Isolation and Structure of Coprine, the *in vivo* Aldehyde Dehydrogenase Inhibitor in *Coprinus atramentarius*; Syntheses of Coprine and Related Cyclopropanone Derivatives

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The disulphiram-like principle of the inky cap mushroom *Coprinus atramentarius* has been identified as N^5-(1-hydroxycyclopropyl)-L-glutamine (coprine) (1). Coprine (1) and several analogous compounds have been synthesised by *N*-acylation of the unstable 1-aminocyclopropanol, generated *in situ* from 1-hydroxycyclopropylammonium chloride (6). The lower 1-alkoxycyclopropylamines are stable, distillable compounds which can be *N*-acylated. Many of the 1-aminocyclopropanol derivatives synthesised have the same physiological activity as coprine.

THE fruiting body of the inky cap mushroom *Coprinus atramentarius*, Bull. (Basidiomycetes) is apparently non-toxic when eaten alone, but is notorious for inducing in some people an over-sensitivity to ethanol.[1,2] This effect is similar to that of the drug disulphiram (antabuse).[3] Thus, when fed with a combination of mushroom and ethanol, rabbits exhibit a significant drop in blood pressure [4] and mice show a marked increase in blood acetaldehyde level.[5] Ethanol alone has a negligible effect. An early claim that disulphiram is present in *C. atramentarius* [6] was later disproved,[2,7] and at least one earlier attempt to isolate the causative agent has been made.[2]

We report that the compound responsible is N^5-(1-hydroxycyclopropyl)-L-glutamine (coprine) (1).[8,†] We have synthesised this substance and many related compounds for a detailed pharmacological and biochemical evaluation. Some of these compounds have the same physiological activity as coprine (1) at similar dosage. Apart from their interest as inhibitors of aldehyde dehydrogenase, they have potential value as disulphiram-like drugs for the treatment of alcoholism.

To our knowledge coprine (1) is the first example of a naturally occurring compound containing a cyclopropanone [9] equivalent. Some known amino-acids, however have a cyclopropane ring in their carbon skeleton.[10]

Isolation of Coprine (1).—In searching for a physiological test for monitoring the isolation experiments we observed that rats react with lachrymation and gradual swelling of the face when fed with an extract of frozen mushrooms and then 6—10 h later given ethanol. The oedema test usually failed with rats which had been given ethanol within the previous few days. A drop in blood pressure and an increased blood acetaldehyde level in rats (apparently due to *in vivo* inhibition of aldehyde dehydrogenase [11]) after being fed with pure coprine followed by ethanol have been confirmed in pharmacological testing.

In the isolation procedure an ethanolic extract of fresh frozen mushrooms which had been freed from lipids and high molecular weight substances was subjected to ion-exchange chromatography by a displacement technique [12] (Scheme 1). Charcoal chromatography was efficient but losses occurred, presumably owing to catalytic oxidation.[13]

The coprine content of *C. atramentarius* is about 160 mg per kg of fresh mushroom (mixed ages), and this value is independent of ordinary cooking [boiling in their own juice (15 min) or frying (5 min)].

Structure and Chemistry of Coprine (1).—Acidic hydrolysis (4M-HCl; 80 °C; 30 min) of coprine (1) ($C_8H_{14}N_2O_4$) afforded L-glutamic acid (2) (t.l.c.; n.m.r. and i.r. spectra) as one of the main products (Scheme 2). Alkaline hydrolysis (potassium carbonate buffer; pH 10;

† During the preparation of this manuscript a further account of the structure of coprine (1) was published (G. M. Hatfield and J. P. Schaumberg, *Lloydia*, 1975, **38**, 489).

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[2] P. H. List and H. Reith, *Arzneim.-Forsch.*, 1960, **10**, 34.

[3] J. Hald, E. Jacobsen, and V. Larsen, *Acta Pharmacol. Toxicol.*, 1948, **4**, 285.

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[5] B. B. Coldwell, K. Genest, and D. W. Hughes, *J. Pharm. Pharmacol.*, 1969, **21**, 176.

[6] J. Simandl and J. Franc, *Chem. listy*, 1956, **50**, 1862.

[7] J. K. Wier and V. E. Tyler, *J. Amer. Pharm. Assoc.* (*Sci. Ed.*), 1960, **49**, 426.

[8] (*a*) First presented at '8:e Organikerdagarna,' Lövånger, Sweden, June 10—13, 1975; (*b*) Preliminary account, P. Lindberg, R. Bergman, and B. Wickberg, *J.C.S. Chem. Comm.*, 1975, 946.

[9] For reviews on cyclopropanone chemistry, see (*a*) W. B. Hammond, Ph.D. Thesis, Columbia University, New York, 1967; (*b*) S. E. Schaafsma, Thesis, University of Amsterdam, 1968; (*c*) N. J. Turro, *Accounts Chem. Res.*, 1969, **2**, 25; (*d*) W. J. M. van Tilborg, Thesis, University of Amsterdam, 1971; (*e*) H. H. Wasserman, G. M. Clark, and P. C. Turley, *Fortschr. Chem. Forsch.*, 1974, **47**, 73.

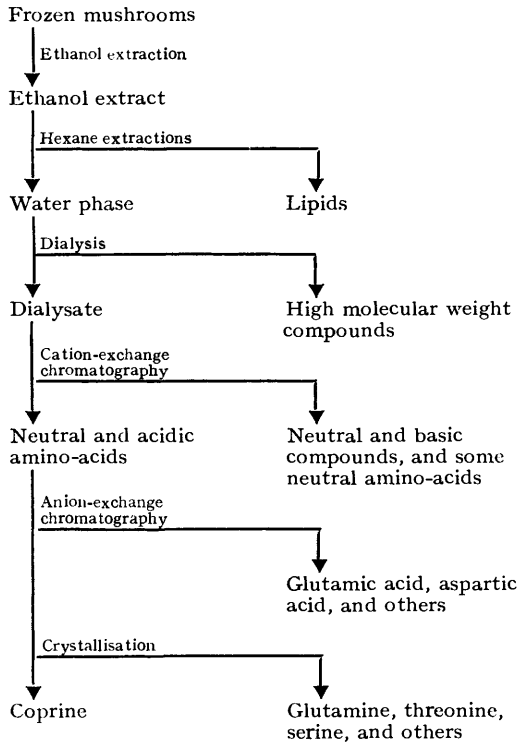
[10] Y. Fujimoto, F. Irreverre, J. M. Karle, I. L. Karle, and B. Witkop, *J. Amer. Chem. Soc.*, 1971, **93**, 3471, and references cited therein.

[11] R. A. Deitrich and L. Hellerman, *J. Biol. Chem.*, 1963, **238**, 1683; R. G. Thurman, T. Yonetani, J. R. Williamson, and B. Chance, 'Alcohol and Aldehyde Metabolizing Systems,' papers presented at the First International Symposium on Alcohol and Aldehyde Metabolizing Systems in Stockholm, Sweden, 1973, Academic Press, New York and London, 1974, pp. 101—147.

