2.7–2.3 (5 H, m), 2.1 (3 H, m), 1.85 (2 H, m), 1.40 (2 H, m), 1.20 (2 H, m).

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Registry No. (±)-**1**, 81370-78-7; (±)-**2**, 59433-37-3; (±)-**3**, 119323-97-6; **4**, 54396-74-6; (±)-**5**, 90382-33-5; (±)-**6**, 102045-26-1; (±)-**7a**, 119323-98-7; (±)-**7s**, 119245-05-5; (±)-**8a**, 119323-99-8; (±)-**8s**, 119245-06-6; (±)-**9a**, 119324-07-1; (±)-**9s**, 119245-07-7; (±)-**10a**, 119324-08-2; (±)-**10s**, 119245-08-8; (±)-**11a**, 119324-09-3; (±)-**11s**, 119245-09-9; (±)-**12**, 119245-10-2; (±)-**13**, 119245-11-3; (±)-**14**, 119245-12-4; **17**, 25662-28-6; **18**, 108384-35-6; (±)-**19**, 119245-13-5; (±)-**20**, 119245-14-6; (±)-**21**, 119324-00-4; (±)-**22a**, 119324-05-9; (±)-**22s**, 119245-15-7; (±)-**23a**, 119324-06-0; (±)-**23s**, 119245-16-8; (±)-**24a**, 119245-17-9; (±)-**24s**, 119324-01-5; (±)-**25a**, 119324-02-6; (±)-**25s**, 119245-18-0; (±)-**26a**, 119324-03-7; (±)-**26s**, 119245-19-1; (±)-**27a**, 119245-20-4; (±)-**27s**, 119324-04-8; (±)-**28**, 119245-21-5; (±)-**29**, 119245-22-6; (±)-**30**, 119245-23-7; (±)-**31**, 119245-24-8; (±)-**32**, 119245-25-9; (±)-**33**, 119245-26-0; cyclopentene, 142-29-0.

Decarboxylation of 1-Aminocyclopropanecarboxylic Acid and Its Derivatives

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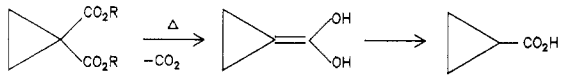
The question of whether the title compounds could be decarboxylated to cyclopropanone derivatives was answered in the affirmative by the following observations. (1) Compound **11a** was decarboxylated by 1,2,3-indantrione in acetonitrile, benzene, or methanol. The initially formed intermediate could be trapped by *N*-phenylmaleimide (to form **3**), by diethyl azodicarboxylate (to form an unstable adduct), by ninhydrin itself (to form **5**) or by a proton (in methanol, to form **8**). (2) Compound **11d** was decarboxylated by phenylbis(trifluoroacetato-*O*)iodine to yield carbinolamine **12d**. *cis*-2,3-Dideuterio-**11d** yielded *cis*-2,3-dideuterio-**12d** under the same conditions. (3) ACC was decarboxylated by phenanthroquinone to yield oxazole **9**, probably by way of oxazoline **10**.

Can cyclopropanecarboxylic acids be decarboxylated in solution under conditions that permit survival of the cyclopropane ring? We are unaware of any examples of such a reaction in the literature. One reported attempt at decarb*alkoxyl*ation in solution was unsuccessful: under conditions that effected the decarbmethoxylation of other substituted malonic esters (KCN, DMF, reflux for 12 h), the cyclopropane analogue **1c** did not decarbalkoxylate.[1] In the absence of solvent, **1a** was decarboxylated at about 200 °C.[2-5] Strained enol **2** is probably an intermediate.

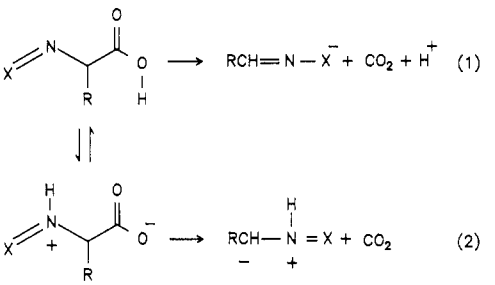


1a R = H
1b R = SiMe3
1c R = CH3

2

The intermediacy of an enol like **2** was demonstrated in the case of **1b**.[6] The observation that **1a** underwent decarboxylation in 98% sulfuric acid at 180 °C faster than did the corresponding cyclobutane- and cyclopentanedicarboxylic acids was at first unexpected.[7] Later it was found that **1a** did not decarboxylate until after it had

Scheme I



isomerized to a five-membered lactone.[8,9]

Amino acids in general are readily decarboxylated by a variety of reagents (the Strecker degradation).[10] For some time the accepted mechanism for this reaction has been the concerted mechanism outlined in eq 1 of Scheme I.[11] Its application to 1-aminocyclopropanecarboxylic acid (ACC) involves the same kind of strained intermediate that apparently inhibited the thermal decarboxylation of **1a**. Recently, however, Grigg has proposed that the decarboxylation of α-imino carboxylic acids (formed from amino acids and carbonyl compounds) involves the formation of a 1,3-dipole from a tautomer of the starting imine (eq 2 of Scheme I).[11] The 1,3-dipole formed by the application of this mechanism to ACC might have a pyramidal structure, its negative site stabilized by the inductive effect of the positive iminium ion. In that event decarboxylation

(1) (a) Krapcho, A. P.; Weimaster, J. M.; Eldridge, J. M.; Jahngen, E. G. E., Jr.; Lovey, A. J.; Stephens, W. P. *J. Org. Chem.* **1978**, *43*, 138. (b) Peace, B. W.; Wulfman, D. S. *Synthesis* **1973**, 137.
(2) Abell, P.; Lennon, D. J. J. *J. Org. Chem.* **1965**, *30*, 1206.
(3) Najer, H.; Clenet, Y. *Bull. Soc. Chim. Fr.* **1966**, 1715.
(4) Mandelshtam, T. V.; Kolesova, S. V.; Polina, T. V.; Solomentsev, V. V.; Osmolovskaya, N. S. *J. Org. Chem. USSR* **1980**, *16*, 1024.
(5) The half-life of malonic acid in the absence of solvent is about 1 h at 135 °C. Clark, L. W. *J. Phys. Chem.* **1963**, *67*, 138.
(6) Bloch, R.; Denis, J. M. *J. Organomet. Chem.* **1975**, *90*, C9.
(7) Abell, P. I.; Tien, R. *J. Org. Chem.* **1965**, *30*, 4212.
(8) Bus, J.; Steinberg, H.; de Boer, T. J. *Tetrahedron Lett.* **1966**, 1979.
(9) Handzo, C. S.; Humphrey, G. L. *J. Org. Chem.* **1979**, *44*, 2146.
(10) Schonberg, A.; Moubacher, R. *Chem. Rev.* **1952**, *50*, 261.
(11) Grigg, R.; Thianpatanagul, S. *J. Chem. Soc., Chem. Commun.* **1984**, 182.

