Isolation and Structure of Coprine, a Novel Physiologically Active Cyclopropanone Derivative from *Coprinus atramentarius* and Its Synthesis *via* 1-Aminocyclopropanol

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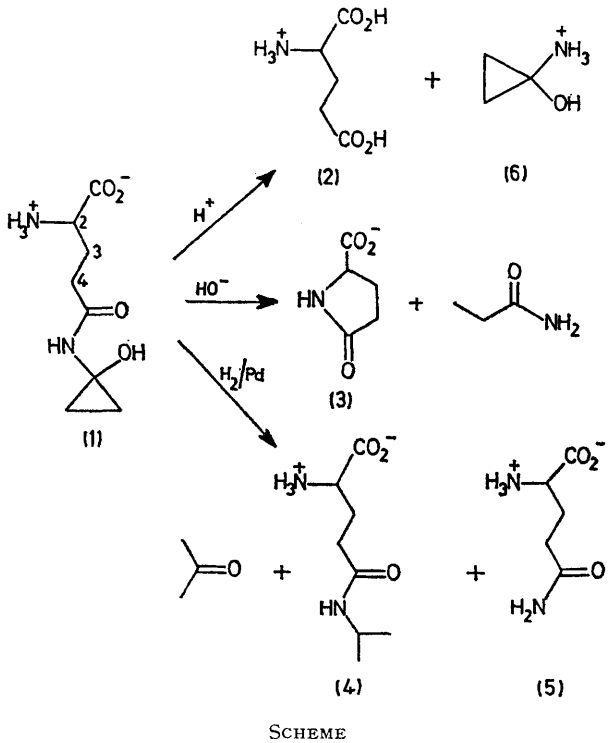
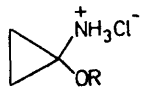
Summary Coprine, the 'antabuse'-like principle of the inky cap mushroom *Coprinus atramentarius* has been isolated; its structure, which includes a cyclopropanone equivalent, has been determined and it has been synthesised from 1-hydroxycyclopropylammonium chloride *via* the unstable 1-aminocyclopropanol.

CYCLOPROPANONE chemistry has received considerable attention in recent years.[1,2] We report that a novel type of cyclopropanone derivative, coprine [N^5-(1-hydroxycyclopropyl)-L-glutamine] (**1**), is produced by the inky cap mushroom *Coprinus atramentarius*, Bull. (Basidiomycetes). Coprine (**1**) has been shown to be identical with the elusive factor responsible for the disulphiram- ('antabuse')-like action of this fungus.[3]† Using a specific rat test specially developed for this assay the active component (coprine) was traced to the amino-acid portion of an ethanol extract of frozen mushrooms and was isolated by ion exchange chromatography (yield: 90 mg/kg fresh mushroom).



SCHEME

Coprine (**1**) analyses for $C_8H_{14}N_2O_4$. Acid hydrolysis of (**1**) affords L-glutamic acid (**2**) as one of the main products (Scheme). Alkaline hydrolysis of (**1**) yields L-pyroglutamic acid (**3**) and propionamide. Catalytic hydrogenation (Pd–C, H_2O) of (**1**) gives N^5-isopropyl-L-glutamine (**4**)[4] as the main product together with minor amounts of acetone



(**6**); R = H
(**7**); R = Me
(**8**); R = Et

and L-glutamine (**5**); model experiments show that reductive alkylation does not occur under these conditions.

These degradations indicate that coprine (**1**) contains an L-glutamine unit with a 3-carbon residue attached in the N^5-position. This is supported by comparison of the n.m.r. spectrum of (**1**) [δ (D_2O; 100 MHz) 0·81—1·14 (4H, m), 1·99—2·24 (2H, m, 3-H_2), 2·31—2·49 (2H, m, 4-H_2), and 3·77 (1H, t, 2-H)] with those of glutamic acid and glutamine. The size and signs of the coupling constants and the shift relative to Me_4Si for the 4H multiplet centred at δ 0·97 (identified as an isolated AA'BB' system; J_{gem} −5·76, J_{cis} +11·24, J_{trans} +7·20 Hz, $\Delta\delta_{A,B}$ 0·136 p.p.m.) are strongly indicative of a cyclopropanone derivative. Taken together, the chemical and n.m.r. spectroscopic evidence shows that coprine has the structure (**1**).

The crude hydrolysate of (**1**) shows a sharp singlet at δ 1·20 which we assign to the ion (**6**)‡ (Scheme). The hydrolytic abstraction of (**6**) as an intact unit may seem somewhat surprising, even taking into account the greater stability of geminally dihetero-substituted cyclopropanes as compared to their ketonic or iminic counterparts.[5] The acid stability of (**6**)[6] may be partly attributed to the positive charge carried by the ammonium group, which renders the cyclopropane ring less susceptible to protonation. This is in agreement with the explanation for the stability of *N*-(1-hydroxycyclopropyl)dimethylammonium chloride.[7] The hydrochloride (**6**) might be expected to give an AA'BB' n.m.r. spectrum. However, as has been suggested[7,8] for the hydrochlorides of 1-piperidinocyclopropanol and 1-dimethylaminocyclopropanol, which also give rise to 4H singlets in their n.m.r. spectra (H_2O), the phenomenon can be attributed to rapid inversion in these molecules *via* *O*-protonation and elimination–addition of water.

† *C. atramentarius* apparently, like 'antabuse', inhibits the enzyme aldehyde dehydrogenase.[3b]

‡ 1-Aminocyclopropanol is unstable.[2]

In order to confirm the structures and to provide material for pharmacological studies, procedures for the synthesis of (**6**), (**1**), and analogous compounds were developed.

Earlier attempts to isolate or trap 1-aminocyclopropanol from a low-temperature reaction between cyclopropanone and ammonia have been unsuccessful.[2] We have now found that HCl quenching of the reaction gives a low yield of the hydrochloride (**6**). However, this compound is obtained pure in high yield by hydrolysis (HCl) of 1-ethoxycyclopropyl isocyanate[9] or of t-butyl *N*-(1-ethoxycyclopropyl)carbamate[9] followed by evaporation. The hydrochloride (**6**) [δ (D_2O) 1·20 (4H, s)] is obtained as an oil, which on treatment with MeOH or EtOH is converted into the crystalline alkoxy derivatives (**7**) and (**8**), respectively.[7] The corresponding 1-alkoxycyclopropylamines are stable, distillable compounds.

N-(1-Hydroxycyclopropyl) carboxamides and the corresponding 1-alkoxycyclopropyl derivatives are formed in fair yields (50—70%) when suspensions of the hydrochlorides (**6**)—(**8**) in tetrahydrofuran containing acylating agents (carboxylic anhydrides or chlorides) are treated with Et_3N. Coprine and *O*-ethylcoprine were obtained from (**6**) and (**7**) respectively by acylation with *N*-phthaloyl-L-glutamic acid anhydride[10] and subsequent removal of the blocking group with hydrazine at pH 8.

To our knowledge coprine (**1**) is the first example of a naturally occurring compound containing a cyclopropanone equivalent.

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