[12] S. M. Partridge and R. C. Brimley, *Biochem. J.*, 1952, **51**, 628.

[13] S. E. Schaafsma, H. Steinberg, Th. J. de Boer, *Rec. Trav. chim.*, 1966, **85**, 70; S. E. Schaafsma, E. J. F. Molenaar, H. Steinberg, and Th. J. de Boer, *ibid.*, 1968, **87**, 1301.

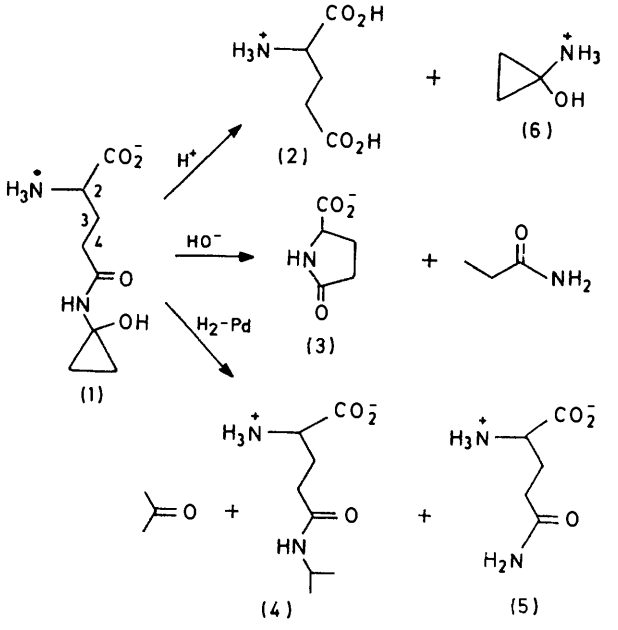
80 °C; 2.5 h) yielded L-pyroglutamic acid (3) (n.m.r.) and propionamide (n.m.r. and i.r. spectra). Catalytic hydrogenation (Pd–C; H_2O) gave N^5-isopropyl-L-glutamine



SCHEME 1 Procedure for large scale isolation of coprine from *C. atramentarius*

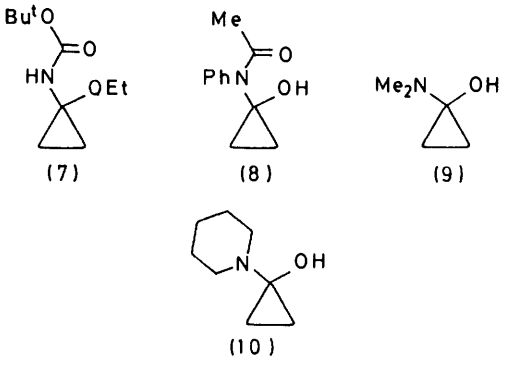
(4) [14,15] (t.l.c.; n.m.r. and i.r. spectra) as the main product together with minor amounts of acetone (n.m.r.; g.l.c.–mass spectrometry) and L-glutamine (5) (t.l.c.; n.m.r. and i.r. data) with a hydrogen consumption of 1.8 mol. equiv.; model experiments show that reductive alkylation does not occur under these hydrogenation conditions.

These degradations indicate that coprine contains an L-glutamine unit with a C_3 residue attached to N^5. This is supported by comparison of the ^1H n.m.r. spectrum (see Experimental section) with those of glutamic acid and glutamine. Thus, whereas both shifts and splitting patterns for the C-2 and C-3 protons are almost identical in the three compounds, the C-4 proton multiplets are shifted increasingly upfield in the series glutamic acid (2), glutamine (5), coprine (1). The 4 H multiplet centred at δ 0.97 was identified as an isolated AA'BB' system. The magnitudes and relative signs of the coupling constants, obtained by use of the LAOCN 3 iterative computer program [16] (J_{gem} − 5.76, J_{cis} + 11.24, J_{trans} + 7.20 Hz, $\Delta\delta_{AB}$ 0.136), are characteristic of the methylenic protons in cyclopropane derivatives such as cyclopropylamine and cyclopropanol.[17] The shift relative to tetramethylsilane of the AA'BB' part is consistent with shifts reported for cyclopropanone derivatives such



SCHEME 2

as t-butyl *N*-(1-ethoxycyclopropyl)carbamate (7) [18] and *N*-(1-hydroxycyclopropyl)-*N*-phenylacetamide (8).[19] Taken together, the chemical and n.m.r. evidence shows that coprine has the structure (1). This is corroborated by ^{13}C n.m.r. data (see Experimental section) and has been confirmed by synthesis (see below).



The crude acidic hydrolysate of coprine shows a sharp singlet at δ 1.2 which we assign to the 1-hydroxycyclopropylammonium ion (6) (Scheme 2). This is in accord with the formation of propionic acid (n.m.r.; g.l.c.–mass

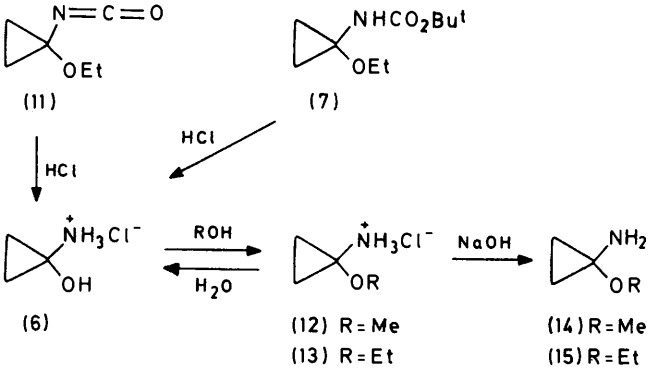
[14] P. Olesen Larsen, *Acta Chem. Scand.*, 1965, **19**, 1071.
[15] C. Gröger and H. Musso, *Angew. Chem.*, 1976, **88**, 415.
[16] S. Castellano and A. A. Bothner-By, *J. Chem. Phys.*, 1964, **41**, 3863.
[17] P. A. Scherr and J. P. Oliver, *J. Mol. Spectroscopy*, 1969, **31**, 109.
[18] (*a*) T. H. Koch and R. J. Sluski, *Tetrahedron Letters*, 1970, 2391; (*b*) T. H. Koch, R. J. Sluski, and R. H. Moseley, *J. Amer. Chem. Soc.*, 1973, **95**, 3957.
[19] N. J. Turro and W. B. Hammond, *Tetrahedron*, 1968, **24**, 6029.