0022-3263/89/1954-1810$01.50/0

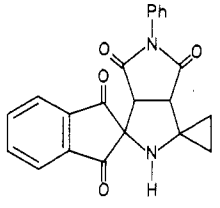
might be possible under relatively mild conditions.

This issue is related to the problem of ethylene biosynthesis in plants, a subject of current interest. One of the mechanisms originally proposed for the biosynthesis of ethylene from ACC started with its decarboxylation.[12] However, this mechanism is no longer considered viable, not because of the decarboxylation step, but because such a mechanism is compatible neither with the observation that the fate of C-1 in ACC is cyanide nor with the observed stereochemistry of the reaction.[13,14]

We sought to test the feasibility of decarboxylation in this system by attaching an electron sink to the nitrogen of several ACC derivatives. The Strecker degradation can be effected by a variety of reagents.[10] The application of many of them (hypochlorite, for example) to ACC and its derivatives resulted in ring opening (probably before decarboxylation).[15] However, in two cases, with ninhydrin and with $PhI(O_2CCF_3)_2$, it has proven possible to isolate a decarboxylation product with the three-membered ring intact.

Results and Discussion

Ninhydrin is well-known for its ability to decarboxylate amino acids. When a mixture of 1 equiv each of ACC, ninhydrin, and *N*-phenylmaleimide was heated in acetonitrile, CO_2 was produced in 70% yield. Adduct **3**, which was identified from its spectra (mass, ^1H NMR, ^{13}C NMR, and infrared), was isolated in 30% yield. We propose the intermediacy of 1,3-dipole **4** by analogy to the work of Grigg,[11] who has trapped similar dipoles from several amino acids.



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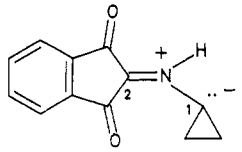
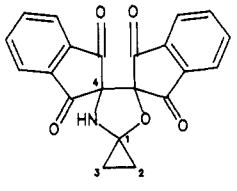
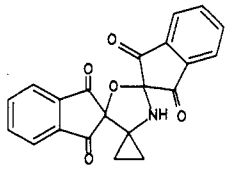


4

An attempt to trap dipole **4** with diethyl azodicarboxylate (DEAD) was only partly successful. A mixture of ACC, ninhydrin, and DEAD heated in benzene produced CO_2 in 50% yield. Two products were formed; the one that appeared to be the triazolidine analogous to **3** was apparently not stable and could not be completely characterized. The other product did not contain the DEAD fragment and was identified as **5** from its spectra (see below). When only ACC and ninhydrin were heated together in benzene, the yield of **5** was 90%.



5



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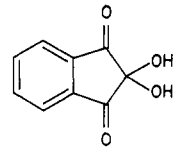


7

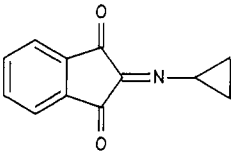
The assignment of structure **5** instead of **6** was based principally on the chemical shift of carbon 1 of the cyclopropane ring. Table I presents the relevant carbon shifts for a series of related compounds, **3**, **5**, **7**, **8**, and **12d**. The critical shift assignments to C-1 and C-4 were made from a coupled spectrum. C-1 shows splitting (from coupling to the cyclopropyl protons) while C-4 is a singlet. From these data it can be concluded that a chemical shift of about 45 ppm is predicted for C-1 with only one hetero atom attached, and that a shift of about 80 ppm is predicted when two hetero atoms are attached.

Table I. ^{13}C NMR Chemical Shifts Used To Assign Structure 5[a]

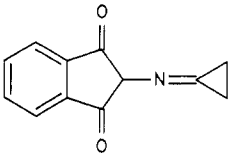
compd	C-1	C-2	C-3	C-4
3	46.18	7.87	15.13	72.63
5	78.18	12.17	12.17	86.05
7				87.7
8	39.28	16.46	16.46	156.15
12d	74.33	16.31	16.31	

[a] The carbon numbering used here is shown in structure **5**.

The cyclopropanone *N,O*-ketal **5**, the product of the addition of **4** to ninhydrin itself, has a regiochemistry analogous to that of the product from the cycloaddition of pyridine-2-carbaldehyde to a dipole derived from tetrahydroisoquinoline.[16] That the analogy would hold was not a foregone conclusion, for the introduction of a cyclopropyl group into benzonitrile ylide apparently reversed the regiochemistry expected for ylides that lack that group.[17] If this azomethine ylide cycloaddition is HOMO-controlled, as is normally the case,[18] the observed regiochemistry means that the HOMO coefficient is largest at C-2 of dipole **4**, not an unreasonable conclusion given the fact that C-2 is flanked by two carbonyls. (The largest LUMO coefficient in the dipolarophile, the carbonyl group, is at carbon.[19]) The fact that **4** gets protonated at C-1 (described below) is probably irrelevant to the cycloaddition regiochemistry, for **8** is formed under conditions that should yield the more stable product even if it were not the first-formed product.



8



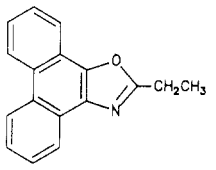
8'

In refluxing methanol, ninhydrin and ACC produced CO_2 in 23% yield. From this reaction mixture was isolated a small amount (10%) of imine **8**. This compound was independently prepared in 50% yield by treatment of cyclopropylamine with ninhydrin in acetonitrile. The chemical shift for the α cyclopropyl proton in **8** is unusually far downfield at 5.20 ppm. The chemical shifts for the cyclopropyl carbons, at 16.46 (CH_2) and 39.28 (CH), however, are consistent with structure **8**, and not with its tautomer **8'**. Compound **8** represents an understandable exception to the finding of Crooks[20] that imines of ninhydrin are stable only when the carbon of the original amine is tertiary. Compound **8**, however, cannot easily tautomerize to **8'**. Dipole **4** is a tautomer of **8** and its probable source.

