ca/$CHCl_3$/diethylamine (9:1) and silica/$CHCl_3$/MeOH/NH_3 (9:1:0.1)] indicated no remaining starting material and one major, non-UV positive material. The reaction mixture was allowed to cool to room temperature and poured into a stirring mixture of methylene chloride/water (200 mL:150 mL). The organic layer was separated, washed with water (3 × 100 mL), dried over anhydrous sodium sulfate, and concentrated in vacuo, affording a pale yellow solid (1.4 g). The solid was chromatographed [silica/$CHCl_3$/MeOH/NH_3 (98:2:0.03)], affording a colorless solid (770 mg), which was crystallized from $CHCl_3$/hexane to afford colorless, crystalling **8** (715 mg, mp 125–129 °C): ^1H NMR ($CDCl_3$) δ 0.9 (t), 1.10–1.40 (m), 1.50–2.00 (m), 2.30 (s), 2.40 (d), 2.50 (m), 2.55 (br s), 2.85 (dq), 3.05 (t), 3.25 (dd), 3.35 (s), 3.40 (br s), 3.45–3.70 (m), 4.05 (dd), 4.15 (br s), 4.55 (br s), 4.70 (dd), 5.00 (br s); ^{13}C NMR ($CDCl_3$) δ 176.5 (off-resonance, s), 101.7 (d), 95.7 (d), 81.7, 79.5, 79.4, 77.5, 77.3, 74.9 (s), 74.5 (s), 74.4, 72.2 (s), 70.8 (d), 68.7 (d), 68.1 (d), 65.8 (d), 64.3 (d), 49.0 (q), 44.6, 40.0 (q), 35.8, 34.6, 33.9, 31.3, 29.2, 21.4, 21.2, 20.9, 19.8, 17.9, 15.8, 14.2, 11.6, 10.8, 8.9; IR ($CHCl_3$) 2110 (N_3) cm^{-1}.

Anal. Calcd for $C_{37}H_{68}O_{12}N_4 \cdot H_2O$: C, 57.04; H, 9.06; N, 7.19. Found: C, 57.28; H, 8.93; N, 7.05.

Preparation of 9-α-Cyanoerythromycin A (10). To a DMF solution (50 mL) of **6** (5.0 g, 6.42 mmol) was added in one portion potassium cyanide (5.0 g, 76.8 mmol) and the resulting solution was allowed to stir at 90 °C for 15 h. After this period, TLC [silica/$CHCl_3$/MeOH/NH_3 (9:1:0.1)] indicated starting material and one major non-UV-positive material (ca. 1:9 ratio). The reaction was allowed to cool to room temperature and poured into a stirring mixture of methylene chloride/water (400 mL:200 mL). The organic layer was separated, washed with water (3 × 200 mL) and aqueous saturated sodium chloride (2 × 100 mL), dried over anhydrous sodium sulfate, and concentrated in vacuo, affording a tan solid (3.9 g). The solid was chromatographed [silica (impregrated with formamide)/$CHCl_3$], affording a colorless solid (3.0 g), which was crystallized from ethanol/water to afford colorless, crystalline **10** (2.85 g, mp 142–147 °C): ^1H NMR ($CDCl_3$) δ 0.90 (t), 1.10–2.00 (m), 2.30 (s), 2.40–2.60 (m), 2.65 (br s), 2.85–2.95 (m), 3.05 (t), 3.30 (s), 3.60 (m), 3.70 (d), 4.00 (dd), 4.15 (br d), 4.45 (d), 4.65 (dd), 4.95 (br d); ^{13}C NMR (MeOH-d_4) δ 177.4 (off-resonance, s), 122.6 (s), 103.3 (d), 97.6 (d), 79.0 (d), 78.7, 78.5, 78.4, 78.0, 75.7, 75.1, 73.5, 72.1, 69.3 (d), 69.1 (d), 66.6 (d), 64.8 (d), 49.6 (q), 47.9, 45.9, 40.5 (q), 36.0, 35.8, 33.6, 31.0, 28.7, 22.2, 21.6, 21.5, 21.0, 18.8, 16.8, 13.9, 11.1, 9.9; IR ($CHCl_3$) 2225 (CN) cm^{-1}.

Anal. Calcd for $C_{38}H_{68}O_{12}N_2 \cdot H_2O$: C, 59.81; H, 9.25; N, 3.67. Found: C, 59.57; H, 9.14; N, 3.75.

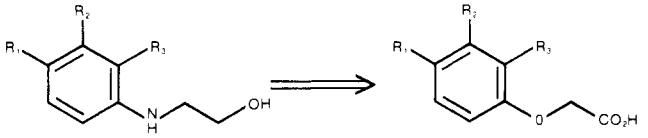
Acknowledgment. We thank R. Ware and Dr. E. Whipple for assistance in obtaining spectral data and invaluable discussions with regard to the interpretations.

Communications

Alkoxide-Accelerated Smiles Rearrangements. Synthesis of *N*-(2-Hydroxyethyl)anilines from *N*-(2-Hydroxyethyl)(aryloxy)acetamides

Summary: The first example of an alkoxide-accelerated Smiles rearrangement is reported. The rearrangement of *N*-(2-hydroxyethyl)(aryloxy)acetamides in dimethylformamide or tetrahydrofuran–18-crown-6 and potassium hydride produces useful yields of substituted *N*-(2-hydroxyethyl)anilines.