spectrometry) on brief treatment of the hydrolysate with alkali (potassium carbonate buffer; pH 10; 80 °C; 3 min), and is analogous to the formation of propionic acid on prolonged heating of 1-dimethylaminocyclopropanol (9) hydrochloride in water.[20] Further acidification and heating (6M-HCl; 80 °C; 2 h) of the coprine hydrolysate leaves the 1-hydroxycyclopropylammonium ion (6) unchanged. This behaviour is closely analogous to the lack of reactivity of 1-dimethylaminocyclopropanol (9) hydrochloride when heated in acid (1M-HCl).[20] 1-Aminocyclopropanol is unstable as a free base.[9d] Thus, the simple addition of ammonia to cyclopropanone gives bis-(1-hydroxycyclopropyl)amine,[9d,21,22] and attempts to trap the 1-aminocyclopropanol by acetylation and silylation have been unsuccessful.[9d,22] However, the great stability of the hydrochloride of 1-aminocyclopropanol in acidic solution has been overlooked. This stability can be attributed to the much lower equilibrium concentration of the corresponding zwitterion, which makes less probable direct ring opening and formation of cyclopropanone (giving 1,1-cyclopropanediol, which isomerises to propionic acid). The sharp singlet at δ 1.2 which appears instead of the expected AA'BB' multiplet in the n.m.r. spectrum of 1-hydroxycyclopropylammonium chloride (6) is analogous to the 4 H singlets in the n.m.r. spectra (H_2O) of the hydrochlorides of 1-dimethylaminocyclopropanol (9) [20] and 1-piperidinocyclopropanol (10).[23] This phenomenon is being investigated further.

The formation of propionamide in the alkaline hydrolysis of coprine (Scheme 2) can be considered to occur by a mechanism similar to that proposed for the alkaline cleavage of 1,1-cyclopropanediols,[9c] and has some analogy in the formation of propionanilide in the thermal decomposition of compound (8).[19]

Synthesis of Coprine (1) *and Other* N-*Acyl Cyclopropanone Derivatives*.—Coprine (1) is the first *N*-acyl 1-aminocyclopropanol to be reported. For the synthesis of coprine and analogous compounds there are two obvious routes: addition of the amide to cyclopropanone [21,24] and *N*-acylation of 1-aminocyclopropanol. The first of these has been tested by us with acetamide as the nucleophile but seems very difficult to accomplish. The second reaction however has turned out very useful.

1-Hydroxycyclopropylammonium chloride (6) can be synthesised in quantitative yield by acidic hydrolysis (2M-HCl) of 1-ethoxycyclopropyl isocyanate (11) [18] or t-butyl *N*-(1-ethoxycyclopropyl)carbamate (7) [18] followed by evaporation. The same treatment of benzyl *N*-(1-ethoxycyclopropyl)carbamate (28) [prepared by treating the isocyanate (11) with benzyl alcohol and a trace of triethylamine] also gives the hydrochloride (6), but the reaction is much slower. Ethyl *N*-(1-ethoxycyclopropyl)carbamate (27) loses only the ring ethoxy-group, giving ethyl *N*-(1-hydroxycyclopropyl)carbamate (25). Further hydrolysis, which requires more severe conditions, gives only ring scission products (n.m.r.). Treatment of the carbamate (27) with strong alkali followed by acidification gives the hydrochloride (6).



2-Ethoxypyrrolin-5-one (*O*-ethylsuccinimide),[25] the starting material for the photochemical production of the isocyanate (11) and the carbamate (7), is conveniently synthesised by treatment of succinimide with triethyloxonium tetrafluoroborate in methylene chloride followed by neutralisation with sodium ethoxide.

Addition of liquid ammonia to cyclopropanone followed by quenching with hydrochloric acid gives the hydrochloride (6) in low yield. Bis-(1-hydroxycyclopropyl)-amine is converted partly into the hydrochloride (6) on treatment with hot aqueous hydrochloric acid (n.m.r.). Treatment of 1-acetoxycyclopropanol [21] or 1-piperidinocyclopropanol (10) with aqueous ammonia–ammonium chloride followed by quenching with hydrochloric acid also gives the hydrochloride (6) (n.m.r.) in low yield. 1-Piperidinocyclopropanol was prepared *via* addition of the carbene reagent methylene iodide–diethylzinc [26,*] to a solution of 1,1-dipiperidinoethene [27] in tetrahydrofuran followed by acidic hydrolysis of the intermediary 1,1-dipiperidinocyclopropane.

Treatment of the hydrochloride (6) with methanol or with ethanol gives the crystalline alkoxy-derivatives, (12) and (13), respectively. These exchange reactions are analogous to those reported for the hydrochloride of 1-dimethylaminocyclopropanol (9).[20] The kinetics of these reactions are being studied in greater detail. The corresponding 1-alkoxycyclopropylamines (14) and (15) are stable, distillable compounds and can be prepared by rapidly dissolving the hydrochlorides (12) and (13) in an

* This reagent has been suggested for an improved synthesis of 1-ethoxycyclopropyl acetate.[9e]

[20] W. J. M. van Tilborg, H. Steinberg, and Th. J. de Boer, *Rec. Trav. chim.*, 1974, **93**, 290.
[21] W. J. M. van Tilborg, H. Steinberg, and Th. J. de Boer, *Synth. Comm.*, 1973, **3**, 189.
[22] *Cf.* W. J. M. van Tilborg, H. Steinberg, and Th. J. de Boer, *Rec. Trav. chim.*, 1974, **93**, 294.
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[24] N. J. Turro and W. B. Hammond, *J. Amer. Chem. Soc.*, 1966, **88**, 3672; S. E. Schaafsma, H. Steinberg, and Th. J. de Boer, *Rec. Trav. chim.*, 1966, **85**, 1170.
[25] W. J. Comstock and H. L. Wheeler, *Amer. Chem. J.*, 1891, **13**, 522.
[26] J. Furukawa, N. Kawabata, and J. Nishimura, *Tetrahedron*, 1968, **24**, 53.
[27] H. Boganz and L. Domaschke, *Chem. Ber.*, 1962, **95**, 2095.

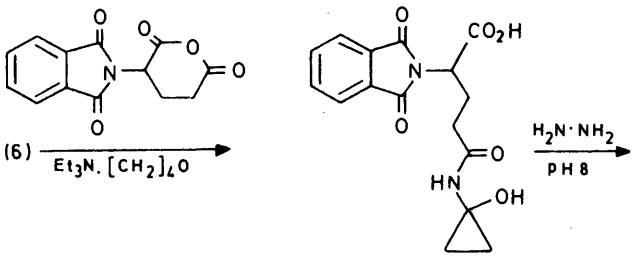
excess of sodium hydroxide and then extracting with methylene chloride. 1-Aminocyclopropanol is formed by similar treatment of the hydrochloride (6), but is unstable and is transformed into bis-(1-hydroxycyclopropyl)amine together with some tris-(1-hydroxycyclopropyl)amine.[21] Clearly, the stability is greatly enhanced by alkylation of the hydroxy-group since this precludes equilibration with cyclopropanone.