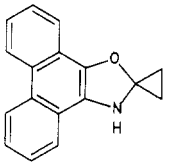
During the search for a decarboxylating agent that would preserve the cyclopropane ring, several quinones were tried

(12) Adlington, R. M.; Aplin, R. T.; Baldwin, J. E.; Rawlings, B. J.; Osborne, D. *J. Chem. Soc., Chem. Commun.* **1982**, 1086.
(13) (a) Adlington, R. M.; Baldwin, J. E.; Rawlings, B. J. *J. Chem. Soc., Chem. Commun.* **1983**, 290. (b) Pirrung, M. *Bioorg. Chem.* **1985**, *13*, 261.
(14) Peiser, G. D.; Wang, T.-T.; Hoffman, N. E.; Yang, S. F.; Liu, H.-W.; Walsh, C. T. *Proc. Natl. Acad. Sci. U.S.A.* **1984**, *81*, 3059.
(15) Vaidyanathan, G.; Wilson, J. W. *J. Org. Chem.* accompanying paper in this issue.
(16) Ardill, H.; Grigg, R.; Sridharan, V.; Surendrakumar, S.; Thianpatanagul, S.; Kanajun, S. *J. Chem. Soc., Chem. Commun.* **1986**, 602.
(17) Padwa, A.; Rasmussen, J. K. *J. Am. Chem. Soc.* **1975**, *97*, 5912.
(18) Lown, J. W. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 1, p 674ff.
(19) Reference 18, p 691.
(20) Crooks, P. A. *Chem. Ind.* **1980**, 467.

in the expectation that the first-formed decarboxylation product would be trapped by an internal nucleophile. In the event, the reaction of ACC with phenanthrenequinone in refluxing dimethylformamide produced CO_2 in about 50% yield. A 40% yield of **9** (structure assigned from spectra) was isolated. Presumably oxazoline **10** was formed first by decarboxylation and then suffered ring opening to oxazole **9** under the reaction conditions.



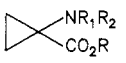
9



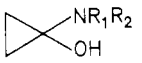
10

The second reagent to yield a stable cyclopropane-ring-containing decarboxylation product was phenylbis(trifluoroacetato-*O*)iodine, $(CF_3CO_2)_2IPh$, sometimes abbreviated as PIFA (for phenyl iodosyl bis(trifluoroacetate)). Although PIFA is not commonly associated with decarboxylation, Loudon, in a study of the scope and mechanism of the PIFA-induced Hofmann rearrangement, noted that several amino acids were decarboxylated by this reagent.[21] For example, phenylalanine was converted to phenylacetaldehyde by PIFA. (It is worth noting that PIFA was used in an attempt to prepare 1,1-diaminocyclopropane by the rearrangement of a protected amide of ACC. The expected cyclopropane-ring-containing product was not formed; a β-alaninamide derivative was formed instead.[22])

ACC and three of its tertiary amino derivatives, **11a–d**, were treated with PIFA. The product from **11a**, obtained in low yield, was a mixture that could not be identified, although ^1H NMR indicated that the cyclopropane ring was not intact and that at least one of the products had an A_2B_2 pattern. In the other three cases, the yield of CO_2 was at least 60%, though the isolated yield of carbinolamine **12** was much smaller, presumably a reflection of the instability of the carbinolamines to the conditions of isolation. The products from **11b** and **11c** appeared, from ^1H NMR evidence, to be the carbinolamines, **12b** and **12c**, but they were not very stable and did not survive attempts at purification. Only in the case of **11d** was it possible to purify and identify the product unambiguously. The treatment of **11d** with PIFA produced CO_2 in 60% yield. A 20% yield of carbinolamine **12d** was isolated by flash chromatography. An authentic sample of **12d** was prepared by the method of Wasserman and Dion.[23]

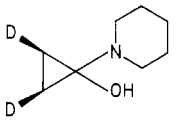


11 a· $R=R_1=R_2=H$
b· $R=H$, $R_1=R_2=CH_3$
c· $R=H$, $R_1=R_2=PhCH_2$
d· $R=H$, $R_1=R_2=(CH_2)_5$
e· $R=CH_3$, $R_1=R_2=H$



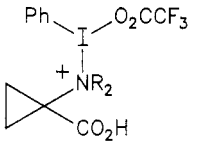
12 b· $R_1=R_2=CH_3$
c· $R_1=R_2=PhCH_2$
d· $R_1=R_2=(CH_2)_5$

Finally, a sample of *cis*-2,3-dideuterio-**11d** was converted to the corresponding labeled carbinolamine, **13**, by treatment with PIFA. It was possible to show that the cis relationship of the two deuterium atoms was maintained in **13**, because **13** could be converted to ethylene-*cis*-1,2-d_2 in a concerted reaction with hypochlorite.[15]



13

The mechanism of the decarboxylation reaction presumably involves hypervalent iodine compound **14**. Whether the decarboxylation results directly in the formation of an iminium compound, which is then hydrated to **12**, or whether a zwitterion analogous to **4** is formed, is not known. The fact that the stereochemistry of the ring hydrogens was maintained over the course of the reaction excludes the possibility of a ring opening, closing equilibrium in the iminium salt under these conditions.[24] Although we were not able to generalize this method to other amines, it is a unique way to prepare stereochemically labeled cyclopropanone derivatives.



14

With the observation of products that still contain a cyclopropane ring, we have demonstrated that some 1-aminocyclopropanecarboxylic acids can be decarboxylated under relatively mild conditions. The decarboxylation reactions provide entry to certain cyclopropanone derivatives from a new source. The intermediacy of a zwitterionic 1,3-dipole is assumed. An investigation of the stability of this intermediate relative to the stabilities of the 1,3-dipoles generated from other amino acids is planned.

