring expansion and loss of a proton and an electron, leaving a quaternized azetidinium ion which could undergo nucleophilic attack

(9) Covalent binding of radioactivity to microsomal protein was determined by one of two methods. Method A involved treating the microsomal suspensions with 4 volumes of MeOH/$CHCl_3$ (4:1) followed by repetitive washing of the precipitate with MeOH/H_2O (4:1) and finally redissolving the precipitate in 1 N NaOH for counting. *This method was shown to remove all detectable heme from the precipitated proteins.* Method B involved treating the microsomal suspensions with 10 volumes of MeOH/H_2SO_4 (95:5) overnight at 4 °C in the dark, followed by centrifugation and washing of the pellet with MeOH/H_2O (4:1). The pellet was dissolved in 1 N NaOH for counting as above. The original MeOH/H_2SO_4 supernatant was then processed for analysis of covalently modified heme as described by Ortiz de Montellano and Mico.[10] Preliminary studies with [^{3}H]-**2** have repeatedly indicated that tritium label becomes covalently bound to *both* heme and protein. Over several experiments with and without glutathione the ratio of heme to protein binding varied from 2:3 to 3:2, but both portions were consistently labeled. Most of the heme-associated tritium was associated with a band of "abnormal green pigments" having an R_f of 0.82 in $CHCl_3$/acetone (3:1) on silica G plates. The nature of the bound material is currently under investigation.

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(11) Although it is not apparent from the experiments shown in Figure 1, inactivation by **2** (or **6**) of aminopyrine-*N*-demethylase in liver microsomes from uninduced rats plateaus after loss of only 70–80% of the original activity, whereas covalent binding continues for a bit longer time before it too plateaus (data not shown). This pattern of activity is consistent with the well-known existence in microsomes of multiple forms of cytochrome P-450 having different but partly overlapping specificities for substrates, inhibitors, and inducers. Thus apparently some demethylases active on aminopyrine are not affected by **2** (or **6**) while others not active on aminopyrine may be capable of activating **2** (and **6**) to species that bind to microsomal proteins; the apparent overall half-lives for the two processes are very similar.

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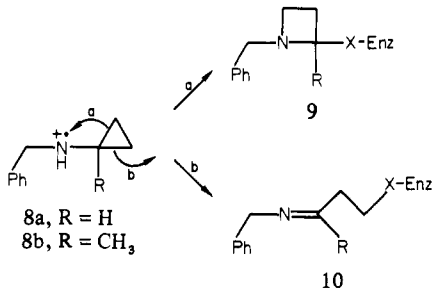
Scheme I



by a group on the enzyme. Precedent for this mode of reactivity is found in the oxidative rearrangement of N-monosubstituted 1-aminocyclopropanols to β-lactams with *t*-BuOCl followed by silver ion.[17] Path b would simply involve opening of the cyclopropyl ring and reaction with a group from the enzyme. However, while this mode of reaction is well precedented in the reaction of cyclopropyl alcohols[18] and thiols[14] by one-electron oxidants, it is doubtful that an adduct such as **10** would be sufficiently stable toward hydrolysis to account for the covalent binding of *benzylic* ^3H and ^{14}C, which is observed even after harsh acid treatment[9] of the microsomal proteins.

While **4** remains a potential intermediate in the metabolic activation of **2** by cytochrome P-450, it is also possible that both **2** and **6** are activated via aminium radical cations as suggested in Scheme I. Several additional observations are consistent with this hypothesis. First, the cyclopropyl moiety is resistant to attack by extremely strong oxidants such as RuO_4[19] or dry ozone,[20] which readily oxidize aromatic and aliphatic positions *adjacent* to a cyclopropane ring. Second, cyclopropyl ethers and thioethers are apparently not inactivators of P-450[12] despite their *potential* for metabolism to reactive cyclopropanone hemiketals or hemithioketals analogous to **4**. However, the contrasting behavior of ethers and thioethers to that of amines **2** and **6** may be understandable in terms of cation-radical intermediates. Oxygen cation radicals are much less likely to form because of the high ionization potential of ethers, and sulfur cation radicals, if formed,[21,22] may react further to give sulfoxide metabolites rather than enzyme inactivation. Finally, the very recent report that **6** is a suicide substrate for monoamine oxidase,[23] which we had independently observed,[24] lends further credence to the possible involvement of aminium cation radicals in the metabolic activation of cyclopropyl amines and possibly in the oxidative metabolism of amines in general. Studies directed toward trapping and identifying of enzymatically activated forms of **2** and **6** are presently under way in our laboratory.

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Registry No. 2, 13324-66-8; [7-^{3}H]-**2**, 80926-12-1; [^{14}C]-**2**, 80926-13-2; **6**, 79432-92-1; [7-^{3}H]-**6**, 80926-14-3; **7**, 3378-72-1; cytochrome P-450, 9035-51-2; *N*-benzylidenecyclopropylamine, 3187-77-7; *N*-benzylidene(1-methylcyclopropyl)amine, 80926-15-4; [*carboxyl*-^{14}C]-benzoic acid, 1589-66-8; cyclopropylamine, 765-30-0.

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Mechanism of Cytochrome P-450 Inhibition by Cyclopropylamines

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The cytochrome P-450 enzymes are a family of heme-containing proteins involved in the metabolism of a range of substances that possess great diversity in structure. These monooxygenase enzymes catalyze several oxidative reactions that have a common unifying feature: the covalent incorporation of one atom of oxygen into the substrate molecule.[4] These enzymes are subject to mechanism-based or suicide inhibition[5] by numerous substrates as a function of the metabolism of uniquely positioned olefinic,[6] acetylenic,[7] or cyclopropylamine[8] moieties. Cyclopropylamines are also suicide inhibitors of mitochondrial monoamine oxidase[9] and of plasma amine oxidase.[5a] The mechanism-based inhibition of these distinct enzyme classes by cyclopropylamines has been postulated to be a consequence of α-hydroxylation to form a cyclopropylcarbinolamine, which reacts with enzyme-bound nucleophiles via a highly reactive iminium ion (Figure 1: **1a** → **2** → **3**).[8,9b] We present evidence here that an alternative mechanism, postulated to involve initial amine nitrogen oxidation to a radical cation, is operative for the suicide inactivation of cytochrome P-450 by cyclopropylamines.

We have investigated the in vitro mixed-function oxidative metabolism of cyclopropylbenzylamine, **1a**, and (1-methylcyclopropyl)benzylamine, **1b**, by hepatic microsomes and by a reconstituted hepatic cytochrome P-450 system, both isolated from phenobarbital-pretreated rats.[10] Cytochrome P-450 content was determined after metabolism of both compounds directly by spectral assay and indirectly by biochemical assay of enzyme activities. Cytochrome P-450 was determined by its ferrous carbonyl Soret absorbance,[11] and total heme was determined as the pyridine hemochromagen.[11,12] *d*-Benzphetamine[10] and am-

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(2) National Research Service Award Fellow supported by USPHS Training Grant ES07028.
(3) Recipient of USPHS Research Career Development Award (ES00041) (1978–1983).
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