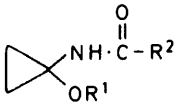
Coprine (1) was readily obtained from the hydrochloride (6) by acylation with *N*-phthaloyl-L-glutamic anhydride [28] in tetrahydrofuran in the presence of triethylamine followed by removal of the blocking group with hydrazine at pH 8. Purification was accomplished by ion-exchange chromatography (displacement technique) and recrystallisation from water–ethanol. The amount of isocoprine [N^1-(1-hydroxycyclopropyl)-L-isoglutamine] (16) formed was normally negligible, since the phthaloyl group induces opening of glutamic anhydride specifically by attack in the 5-position.[28] However, in a large-scale synthesis of coprine (250 g) we were able to isolate a minor amount of isocoprine (16) (13 g). The use of trifluoroacetamido-L-glutamic anhydride [29] as acylating agent gave more isocoprine (16) than coprine (1) (t.l.c.), but the overall yields were low. *O*-Ethylcoprine [N^5-(1-ethoxycyclopropyl)-L-glutamine] (17) was obtained by using the ethoxy-derivative (13) instead of the alcohol (6) in the synthesis. In an analogous way N^4-(1-hydroxycyclopropyl)-L-asparagine (18) was prepared by acylation of the hydrochloride (6) with phthaloyl-L-aspartic anhydride.[30] In this case however the N^1-isomer was a more substantial by-product, but was not isolated in pure form.

N-(1-Hydroxycyclopropyl)carboxamides and the corresponding 1-alkoxycyclopropyl derivatives are formed in 50—70% yields when the hydrochlorides (6), (12), and (13) are treated with acylating agents (carboxylic anhydrides or chlorides) in the presence of triethylamine. Thus we have synthesised the amides (19)—(24). *N*-(1-Alkoxycyclopropyl)carbamates, *e.g.* compounds (26) and (27), can be synthesised in an analogous manner. The related compound *NN'*-bis-(1-ethoxycyclopropyl)urea (29) is obtained as a by-product in the photochemical synthesis of the isocyanate (11) and the carbamate (7) if the solvent is not perfectly dry.

All the amides described above, including the amino-acid derivatives and carbamates, appear stable in pure (1) crystalline form at room temperature. In solution, however, the 1-aminocyclopropanol derivatives, which have a free hydroxy-group, seem to be more labile than the corresponding ethers. Derivatives which have a free hydroxy-group are very easily oxidised by metal ions such as Cu^{2+} and Fe^{3+}.[13] This has been utilised here for the specific detection of these compounds on t.l.c. plates (see Experimental section).

On acidic hydrolysis (HCl) of the carboxamides the 1-aminocyclopropanol unit is split off, forming the hydrochloride (6) in quantitative yield. The *N*-(1-alkoxycyclopropyl)amides however first lose their alkoxy-group on treatment with acid, affording the corresponding hydroxy-compounds. *O*-Ethylcoprine (17) for example, on brief treatment with hydrochloric acid, yields coprine (1) [with some 1-hydroxycyclopropylammonium chloride (6) accompanied by an equivalent amount of glutamic acid]. Alkaline hydrolysis of *O*-ethylcoprine, which requires forcing conditions, affords 1-ethoxycyclopropylamine. When there is a free hydroxy-group present (*e.g.* in coprine), however, propionamide is formed, even under mild conditions.





(16) R^1=H, R^2=CH(NH_2)·[CH_2]$_2$·CO_2H
(17) R^1=Et, R^2=[CH_2]$_2$·CH(NH_2)·CO_2H
(18) R^1=H, R^2=CH_2·CH(NH_2)·CO_2H
(19) R^1=H, R^2=Me
(20) R^1=Et, R^2=Me
(21) R^1=H, R^2=Ph
(22) R^1=Me, R^2=Ph
(23) R^1=Et, R^2=Ph
(24) R^1=Et, R^2=[CH_2]$_4$·CH_3
(25) R^1=H, R^2=OEt
(26) R^1=Me, R^2=OEt
(27) R^1=Et, R^2=OEt
(28) R^1=Et, R^2=O·CH_2Ph
(29) R^1=Et, R^2=NH

OEt

[28] F. E. King and D. A. A. Kidd, *J. Chem. Soc.*, 1949, 3315.
[29] F. Weygand and M. Reiher, *Chem. Ber.*, 1955, **88**, 26.
[30] F. E. King and D. A. A. Kidd, *J. Chem. Soc.*, 1951, 2976.

EXPERIMENTAL

M.p.s were obtained with a Kofler hot-stage apparatus. I.r. spectra were determined with a Perkin-Elmer 257 spectrophotometer. Optical rotations were measured with a Perkin-Elmer 141 automatic polarimeter (1 dm cell). ^{1}H N.m.r. spectra (60 MHz if not otherwise stated) were recorded with a JEOL JNM 60 or Varian T-60 spectrometer. A Varian XL-100 spectrometer was used for the 100 MHz ^{1}H n.m.r. and the ^{13}C n.m.r. spectra. Tetramethylsilane ($CDCl_3$ as solvent) and sodium 3-(trimethylsilyl)propionate (D_2O as solvent) were used as internal standards in ^{1}H n.m.r., and dioxan (δ 67.4; D_2O as solvent) and deuteriochloroform (δ 76.9; $CDCl_3$ as solvent) in ^{13}C n.m.r. spectroscopy.

R_F Values refer to t.l.c. on cellulose F_{254} plates in the following systems (v/v): (1) butan-1-ol–acetone–water–diethylamine (10 : 5 : 5 : 2); (2) ethyl acetate–acetic acid–water (2 : 1 : 1). The amino-acids were developed with ninhydrin (2% in ethanol). For the specific detection of *N*-(1-hydroxycyclopropyl)amides the plates were sprayed with a fresh mixture of equal volumes of 2% iron(III) chloride solution in 20% ethanol and 1% potassium hexacyanoferrate(III) solution in 20% ethanol (gives an instant blue stain).[31]

Ion-exchange chromatography was carried out, unless otherwise stated, with Amberlite CG 120, 200—400 mesh (strongly acidic cation exchanger), and Amberlite CG 4B, 200—400 mesh (weakly basic anion exchanger), resins.

For monitoring the isolation of coprine, rats (Sprague-Dawley females, 150—300 g) were fed (stomach tube) with the sample to be tested (equivalent to 1 g of total extracted solids per kg of rat). Ethanol (4.5 g per kg; 43% by volume in water) was given 6—10 h later. After initial lachrymation, maximal oedema appeared after about 18 h and lasted for a few days.