Experimental Section

Melting points are uncorrected. ^1H NMR chemical shifts in D_2O were referenced to HOD in most of these cases. (In some cases TSP, sodium 3-(trimethylsilyl)propionate, or dioxane were used as reference.) Gas chromatography of ethylene and CO_2 was performed on a 6 ft × $^1/_8$ in. copper column of PORAPAK N 80/100 (from Alltech) at 50 °C. The apparatus employed in all decarboxylation reactions consisted of a flask with a septum-fitted side arm that served as an argon inlet and an outlet that was connected to a series of traps containing saturated barium hydroxide. The precipitated barium carbonate was collected by filtration, washed with water and with acetone, and dried to a constant weight. Preparative thin-layer chromatography (TLC) was performed on 20 × 20 cm plates, prepared from E. Merck silica gel or, for small quantities, on 20 × 20 cm precoated silica gel analytical plates (Aldrich). Bands were visualized by UV or by I_2 vapor. Analytical TLC was performed on 250 μm silica gel coated polyester plates (Aldrich or Kodak). Column chromatography was performed with silica gel (60–200 mesh) from Davison Chemicals. Flash chromatography was performed with E. Merck silica gel 60. Unless otherwise specified, evaporation of solvent was accomplished under reduced pressure on a rotary evaporator.

1-Aminocyclopropanecarboxylic acid (ACC, **11a**) was prepared from methyl *N*-acetylmethioninate, which was in turn prepared from *N*-acetyl-DL-methionine (50 g; Sigma) with 2,2-dimethoxypropane (70 mL) and *p*-toluenesulfonic acid (650 mg) in methanol (50 mL) at room temperature over 48 h. Solvent removal, solution in EtOAc, washing with bicarbonate, and drying yielded 45 g (84%) of the ester; mp 82 °C (lit.[25] mp 82.6–83.2 °C).

(21) Loudon, G. M.; Radhakrishna, A. S.; Almond, M. R.; Blodgett, J. K.; Boutin, R. H. *J. Org. Chem.* **1984**, *49*, 4272.
(22) Tamura, M.; Jacyno, J.; Stammer, C. H. *Tetrahedron Lett.* **1986**, *27*, 5435.
(23) Wasserman, H. H.; Dion, R. P. *Tetrahedron Lett.* **1982**, *23*, 785.
(24) Vilsmaier, E.; Schwaben, B.; Joerg, K. *Chem. Ber.* **1984**, *117*, 2900.

The ester (10 g, 0.05 mol) was converted to ACC by the method of Gallenkamp.[26] The crude product from the cyclization reaction (65% yield) was refluxed for 4 h in 200 mL of 6 M HCl. Charcoal was added, and the solution was refluxed for another half hour. Water was evaporated from the filtrate, and the solid residue was dried overnight in a vacuum desiccator over sodium hydroxide. Propylene oxide (50 mL) was added to the dried solid, and the mixture was stirred for 6 h. The amino acid was collected, washed with acetone, and recrystallized from water–acetone to yield 2 g (60%) of crystalline solid: mp 235 °C (sublimes) (lit.[27] mp 229–231 °C).

Methyl 1-aminocyclopropanecarboxylate (11e) was prepared from the acid (1 g, 10 mmol) in HCl-saturated methanol (overnight at room temperature).[28] The hydrochloride of **11e** was isolated [NMR (D_2O) δ 0.00 (TSP), 4.68 (HOD), 1.47 (m, 2 H), 1.93 (m, 2 H), 3.77 (s, 3 H)]. A concentrated aqueous solution of the salt was cooled, and ether (20 mL) was added. Solid K_2CO_3 was added in portions to neutralize the hydrochloride and to absorb all the water. After the ether was decanted, the cake was extracted with four 20-mL portions of ether. Drying and solvent removal yielded 900 mg (80%) of **11e**, identified by its ^1H NMR spectrum.[27]

1-Aminocyclopropane-*cis*-2,3-d_2-carboxylic Acid. Pirrung's procedure,[29] based on the Schöllkopf method,[30] was used. For use in that procedure, labeled 1,2-dibromoethane was prepared from ethylene-*1,2-d_2*, which was prepared from 25 g of calcium carbide and 10 mL of D_2O according to the method of Nicholas and Carroll.[31] It was slowly displaced into a trap containing bromine in methylene chloride (20 g in 100 mL) at −23 °C. The CH_2Cl_2 solution was washed with $NaHSO_3$ solution, dried (Na_2SO_4), and evaporated, and the residual oil was distilled at atmospheric pressure to obtain 10 g (10%) of *meso*-1,2-dibromoethane-*1,2-d_2*: NMR ($CDCl_3$) δ 3.65 (s).

1-(*N*,*N*-Dimethylamino)cyclopropanecarboxylic Acid (11b). In a hydrogenation bottle were placed 505 mg (5 mmol) of ACC, 250 mg of 10% Pd/C, 0.75 mL of 37% aqueous formaldehyde, and 20 mL of water.[32] The contents were shaken under hydrogen (10 psi) for 24 h. The catalyst was removed by filtration, and the water was evaporated. More water was added and evaporated to obtain 400 mg (62%) of a white solid (**11b**). It was recrystallized from methanol: mp 200–210 °C with sublimation; NMR (D_2O) δ 4.53 (HOD), 1.33 (br s, 4 H), 2.83 (s, 6 H); IR (KBr) 3440, 3040, 2990, 2300, 1620, 1375 cm^{-1}; MS *m/z* 129, 114, 84; calcd for $C_6H_{11}NO_2$ 129.078 85, found 129.0789.

1-(*N*,*N*-Dibenzylamino)cyclopropanecarboxylic Acid (11c). A mixture of 505 mg (5 mmol) of ACC, 2 g of anhydrous potassium carbonate, and 10 mL of acetonitrile was heated to boiling, and to it was added dropwise a solution of 3.0 g (17.5 mmol) of benzyl bromide in 5 mL of acetonitrile. It was refluxed for 3 h, cooled, and filtered. The filtrate was evaporated. Unreacted benzyl bromide was removed from the residue by chromatography on silica gel with hexane, and the benzyl ester of dibenzyl ACC was eluted with EtOAc: yield 1.8 g (100%) of white solid; mp 38–40 °C; NMR ($CDCl_3$) δ 0.77 (m, 2 H), 1.13 (m, 2 H), 4.0 (s, 4 H), 5.13 (s, 2 H), 7.13–7.4 (m, 15 H). The ester was mixed with a little tetraoctylammonium bromide in 5 mL of 50% propylene glycol–water that contained 20% KOH. The mixture was refluxed overnight. On cooling it was diluted with water and neutralized with HOAc or $KHSO_4$. The precipitated dibenzyl ACC was taken up into $CHCl_3$. The solution was washed with water, dried (Na_2SO_4), and evaporated to yield 1.35 g (96%) of a white solid (**11c**). It was recrystallized from hexane: mp 143–144 °C; NMR ($CDCl_3$) δ 0.9 (m, 2 H), 1.27 (m, 2 H), 4.0 (s, H), 7.27 s, 10 H); IR (KBr) 3050, 3010, 2870, 2840, 2400, 1680, 1605 cm^{-1}; MS *m/z* 281, 263, 236, 190, 146, 91, 77; ^{13}C NMR ($CDCl_3$) δ 20.28 (two CH_2 cyclopropyls), 44.77 (quaternary cyclopropyl), 57.35, 126.95, 128.15, 129.08, 181.54; calcd for $C_{18}H_{19}NO_2$ 281.141 47, found 281.1415.

1-(1-Piperidino)cyclopropanecarboxylic Acid (11d). To a boiling mixture of 1.72 g (15 mmol) of **11e**, 8.9 g of powdered potassium carbonate, 600 mg of tetrabutylammonium bromide, and 100 mL of acetonitrile was added dropwise a solution of 2.72 mL (18.3 mmol) of diiodopentane in 20 mL of acetonitrile. The mixture was refluxed for 36 h with vigorous stirring, the insoluble material was removed by filtration, and the filtrate was evaporated. The residue, which contained some inorganic salts, was chromatographed (silica gel; the excess diiodopentane was eluted with hexane and the ester of **11d** was eluted with EtOAc.) The ester was a yellow oil weighing 2.7 g (77%): NMR ($CDCl_3$) δ 0.93 (m, 2 H), 1.23 (m, 2 H), 1.43 (br s, 6 H), 2.83 (distorted t, 4 H), 3.6 (s, 3 H). The ester was hydrolyzed by refluxing it in 60 mL of 6 N HCl for 4 h. Water was removed under vacuum, and the solid residue was dried under vacuum overnight in a desiccator containing sodium hydroxide. It was stirred with propylene oxide (20–30 mL) for 4–5 h, filtered, and washed with acetone. Recrystallization from acetone–methanol yielded 650 mg (34%) of a white solid (**11d**): mp 220 °C (sublimation starts at 200 °C). NMR (D_2O) δ 4.8 (HOD), 1.52 (s, 4 H) (in some samples, identical in all other respects, this peak appeared as two multiplets), 2.03 (br m, 6 H), 3.53 (distorted t, 4 H); IR (KBr) 3460, 3020, 2975, 2880, 2290, 1625 cm^{-1}; MS *m/z* 169, 154, 124; calcd for $C_9H_{15}NO_2$ 169.110 19, found 169.1102.

Reaction of ACC with 1,2,3-Indantrione and *N*-Phenylmaleimide. A mixture of 50 mg (0.5 mmol) of ACC, 80 mg (0.5 mmol) of 1,2,3-indantrione, and 87 mg (0.5 mmol) of *N*-phenylmaleimide in 5 mL of acetonitrile was refluxed for 4 h. As it formed, CO_2 was carried into a solution of barium hydroxide by a stream of argon. The barium carbonate that formed was collected and dried; weight, 70 mg (70%). Acetonitrile was removed from the reaction mixture, and the crude product was chromatographed twice (prep TLC, $CHCl_3$) to get 55 mg (30%) of an oil, which solidified on standing (**3**): mp 95 °C; NMR ($CDCl_3$) δ 1.0 (m, 4 H), 3.47 (d, *J* = 8.7 Hz, 1 H), 3.83 (d, *J* = 8.7 Hz, 1 H), 7.4 (m, 5 H), 7.93 (m, 4 H); IR ($CHCl_3$) 3300, 3020, 1790, 1760, 1730, 1610 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 7.87, 15.13, 46.81, 52.87, 54.80, 72.63, 124.20, 124.38, 126.62, 128.85, 129.21, 129.26, 131.55, 136.67, 136.83, 140.4, 141.44, 174.29, 175.12, 197.68, 197.75; MS *m/z* 372, 251, 225, 210, 106, 91, 77, 76; calcd for $C_{22}H_{16}N_2O_4$ 372.1109, found: 372.1109.

Reaction of ACC, 1,2,3-Indantrione, and Diethyl Azodicarboxylate. A mixture of ACC (202 mg, 2 mmol), 1,2,3-indantrione (320 mg, 2 mmol), and diethyl azodicarboxylate (350 mg, 2 mmol) in 40 mL of dry benzene (washed with concentrated sulfuric acid, distilled twice over phosphorous pentoxide, and stored over sodium wire) was refluxed for 2 h. The initially yellow reaction mixture turned green on heating, and at the end of 2 h turned yellow again. The barium carbonate formed from the CO_2 evolved during the reaction weighed 206 mg (50%). The precipitate that formed during the reaction was collected (270 mg) and mixed with 75 mL of $CHCl_3$ to remove 60 mg of unreacted ACC, which is insoluble in $CHCl_3$. The filtrate was evaporated to yield 200 mg (56% based on indanetrione) of a solid, **5**, which was recrystallized from CH_2Cl_2–ether: mp 190 °C with decomposition; NMR ($CDCl_3$) δ 1.30 (m, 2 H), 1.47 (m, 2 H), 7.7 (m, 4 H); IR (KBr) 3480, 3300, 3100, 3040, 1730, 1600 cm^{-1}; ^{13}C NMR APT ($CDCl_3$) δ 12.17 (CH_2), 78.18 (C), 86.05 (C), 88.41 (C), 123.40 (CH), 123.66 (CH), 136.50 (CH), 136.63 (CH), 139.72 (C), 140.69 (C), 191.67 (CO), 193.70 (CO); ^{13}C NMR APT (CD_2Cl_2) δ 12.34 (CH_2), 79.06 (C), 86.29 (C), 89.39 (C), 123.54 (CH), 123.81 (CH), 137.05 (CH), 137.17 (CH), 140.01 (C), 141.03 (C), 192.11 (CO), 194.05 (CO); MS *m/z* 359 (M^+), 304, 199, 132, 104, 76; calcd for $C_{21}H_{13}NO_5$ 359.079 28, found 359.07950.