Large Scale Isolation of Coprine [N^5-(1-*Hydroxycyclopropyl*)-L-*glutamine*] (1) *from* Coprinus atramentarius.—Frozen fresh mushrooms (65.2 kg), averaged with respect to maturity and growth place and minced in a Waring blender with 95% ethanol (62 l), were mixed with Celite and the mixture was filtered. The filter cakes were pressed (20 kp cm^{-2}). The extract was evaporated under reduced pressure (bath temperature 40 °C), diluted with water to about 5 l, and extracted with hexane (3 × 2.5 l). The water phase (dry weight: 1.5 kg) was dialysed * (cellophane membrane) repeatedly against pure water (total high molecular weight residue 78 g). The dialysable material (in 93 l of solution) was subjected to displacement chromatography [12] on a strongly acidic cation exchanger. The dilute solution divided into seven equal batches was added to ion-exchange columns (15 × 8 cm; H^+ form). The columns were washed with water and the adsorbed material was eluted with 0.15M-sodium hydroxide (until the visible alkaline front began to emerge). The fractions containing the acidic amino-acids, which were eluted first, and the greater part of the neutral amino-acids, were combined (total 120 g) and rechromatographed (0.25M-NaOH) on a similar column (21 × 8 cm). The first fractions, containing coprine, together with glutamic acid, aspartic acid, threonine, and parts of the serine and the glutamine, were combined. Glutamic acid, aspartic acid, and some other acidic compounds (13.2 g) were eliminated by passing the solution through an acetate-saturated anion exchanger (Amberlite CG 400, 200—400 mesh; 6 × 8 cm diam.) and washing with water. The combined eluate was concentrated and the residue (23.6 g) was purified by alternating recrystallisation (from water–ethanol) and ion-exchange displacement chromatography of the mother liquors, affording pure *coprine* (1) (7.3 g), m.p. 197—199°, $[\alpha]_D^{25}$ +7.6° (*c* 4.1 in H_2O) (Found: C, 47.6; H, 6.7; N, 13.9. $C_8H_{14}N_2O_4$ requires C, 47.5; H, 7.0; N, 13.8%); $\nu_{max.}$ (KBr) 3 330, 1 675, 1 590, 1 535, 1 415, 1 315, 1 255, 1 020, 815, and 770 cm^{-1}; δ_H (100 MHz; D_2O) 0.81—1.14 (4 H, m, cyclopropane), 1.99—2.24 (2 H, m, H_2-3), 2.31—2.49 (2 H, m, H_2-4), and 3.77 (1 H, t, *J* 6 Hz, H-2); δ_C (D_2O) 14.6 (t, C-7 and -8), 26.9 (t, C-3), 32.4 (t, C-4), 55.0 (d, C-2), 60.6 (s, C-6), and 174.7 and 176.3 (2 s, C-1 and -5); $R_F(1)$ 0.3 (blue with ninhydrin), $R_F(2)$ 0.6 (red with ninhydrin).

1-*Hydroxycyclopropylammonium Chloride* (6).—(a) *Preferred method.* t-Butyl *N*-(1-ethoxycyclopropyl)carbamate (7) [18] (21.5 g, 107 mmol) was treated with hydrochloric acid (1.5M; 500 ml) at 70 °C for 1 h. The solution was evaporated at 40 °C under reduced pressure giving an oily residue. Further drying at 0.01 mmHg yielded pure crystalline (hygroscopic) *hydrochloride* (6) (11.4 g, 98%) (Found: C, 32.6; H, 7.6; N, 13.1; O, 14.4. C_3H_8ClNO requires C, 32.9; H, 7.35; N, 12.8; O, 14.6%); $\nu_{max.}$ (KBr) 3 300, 2 980, 1 700, 1 590, 1 495, 1 470, 1 340, 1 235, 1 155, and 1 030 cm^{-1}; δ (0.4M in D_2O) 1.15 † (4 H, s, cyclopropane).

1-*Piperidinocyclopropanol* (10) *from* 1,1-*Dipiperidinoethene*.—Methylene iodide (22.4 g, 60 mmol) dissolved in tetrahydrofuran (20 ml) was added dropwise at −78° with stirring to a mixture of 1,1-dipiperidinoethene [27] (10.1 g, 52 mmol) and diethylzinc (5.2 ml, 52 mmol) in tetrahydrofuran ‡ (20 ml). The temperature was allowed to rise with continued stirring. It rapidly reached the b.p. and the solution became yellow. After 15 min the mixture was poured into aqueous hydrochloric acid (1M; 100 ml). Potassium carbonate was added (to pH 8.5) and the mixture was extracted with ether (5 × 100 ml). The combined extract was dried ($MgSO_4$) and evaporated giving a crystalline residue (6.3 g, 86%). Sublimation (0.01 mmHg) yielded 1-piperidinocyclopropanol (10) (4.35 g, 59%), m.p. 82—85° (lit.,[23] 82—83°) (Found: C, 67.7; H, 10.8; O, 11.6. Calc. for $C_8H_{15}NO$: C, 68.0; H, 10.7; O, 11.3%); $\nu_{max.}$ (KBr) 3 250, 2 940, 2 860, 2 830, 1 460, and 1 215 cm^{-1} (*cf.* ref. 23).

2-*Ethoxypyrrolin-5-one*.—Succinimide (232 g, 2.36 mol) was added to a solution of triethyloxonium tetrafluoroborate (450 g, 2.36 mol) in dry methylene chloride (1 000 ml). The mixture was stirred at room temperature for 10 h, and the two phases were allowed to separate. The upper phase was decanted into a flask fitted with two dropping funnels, one of which was charged with the lower, salt-rich phase and the other with freshly prepared sodium ethoxide [from sodium (56 g, 2.44 mol)] in ethanol (1 000 ml). A small amount of phenolphthalein was added. The contents of the funnels were then added simultaneously with vigorous stirring and external cooling (solid CO_2–ethanol). The rate of addition

* The dialysis is necessary since the high molecular weight substances present would clog the ion-exchange resin.

† This singlet is slightly broadened, but becomes sharper and is shifted downfield in the presence of an excess of hydrochloric acid.

‡ When run in diethyl ether the reaction did not occur. The more basic tetrahydrofuran probably masks the Lewis acid character of the zinc compounds, which can induce side reactions with acid-labile olefins such as enediamines and keten acetals (*cf.* ref. 26).

[31] M. Gillio-Tos, S. A. Previtera, and A. Vimercati, *J. Chromatography*, 1964, **13**, 571.

was adjusted to keep the temperature below −30 °C and the mixture basic. Precipitated sodium tetrafluoroborate was filtered off with exclusion of moisture and the filtrate was evaporated under reduced pressure. The residue was distilled (short path) giving a mixture (250 g; b.p. 50—105° at 10 mmHg), which on redistillation through a Vigreux column (35 cm; alkali-treated) yielded pure 2-ethoxypyrrolin-5-one (165 g, 55%), b.p. 75—76° at 0.3 mmHg (lit.,[25] 144—146° at 20 mmHg); δ ($CDCl_3$) 1.4 (3 H, t, *J* 7 Hz, CH_3), 2.75 (4 H, m, $CH_2{\cdot}CH_2$), and 4.45 (2 H, q, *J* 7 Hz, OCH_2) (*cf.* ref. 18*b*).

1-*Methoxy- and* 1-*Ethoxy-cyclopropylammonium Chlorides*, (12) *and* (13).—1-Hydroxycyclopropylammonium chloride (6) was dissolved in a large excess of the appropriate alcohol (methanol or 99.5% ethanol). After 30 min at room temperature, the solution was evaporated. The residue was redissolved in an excess of alcohol and the solution concentrated to a few ml. On addition of dry ether and cooling, the pure amino-ether hydrochloride [(12) or (13)] was precipitated.

The hydrochloride (6) (1.09 g, 10 mmol) yielded the *methoxy-salt* (12) (0.98 g, 80%), m.p. 106—108° (Found: C, 39.0; H, 8.3; N, 11.4; O, 13.1. $C_4H_{10}ClNO$ requires C, 38.9; H, 8.15; N, 11.3; O, 12.9%); $\nu_{max.}$ (KBr) 3 430br, 2 920br, 1 580, 1 510, 1 360, 1 245, 1 085, and 1 045 cm^{-1}; δ ($CDCl_3$) 0.99—1.51 (4 H, m, cyclopropane), 3.58 (3 H, s, CH_3), and 9.0br (3 H, s, H_3N^+).

The hydrochloride (6) (2.2 g, 20.2 mmol) yielded the *ethoxy-salt* (13) (2.3 g, 83%), m.p. 96—98° (Found: C, 43.4; H, 8.85; N, 10.3; O, 11.7. $C_5H_{12}ClNO$ requires C, 43.6; H, 8.8; N, 10.2; O, 11.6%); $\nu_{max.}$ (KBr) 3 450br, 2 950br, 1 525, 1 355, 1 255, 1 080, and 1 050 cm^{-1}; δ ($CDCl_3$) 0.98—1.49 (4 H, m, cyclopropane), 1.23 (3 H, t, *J* 7 Hz, CH_3), 3.85 (2 H, q, *J* 7 Hz, OCH_2), and 9.0br (3 H, s, H_3N^+).

1-*Methoxy- and* 1-*Ethoxy-cyclopropylamine* (14) *and* (15).—1-Methoxy- (12) or 1-ethoxy-cyclopropylammonium chloride (13) was dissolved rapidly in an excess of sodium hydroxide (3M), and the alkaline solution was extracted with methylene chloride. After drying (Na_2SO_4) the solvent was distilled off at atmospheric pressure and the amino-ether was then distilled at reduced pressure.

The methoxy-salt (12) (3.70 g, 30 mmol) gave the *methoxyamine* (14) (1.55 g, 61%), b.p. 104° at 760 mmHg (Found: C, 55.4; H, 10.9; O, 18.2. C_4H_9NO requires C, 55.1; H, 10.4; O, 18.4%); $\nu_{max.}$ (film) 3 390, 2 940, 2 830, 1 330, 1 220, and 1 065 cm^{-1}; δ ($CDCl_3$) 0.60—0.99 (4 H, m, cyclopropane), 2.25br (2 H, s, NH_2), and 3.30 (3 H, s, OCH_3).

The ethoxy-salt (13) (1.5 g, 11 mmol) gave the *ethoxyamine* (15) (0.79 g, 72%), b.p. 118° at 760 mmHg (Found: C, 58.4; H, 11.2; O, 16.7. $C_5H_{11}NO$ requires C, 59.4; H, 11.0; O, 15.8%); $\nu_{max.}$ (film) 3 380, 2 980, 2 870, 1 330, 1 215, and 1 065 cm^{-1}; δ ($CDCl_3$) 0.62—1.03 (4 H, m, cyclopropane), 1.19 (3 H, t, *J* 7 Hz, CH_3), 2.22br (2 H, s, NH_2), and 3.57 (2 H, q, *J* 7 Hz, OCH_2).

Coprine [N^5-(1-*Hydroxycyclopropyl*)-L-*glutamine*] (1) *and* O-*Ethylcoprine* [N^5-(1-*Ethoxycyclopropyl*)-L-*glutamine*] (17).—Triethylamine (14.0 g, 0.135 mol) dissolved in dry tetrahydrofuran (75 ml) was added dropwise (1 h) to an ice-cooled solution of phthaloyl-L-glutamic anhydride [28] (35.0 g, 0.135 mol) in dry tetrahydrofuran (225 ml) containing suspended 1-hydroxycyclopropylammonium chloride (6) (13.6 g, 0.124 mol) [or dissolved 1-ethoxycyclopropylammonium chloride (13) (18.5 g, 0.135 mol)]. The mixture was stirred for 1 h at room temperature, the precipitate was filtered off, and the filtrate was evaporated under reduced pressure. The residue was dissolved in water (500 ml) with the aid of sodium carbonate (to pH 8). Hydrazine hydrate (7.5 g, 0.15 mol) was added and the mixture was left at room temperature for 4 h, and then acidified (to pH 1.5) with concentrated hydrochloric acid. The phthalohydrazide crystallised out overnight and was filtered off. The filtrate was eluted through a cation-exchange column (50 × 3 cm; H^+ form). The column was washed with water and eluted with 0.3M-sodium hydroxide (displacement chromatography). The fractions containing coprine (or *O*-ethylcoprine) were combined and passed through an acetate-saturated anion exchanger (10 × 4 cm) to eliminate glutamic acid and other impurities. Evaporation of the eluate yielded a crystalline residue of practically pure coprine (16 g, 64%) [or *O*-ethylcoprine (21 g, 68%)].

Coprine (1) [14.0 g, 56% based on (6)] had m.p. 197—199° (from water–ethanol), $[\alpha]_D$ +7.6° (*c* 5.2 in H_2O) (Found: C, 47.4; H, 7.15; O, 31.4. $C_8H_{14}N_2O_4$ requires C, 47.5; H, 7.0; O, 31.7%); i.r. and t.l.c. data identical with those of the natural product (see above); δ (D_2O) 0.73—1.20 (4 H, m, cyclopropane), 1.93—2.55 (4 H, m, H_2-3 and -4), and 3.74 (1 H, t, H-2).

O-*Ethylcoprine* (17) (18.7 g, 60%) had m.p. 183—184° (from water–methanol–ethanol), $[\alpha]_D$ +5.2° (*c* 7.8 in H_2O) (Found: C, 52.2; H, 8.0; O, 28.0. $C_{10}H_{18}N_2O_4$ requires C, 52.2; H, 7.9; O, 27.8%); $\nu_{max.}$ (KBr) 3 380, 2 990, 1 650, 1 525, 1 420, 1 255, and 1 070 cm^{-1}; δ (D_2O) 0.75—1.23 (4 H, m, cyclopropane), 1.11 (3 H, t, *J* 7 Hz, CH_3), 1.94—2.58 (4 H, m, H_2-3 and -4), 3.63 (2 H, q, *J* 7 Hz, $O{\cdot}CH_2$), and 3.75 (1 H, t, *J* 6 Hz, H-2); $R_F(1)$ 0.5, $R_F(2)$ 0.6.