Evaporation of benzene from the original filtrate gave 500 mg of a sticky solid. This solid was chromatographed (silica gel column, 3:2 EtOAc/hexane) to yield 200 mg of an oil. This oil was further chromatographed on a thick-layer plate with the same solvent. The fraction with R_f = 0.5 (3:2 EtOAc–hexane) was collected and crystallized from ether to yield 85 mg of crystalline solid: mp 156 °C; NMR ($CDCl_3$) δ 0.7 (0.8 H, broad multiplet), 1.0–1.5 (a sharp triplet centered at 1.36 with approximate area

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of 4 h was superimposed on several broad multiplets in this region; total area: 9.3), 1.58 (0.9 H, sharp singlet), 2.06 (1.3 H, sharp multiplet, close to a quartet), 3.50 (1.0 H, singlet), 4.15 and 4.33 (4.4 H total area, broad multiplet and quartet overlapping), 8.0 (4.0 H, sharp multiplet); IR (KBr) 3470 (w), 3280, 3110 (w), 2990, 2920, 1740 (vs), 1600 cm^{-1}; ^{13}C NMR APT ($CDCl_3$) δ 8.91 (CH_2), 14.27 (CH_3), 14.39 (CH_2), 62.94 (C), 63.04 (C), 63.17 (CH_2), 123.83 (CH), 123.97 (CH), 135.97 (CH), 137.02 (CH), 138.86 (C), 141.01 (C), 158.43 (CO_2Et), 193.37 (CO), 196.17 (CO); MS m/z 373 (M^+), 301, 228 (base peak), 200, 199, 158, 132, 104, 76; calcd for $C_{18}H_{19}N_3O_6$ 373.1273, found 373.1270.

Reaction of ACC and 1,2,3-Indantrione in Benzene. As a mixture of ACC (101 mg, 1 mmol) and 1,2,3-indantrione (320 mg, 2 mmol) in 20 mL of dry benzene was refluxed for 2 h, the color of the mixture turned from green to yellow. The barium carbonate formed from the CO_2 that evolved during the reaction weighed 163 mg (83%). The reaction mixture was filtered, and the off-white solid that was collected was air dried; weight, 164 mg. Most of the benzene was evaporated from the filtrate, and the resultant slurry was filtered to get another 190 mg of the solid. The total yield of the combined solids, which were identified as **5** (see above), was more than 90%.

2-(Cyclopropylimino)-1,3-indandione (8). Cyclopropylamine (70 mg, 1.23 mmol), 1,2,3-indantrione (160 mg, 1 mmol), and 5 mL of dry acetonitrile (distilled over calcium hydride) were mixed. During the course of the reaction the dark magenta color of indantrione disappeared and a white powder formed. After the mixture had been stirred for an hour at room temperature, the reaction mixture became a yellow homogeneous solution. It was stirred for an additional 2 h. Acetonitrile and the excess cyclopropylamine were removed on the rotary evaporator. The resultant solid was chromatographed on a thick-layer plate with chloroform as eluent. The bright yellow band (R_f = 0.3) was isolated and extracted with EtOAc. Ethyl acetate was evaporated to yield 98 mg (50%) of bright yellow crystals: mp 165 °C dec; NMR ($CDCl_3$) δ 1.40 (d, 4.2 Hz, 4 H), 5.22 (m, 1 H), 7.6–8.2 (m, 4 H); IR ($CHCl_3$) 3020, 1750, 1640, 1615 cm^{-1}; ^{13}C NMR APT ($CDCl_3$) δ 16.46 (CH_2), 39.28 (CH), 124.07, 124.24, 136.33 (aromatic CH's), 140.33, 140.99 (aromatic C's), 156.15 (C=N), 184.45, 186.40 (CO's); MS m/z calcd for $C_{12}H_9NO_2$ 199.063 27, found 199.0632.

Reaction of ACC and 1,2,3-Indantrione in Methanol. To 50 mg (0.5 mmol) of ACC and 80 mg (0.5 mmol) of indantrione was added 8 mL of dry methanol. The heterogeneous reaction mixture was refluxed for 2.5 h. The barium carbonate that formed from the CO_2 that was evolved weighed 23 mg (23%). The dark reaction mixture was chromatographed (silica gel column, $CHCl_3$ eluent) to yield 25 mg of solid. This solid was further chromatographed on a thick-layer plate ($CHCl_3$) to get 10 mg (44% based on 23% decarboxylation) of a bright yellow solid. It was found to be identical (TLC, NMR, MS) to **8**, the compound obtained from the reaction of cyclopropylamine and indanetrione.

Reaction of ACC with Phenanthrenequinone. A mixture of ACC (50 mg, 0.5 mmol) and phenanthrenequinone (104 mg, 0.5 mmol) in 10 mL of DMF was refluxed for 4 h. The barium carbonate formed from the CO_2 that evolved weighed 50 mg (50%). DMF was removed in vacuo, and the residual oil was taken up in chloroform. The solid that precipitated from this solution (18 mg) was identified as ACC. Chloroform from the filtrate was evaporated, and the residue was chromatographed (silica gel column, $CHCl_3$) to yield 40 mg of a solid. It was rechromatographed (thick-layer plate, $CHCl_3$) to obtain 30 mg (40% from 32 mg of ACC) of a crystalline solid, **9**: mp 90–92 °C; NMR ($CDCl_3$) δ 1.53 (t, J = 7.2 Hz, 3 H), 3.15 (q, J = 7.2 Hz, 2 H), 7.5–8.9 (m, 8 H); IR (KBr) 3070, 2980, 2930, 1585, 1525, 1055, 1035, 750, 720 cm^{-1}; ^{13}C NMR APT ($CDCl_3$) δ 11.56 (CH_3), 22.42 (CH_2), 120.61 (CH), 121.13 (C), 122.65 (CH), 123.38 (CH), 123.66 (CH), 125.81 (CH), 126.06 (CH), 126.14 (C), 127.14 (CH), 127.32 (CH), 128.65 (C), 128.88 (C), 13426 (C), 144.70 (C), 166.96 (C=N); MS m/z 247 (M^+, base peak), 232, 163; calcd for $C_{17}H_{13}NO$ 247.099 70, found 247.099 66.

Reaction of ACC with PIFA. Pyridine (40 mg, 0.5 mmol), ACC (50 mg, 0.5 mmol), and dry benzene (3.5 mL) were placed in a flame-dried flask with a side arm to which an argon inlet was attached. To this stirred mixture was added 216 mg (0.5 mmol) of PIFA (prepared by recrystallizing iodobenzene diacetate [Aldrich Chemical Co.] from trifluoroacetic acid[21]), and the mixture was heated in an oil bath maintained at 60 °C for 45 min. The barium carbonate formed from the CO_2 that evolved weighed 50 mg (50%). Benzene was evaporated, and 10 mL of dry methanol was added to the dark oil that remained. This solution was stirred for 5 h at room temperature. Methanol was removed, 1 mL of cold 3 M sodium hydroxide was added, and the solution was extracted with methylene chloride (3 × 15 mL). The methylene chloride solution was dried (Na_2SO_4) and evaporated to yield 30 mg of an oil. Besides pyridine and iodobenzene, NMR showed a pair of triplets at δ 2.6 and 2.95. No signals from cyclopropyl protons were present. The basic wash water was also evaporated, and the NMR spectrum of the residue was recorded in D_2O reference to TSP. Two multiplets at 0.87 and 1.1 were assigned to the sodium salt of unreacted ACC.

Reaction of 11b with PIFA. A mixture of 40 mg (0.5 mmol) of pyridine, 65 mg (0.5 mmol) of **11b**, and 216 mg (0.5 mol) of PIFA in 3.5 mL of dry benzene was stirred at 60 °C for 45 min. The yield of CO_2 was 65%. Benzene was evaporated, and the residue was neutralized with cold saturated sodium bicarbonate solution. This solution was extracted with ether, and the extract was dried (Na_2SO_4) and evaporated to yield 60 mg of a dark oil. The NMR spectrum of this crude product indicated the presence of 1-(*N*,*N*-dimethylamino)cyclopropanol **12b**: NMR ($CDCl_3$) δ 0.86 (m, 4 H), 2.40 (s, 6 H). [Cf. lit.[33] 0.85 (m, 4 H), 2.42 (s, 6 H).] Chromatography did not improve its purity.

Reaction of 11c with PIFA. A mixture of 281 mg (1 mmol) of **11c**, 80 mg (1 mmol) of pyridine, and 432 mg (1 mmol) of PIFA in 7 mL of benzene was heated at 60 °C for 45 min. The yield of CO_2 was 65%. Benzene was evaporated, the residue was neutralized with cold saturated bicarbonate solution, and the solution was extracted with ether. The ether was dried and evaporated to yield 350 mg of an oil. Flash chromatography (initial elution with hexane to remove iodobenzene, followed by EtOAc) was followed by preparative TLC on an analytical plate with 3:2 hexane/EtOAc to obtain 78 mg (30%) (in two repetitions of this procedure, the yields were 6% and 3%) of an oil. Its spectra are consistent with the assignment of structure **12c**: NMR ($CDCl_3$) δ 0.70 (m, 2 H), 0.80 (m, 2 H), 2.03 (br s, OH), 3.87 (s, 4 H), 7.27 (br s, 10 H); IR ($CHCl_3$) 3400, 3000, 2930, 2840, 1600, 1460 cm^{-1}; MS m/z 253, 196 ($M^+ - C_3H_5O$), 162, 146, 106, 91, 77, but the exact mass is not: calcd for $C_{17}H_{19}NO$ 253.146 56, found 252.9990. In the crude product **12c** was the major component, apart from iodobenzene and pyridine, as indicated by the NMR spectrum. The sodium salt of dibenzyl ACC was another. In one run dibenzylamine was identified as a product. Another product was isolated (7 mg), but not identified: NMR ($CDCl_3$) δ 0.50 (m), 0.67 (m), 2.6 (s), 3.63 (s), 4.2 (s), 7.2 (br s) with relative areas of 2, 2, 2, 4, 2, 10; IR ($CHCl_3$) 3500, 3060, 3020, 2940, 2860, 1725, 1650, 1500, 1460 cm^{-1}; MS m/z 225, 196, 134, 106, 91, 83, 77.

Reaction of 11d with PIFA. A mixture of **11d** (169 mg, 1 mmol), pyridine (79 mg, 1 mmol), and PIFA (432 mg, 1 mmol) in 7 mL of benzene was heated at 60 °C for 1 h. The yield of CO_2 was 60%. Then 0.5 mL of cold 6 M HCl was added, and benzene was evaporated. The aqueous residue was washed with ether, neutralized with cold, saturated sodium bicarbonate solution, and extracted with ether. The ether was dried (Na_2SO_4) and evaporated to obtain 250 mg of an oil, which was purified by flash chromatography (silica gel, EtOAc) to yield 26 mg (19%) of a solid. An analytical sample was obtained by subliming this sample at room temperature at 0.5 Torr. The compound was identical in all respects (mp, IR, proton and carbon NMR, MS, and reaction with hypochlorite) with an authentic sample of **12d** prepared according to the literature[34] method: mp 78–80 °C (the authentic sample after sublimation melted at 77–80 °C; lit.[34] mp 81–82 °C); NMR ($CDCl_3$) δ 0.80 (m, 2 H), 0.87 (m, 2 H), 1.57 (br m, 6 H), 2.13 (br s, OH), 2.78 (distorted t, 4 H); ^{13}C NMR ($CDCl_3$) δ 16.31 (two cyclopropyl methylenes), 24.57, 25.94, 48.92 (all piperidine ring carbons), 74.33 (quaternary cyclopropyl); IR (KBr) 3220, 3080, 3000, 2922, 2850, 2810, 1210 cm^{-1}; MS m/z calcd for $C_8H_{15}NO$ 141.115 28, found 141.115 30. A sample of this compound produced ethylene on treatment with 2 equiv of hypochlorite (GC, IR spectrum).