Isocoprine [N^1-(1-*Hydroxycyclopropyl*)-L-*isoglutamine*] (16).—Separation of the combined mother liquors from the synthesis of a 250 g batch of pure coprine (1) on a cation-exchange column (displacement technique) gave, in addition to coprine, a more strongly retained fraction (12.7 g). This contained primarily isocoprine (n.m.r.). Isolation was difficult owing to the extreme solubility of the compound. Repeated crystallisation from water–methanol–ethanol gave pure *isocoprine* (16) (0.8 g), m.p. 158—161°, $[\alpha]_D$ +41.0° (*c* 3.0 in H_2O) (Found: C, 47.6; H, 7.15; O, 31.9. $C_8H_{14}N_2O_4$ requires C, 47.5; H, 7.0; O, 31.7%); $\nu_{max.}$ (KBr) 3 420br, 3 105, 1 675, 1 560, 1 390, 1 310, 1 240, and 1 025 cm^{-1}; δ (D_2O) 0.77—1.25 (4 H, m, cyclopropane), 1.83—2.50 (4 H, m, H_2-3 and -4), and 3.93 (1 H, t, *J* 6 Hz, H-2); $R_F(1)$ 0.3 (yellow, later blue, with ninhydrin), $R_F(2)$ 0.6.

N^4-(1-*Hydroxycyclopropyl*)-L-*asparagine* (18).—A synthesis analogous to that of coprine, from 1-hydroxycyclopropylammonium chloride (6) (5.45 g, 50 mmol), phthaloyl-L-aspartic anhydride [30] (12.3 g, 50 mmol), and triethylamine (5.5 g, 54.5 mmol), gave a mixture of compound (18) and the corresponding isoasparagine derivative. Recrystallisation from water–ethanol gave a small amount of pure N^4-(1-*hydroxycyclopropyl*)-L-*asparagine* (18) (1.0 g, 10.5%), m.p. 211—213°, $[\alpha]_D$ −6.4° (*c* 4.2 in H_2O) (Found: C, 44.4; H, 6.8; O, 33.9. $C_7H_{12}N_2O_4$ requires C, 44.7; H, 6.45; O, 34.0%); $\nu_{max.}$ (KBr) 3 290, 1 650, 1 540, 1 420, 1 305, 1 260, and 1 025 cm^{-1}; δ (D_2O) 0.75—1.22 (4 H, m, cyclopropane), 2.70—2.97 (2 H, m, H_2-3), and 4.00 (1 H, dd, *J* 5.0 and 6.6 Hz, H-2); $R_F(1)$ 0.36, $R_F(2)$ 0.35.

N^1-(1-Hydroxycyclopropyl)-L-isoasparagine [$R_F(1)$ 0.36, $R_F(2)$ 0.45] was not isolated in pure form.

N-(1-*Hydroxycyclopropyl*)*acetamide* (19).—Triethylamine (6.0 g, 60 mmol) was added dropwise at 0 °C to a solution of 1-hydroxycyclopropylammonium chloride (6) (2.88 g,

26.5 mmol) and acetic anhydride (5.60 g, 55 mmol) in dioxan–water (10 : 1; 50 ml) and the mixture was stirred at room temperature for 1 h. The precipitate was filtered off and the filtrate was evaporated under reduced pressure. The oily residue dissolved in water (50 ml) was passed through a cation-exchange column (15 × 1.5 cm; H^+ form). The column was washed with water and the total aqueous eluate was filtered through an anion-exchange column (7 × 3 cm; basic form). After washing with water the filtrate was evaporated under reduced pressure (30 °C). The residue was dissolved in water (5 ml) and extracted once with chloroform (1 ml). The aqueous phase was then evaporated (0.1 mmHg; 30 °C) giving a crystalline residue (2.5 g). The residue was sublimed (0.01 mmHg; 60 °C) yielding the pure *acetamide* (19) (1.90 g, 62%), m.p. 81—85° (Found: C, 52.2; H, 8.05; O, 27.9. $C_5H_9NO_2$ requires C, 52.2; H, 7.9; O, 27.8%); $\nu_{max.}$ (KBr) 3 320, 1 665, 1 540, 1 290, 1 250, 1 030, and 715 cm^{-1}; δ_H ($CDCl_3$) 0.70—1.26 (4 H, m, cyclopropane), 1.98 and 2.26 [3 H, 2s, Ac, intensity ratio s (1.98) : s (2.26) >3.8, increasing at lower concentrations], 5.0br (1 H, s, OH), and 7.2br (1 H, s, NH) (two rotamers); δ_C ($CDCl_3$) 14.7 and 16.1 (weak) (CH_2·CH_2), 21.4 (weak) and 23.1 (CH_3), 61.0 and 62.4 (weak) [C(OH)NH], and 172.2 and 176.4 (weak) (CO) (two rotamers).

N-(1-*Ethoxycyclopropyl*)*acetamide* (20).—Triethylamine (2.2 g, 22 mmol) was added dropwise at 0 °C with stirring to a solution of 1-ethoxycyclopropylammonium chloride (13) (1.25 g, 9.15 mmol) and acetic anhydride (2.2 g, 21.6 mmol) in dry tetrahydrofuran (25 ml). The precipitate was filtered off and the filtrate was evaporated under reduced pressure. The residue dissolved in ethanol–water (3 : 2; 100 ml) was passed successively through a strongly acidic cation-exchange column (5 × 1.5 cm; H^+ form) and a weakly basic anion-exchange column (5 × 2 cm; basic form). The filtrate was evaporated under reduced pressure and the residue was washed with cyclohexane (5 ml). The crystalline residue (0.90 g, 69%) thus obtained was the acetamide (20) in almost pure form (n.m.r.), but contained a small fraction of an unknown compound [singlet at δ ($CDCl_3$) 2.00]. Sublimation twice followed by recrystallisation three times from petroleum–ethyl acetate yielded pure N-(1-*ethoxycyclopropyl*)*acetamide* (20) (0.25 g, 19%), m.p. 78—80° (Found: C, 58.5; H, 9.2; O, 22.6. $C_7H_{13}NO_2$ requires C, 58.7; H, 9.15; O, 22.4%); $\nu_{max.}$ (KBr) 3 280, 1 680, 1 550, 1 330, 1 255, 1 130, and 1 070 cm^{-1}; δ ($CDCl_3$) 0.79—1.23 (4 H, m, cyclopropane), 1.14 and 1.16 (3 H, 2 t, *J* 7 Hz, CH_3), 1.98 and 2.24 (3 H, 2 s, Ac), 3.54 and 3.63 (2 H, 2 q, *J* 7 Hz, OCH_2), and 6.7br and 7.3br (1 H, s, NH) (two rotamers).

The Amides (21)—(24) *and the Carbamates* (26) *and* (27).—Triethylamine (25 mmol) in dry tetrahydrofuran (15 ml) was added dropwise (30 min) at 0 °C with stirring to suspensions of 1-hydroxy- (6) or 1-methoxy- (12) or a solution of 1-ethoxy-cyclopropylammonium chloride (13) (10 mmol) in dry tetrahydrofuran (25 ml) containing the acylating reagent (benzoyl or hexanoyl chloride or ethyl chloroformate) (10 mmol). The mixture was stirred at room temperature for 30 min. The precipitate was filtered off and washed with tetrahydrofuran, and the solution evaporated under reduced pressure.