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1-(1-Piperidino)cyclopropanol-*cis*-2,3-d_2 was prepared from **11d**-d_2 (from ACC-d_2) and PIFA in the same amounts and by the same procedure as described above. The yield was approximately 20%. MS m/z calcd for $C_8D_2H_{13}NO$, 143.127 84, found 143.1307.

Registry No. **3**, 119326-93-1; **5**, 119326-90-8; **7**, 485-47-2; **8**, 119326-91-9; **9**, 119326-92-0; **11a**, 22059-21-8; **11b**, 119111-65-8; **11c**, 119111-63-6; **11c** (benzyl ester), 119326-95-3; **11d**, 119111-64-7; **11d**-d_2, 119111-71-6; **11d** (ester), 119326-96-4; **11e**, 72784-43-1; **11e**·HCl, 72784-42-0; **12b**, 37520-26-6; **12c**, 119326-94-2; **12d**, 27161-21-3; **13**, 119111-76-1; PIFA, 2712-78-9; methyl *N*-acetylmethioninate, 7451-74-3; ethylene-*1,2*-d_2, 2382-91-4; *meso*-1,2-dibromoethane-*1,2*-d_2, 86860-52-8; benzyl bromide, 100-39-0; diiodopentane, 628-77-3; 1,2,3-indantrione, 938-24-9; *N*-phenylmaleimide, 941-69-5; diethyl azodicarboxylate, 1972-28-7; cyclopropylamine, 765-30-0; phenanthrenequinone, 84-11-7.

Reaction of Cyclopropanamines with Hypochlorite

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Ethylene was formed in 65% yield when 1-(1-piperidino)cyclopropanol, **6**, was treated with hypochlorite. This observation raised the possibility that 1-aminocyclopropanecarboxylic acids (ACCs) could yield ethylene by a mechanism that involves (1) decarboxylation to a 1-aminocyclopropanol, followed by (2) a fragmentation of the carbinolamine to ethylene induced by a hypochlorite equivalent. Although this mechanism could be ruled out only for **1e**, no evidence could be found for it in the reactions of other ACCs, **1a–f**, with hypochlorite. The fact that **1b**-*cis*-2,3-d_2 yielded only ethylene-*cis*-1,2-d_2 is consistent with either the mechanism described above or a nitrenium ion mechanism. In the reaction of cyclopropanamines with neutral hypochlorite, ethylene is not the major product. From the primary and secondary amino acids **1a–c**, a 3-hydroxypropanenitrile or propanamide, **2a–c**, probably the product of a nucleophilic ring-opening step followed by decarboxylation, is formed. Similar products are formed from other cyclopropanamines: **2a** from **1g**, **2d** from **1h**, **2e** and **2f** from **1i**, and lactone **5** from **1j**.

Decarboxylation to an imine is the normal course of the reaction of amino acids with hypochlorite.[1] In the case of 1-aminocyclopropanecarboxylic acid (ACC), the product expected from such a reaction is an imine of cyclopropanone. However, it has been known for some time that when ACC is treated with basic hypochlorite and mercuric ion, *ethylene* is formed in good yield.

In this paper we report on the reactions of hypochlorite with ACC and related cyclopropanamines. Our initial aim was to investigate the possibility that some of the ethylene produced by the reaction of hypochlorite with N-substituted ACCs begins with a decarboxylation, i.e., that there is a connection between the two types of reactions mentioned in the first paragraph. In the process of that investigation, we uncovered several new reactions and recorded observations relevant to the mechanism by which ethylene is formed.

Results

The products of the reaction of hypochlorite with a series of cyclopropanamines—primary, secondary, and tertiary amines, with and without carboxyl groups (**1a–j**)—are summarized in Table I. Ethylene was not the major product in any of these reactions. From most of the primary and secondary amines, the chief isolable organic product was a 1,2-substituted ethane, **2**, a product of cyclopropane ring-opening. From ACC, for example, 3-hydroxypropanenitrile, **2a**, was the major product. In D_2O the same product, without deuterium incorporation, was isolated.

No ethylene was produced from the tertiary amines. In two cases, **1e** and **1f**, intractable mixtures were formed. Repeated attempts at reaction under a variety of conditions (including the use of *tert*-butyl hypochlorite in chloroform) gave mixtures that exhibited many spots by thin-layer chromatography and could not be separated by that technique. An indication of what might be happening with **1e** and **1f** was provided by the reaction of 1-(*N,N*-dibenzylamino)cyclopropanecarboxylic acid, **1d**, with *tert*-butyl hypochlorite in chloroform. The secondary amino acid **1c** was isolated as its hydrochloride in 63% yield along with a quantitative yield of benzaldehyde, **3**. Its formation is rationalized as a β-elimination of HCl from the *N*-chloroammonium salt followed by hydrolysis to the aldehyde with adventitious water.[2] (From the treatment of **1d** with aqueous hypochlorite, only benzaldehyde and benzylamine, in varying yields, were isolated in a state pure enough for identification.) A similar process applied to **1e** would introduce a double bond in the piperidine ring, from which point a variety of reactions would occur.

When the decarboxylation product of **1e**, 1-(1-piperidino)cyclopropanol (**6**), was treated with hypochlorite, ethylene was formed in 65% yield. *N*-Chloropiperidine and CO_2 were identified as other products. (With alkaline hydrogen peroxide and **1e**, in addition to ethylene and CO_2, two products of ring-opening reactions, described in the Experimental Section, were observed.) Labeled **6**, 1-(1-piperidino)cyclopropanol-*cis*-2,3-d_2, yielded only ethylene-*cis*-1,2-d_2, according to infrared spectroscopy.

In the case of the secondary amine **1j**, it was possible to isolate an *N*-chloroamine. The product of the treatment of **1j** with *tert*-butyl hypochlorite in chloroform was an oil, which was characterized by proton NMR. The principal change from the spectrum of **1j** was a downfield shift of the *N*-methyl protons from 2.40 ppm in the original ester **1j** to 3.15 ppm in the *N*-chloro ester, shifts consistent with

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