(a) N-(1-*Hydroxycyclopropyl*)*benzamide* (21). 1-Hydroxy-cyclopropylammonium chloride (6) (2.67 g, 24.5 mmol) gave the *benzamide* (21) (3.0 g, 69%), m.p. 153—155° (sealed tube; N_2) (from chloroform) (Found: C, 67.5; H, 6.3; O, 17.9. $C_{10}H_{11}NO_2$ requires C, 67.8; H, 6.25; O, 18.1%); $\nu_{max.}$ (KBr) 3 310, 1 655, 1 525, 1 300, 1 265, 1 030, and 695 cm^{-1}; δ ($CDCl_3$) 0.87—1.38 (4 H, m, cyclopropane), 4.7br (1 H, s, OH), and 7.3—7.9 (6 H, m, aromatic and NH).

(b) N-(1-*Methoxycyclopropyl*)*benzamide* (22). 1-Methoxycyclopropylammonium chloride (12) (1.82 g, 13.0 mmol), gave the *benzamide* (22) (1.2 g, 55%), m.p. 190—191° (from methanol) (Found: C, 69.1; H, 7.0; O, 17.0. $C_{11}H_{13}NO_2$ requires C, 69.1; H, 6.85; O, 16.7%); $\nu_{max.}$ (KBr) 3 300, 1 655, 1 525, 1 315, 1 250, 1 055, and 695 cm^{-1}; δ ($CDCl_3$) 1.00—1.30 (4 H, m, cyclopropane), 3.40 (3 H, s, CH_3), 7.0br (1 H, s, NH), and 7.35—7.95 (5 H, m, aromatic).

(c) N-(1-*Ethoxycyclopropyl*)*benzamide* (23). 1-Ethoxy-cyclopropylammonium chloride (13) (1.25 g, 9.15 mmol) gave the *benzamide* (23) (0.95 g, 51%), m.p. 108—109° (from cyclohexane followed by sublimation at 0.01 mmHg) (Found: C, 70.2; H, 7.4; O, 15.7. $C_{12}H_{15}NO_2$ requires C, 70.2; H, 7.35; O, 15.6%); $\nu_{max.}$ (KBr) 3 310, 1 655, 1 540, 1 315, 1 265, 1 075, and 730 cm^{-1}; δ ($CDCl_3$) 0.90—1.38 (4 H, m, cyclopropane), 1.16 (3 H, t, *J* 7 Hz, CH_3), 3.77 (2 H, q, *J* 7 Hz, OCH_2), and 7.0—8.0 (6 H, 1 m and 1 br s, aromatic and NH).

(d) N-(1-*Ethoxycyclopropyl*)*hexanamide* (24). 1-Ethoxy-cyclopropylammonium chloride (13) (1.37 g, 10 mmol) gave a crystalline residue (1.85 g) which was dissolved in light petroleum (20 ml) and filtered through a short silica gel column (10 × 2 cm). The eluate was evaporated and the residue (1.30 g) was recrystallised from light petroleum (at low temperature) yielding the pure *amide* (24) (1.0 g, 50%), m.p. 47—48.5° (Found: C, 66.3; H, 10.6; O, 16.4. $C_{11}H_{21}NO_2$ requires C, 66.3; H, 10.6; O, 16.1%); $\nu_{max.}$ (KBr) 3 310, 2 950, 1 670, 1 540, 1 250, 1 070, and 735 cm^{-1}; δ ($CDCl_3$) 0.7—1.9 (16 H, m, cyclopropane, 2 CH_3 and $[CH_2]_3$), 2.0—2.4 and 2.4—2.8 (2 H, 2 m, $COCH_2$), 3.57 and 3.63 (2 H, 2 q, *J* 7 Hz, OCH_2), and 6.7br (1 H, s, NH) (two rotamers).

(e) *Ethyl* N-(1-*methoxycyclopropyl*)*carbamate* (26). 1-Methoxycyclopropylammonium chloride (12) (1.23 g, 10 mmol), gave a liquid residue, which was distilled under vacuum (Vigreux column) yielding the *carbamate* (26) (0.72 g, 45%), b.p. 62° at 0.8 mmHg (Found: C, 52.7; H, 8.4; O, 30.3. $C_7H_{13}NO_3$ requires C, 52.8; H, 8.25; O, 30.2%); $\nu_{max.}$ (KBr) 3 320, 2 980, 1 720, 1 515, 1 330, 1 235, and 1 080 cm^{-1}; δ ($CDCl_3$) 0.80—1.27 (4 H, m, cyclopropane), 1.26 (3 H, t, *J* 7 Hz, CH_3), 3.35 (3 H, s, OCH_3), 4.15 (2 H, q, *J* 7 Hz, OCH_2), and 6.0br (1 H, s, NH).

(f) *Ethyl* N-(1-*ethoxycyclopropyl*)*carbamate* (27). 1-Ethoxy-cyclopropylammonium chloride (13) (1.37 g, 10 mmol), gave a liquid residue, which was distilled under vacuum (Vigreux column) yielding the *carbamate* (27) (1.5 g, 86%), b.p. 69° at 0.8 mmHg (Found: C, 55.3; H, 8.7; O, 27.8. $C_8H_{15}NO_3$ requires C, 55.5; H, 8.75; O, 27.7%); $\nu_{max.}$ (film) 3 350, 3 000, 1 725, 1 520, 1 240, and 1 085 cm^{-1}; δ ($CDCl_3$) 0.80—1.27 (4 H, m, cyclopropane), 1.16 (3 H, t, *J* 7 Hz, ring O·CH_2·CH_3), 1.26 (3 H, t, *J* 7 Hz, carbamate O·CH_2·CH_3), 3.65 (2 H, q, *J* 7 Hz, ring O·CH_2·CH_3), 4.15 (2 H, q, *J* 7 Hz, carbamate O·CH_2·CH_3), and 6.0br (1 H, s, NH).

Acidic Hydrolysis of O-*Ethylcoprine* (17).—*O*-Ethylcoprine (50 mg, 0.22 mmol) on treatment with hydrochloric acid (2M; 0.5 ml) at 80 °C for 35 min gave a mixture of coprine (1) (55%), the hydrochloride (6) (25%), unchanged *O*-ethylcoprine (17), (20%) ethanol, and glutamic acid (n.m.r.).

Alkaline Hydrolysis of O-*Ethylcoprine* (17).—Treatment of *O*-ethylcoprine (17) (35 mg, 0.15 mmol) with aqueous sodium hydroxide (2M; 0.5 ml) at 80 °C for 2 h gave no

reaction (n.m.r.). Addition of solid sodium hydroxide (to give 6M-NaOH) followed by heating at 80 °C for 7 h resulted in partial hydrolysis (*ca.* 50%) to 1-ethoxycyclopropylamine (15) (which is stable under these conditions) and an equivalent amount of glutamic acid (n.m.r.).

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