Sir: In connection with a program directed toward the preparation of new therapeutic agents, we required a synthesis of substituted *N*-(2-hydroxyethyl)anilines from the corresponding (aryloxy)acetic acids. It occurred to



us that a potential entry into this series of compounds would be the Smiles rearrangement.[1] Turner and coworkers have described a Smiles rearrangement of 2-(aryloxy)-2-methylpropanamides.[2] They found that the rearrangement gave good yields of *N*-aryl-2-hydroxy-2-methylpropanamides when conducted in sodium hydride and dimethylformamide. Electron-withdrawing substituents on the benzene ring allowed the rearrangement to proceed at room temperature. Electron-donating groups on the ring slowed the rate of rearrangement.[3] In this paper, we report the first example of an alkoxide accelerated Smiles rearrangement. When *N*-(2-hydroxyethyl)(aryloxy)acetamides undergo a Smiles rearrangement, the rate of the reaction is accelerated by a neighboring alkoxide anion.

A series of model compounds were prepared to test the feasibility of the Smiles rearrangement. The primary amide **2** was prepared by the reaction of gaseous ammonia and the ethyl ester of the known acid **1**[4] in ethanol. The secondary amides **3** and **5** were synthesized by the condensation of ethanolamine and *n*-butylamine with the acyl imidazole derived from **1** in 98% and 87% yield, respectively. Finally, amide **4** was obtained from **3** by silylation with *tert*-butyldimethylsilyl chloride and imidazole in dichloromethane at room temperature (Scheme I). When a solution of **2** in dimethylformamide was added to suspension of 2.1 equiv of sodium hydride in dimethylformamide at room temperature for 75 min, the rearranged product **6** was obtained in 48% yield. This result parallels the findings of Turner, except that the geminal dimethyl groups were not needed in our case. We then turned our attention to the rearrangement of secondary amides. When compound **3** was subjected to the same reaction conditions as the primary amide, *a rapid and exothermic reaction resulted.* Aniline **7** was obtained in 54% yield. The direct isolation of **7** can be rationalized by acyl transfer from the nitrogen to the alkoxide. The resulting hydroxy acetate was hydrolyzed to the alcohol during aqueous workup. This result was surprising in light of literature precedent[2] and prompted us to explore the reaction further.

The rate of the rearrangement of **3** to **7** was dependent on the counterion and solvent. The relative rate of the

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(3) Bayles, R.; Johnson, M. C.; Maisey, R. F.; Turner, R. W. *Synthesis* **1977**, 33.
(4) Jones, P. H.; Bariana, D. S.; Fung, A. K. L.; Martin, Y. C.; Kyncl, J.; Lall, A. U.S. Patent No. 4 166 819, 1979.

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Scheme I

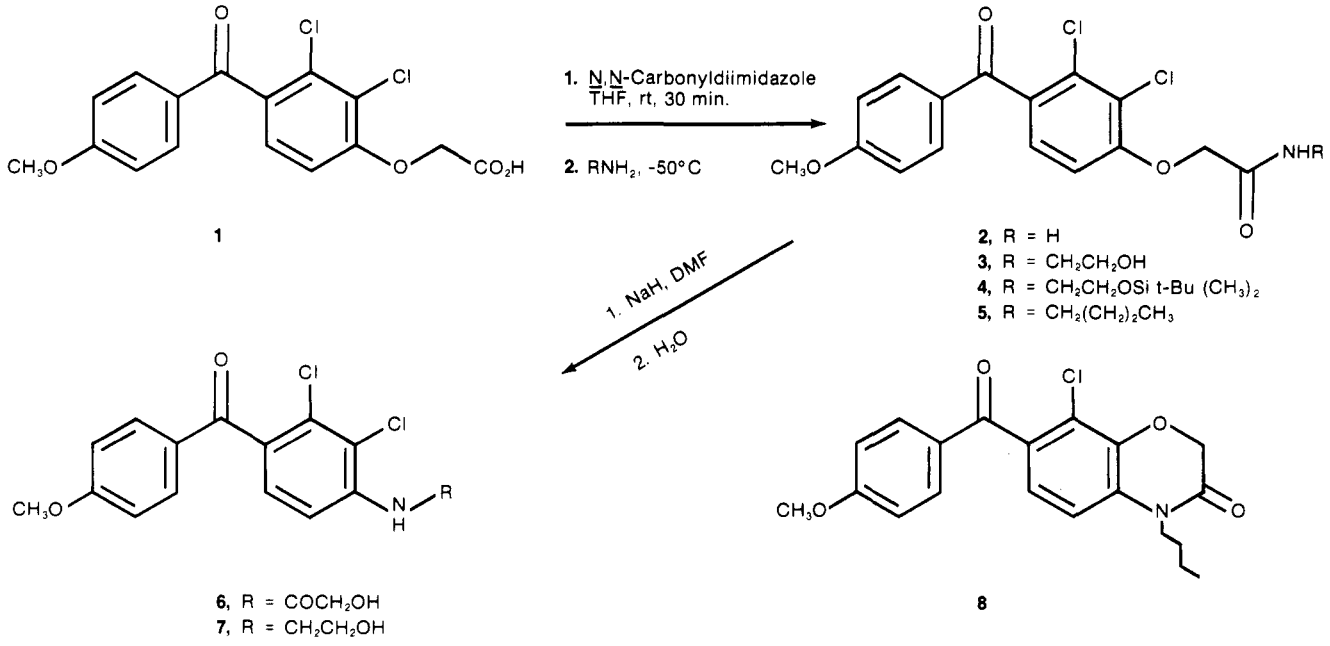
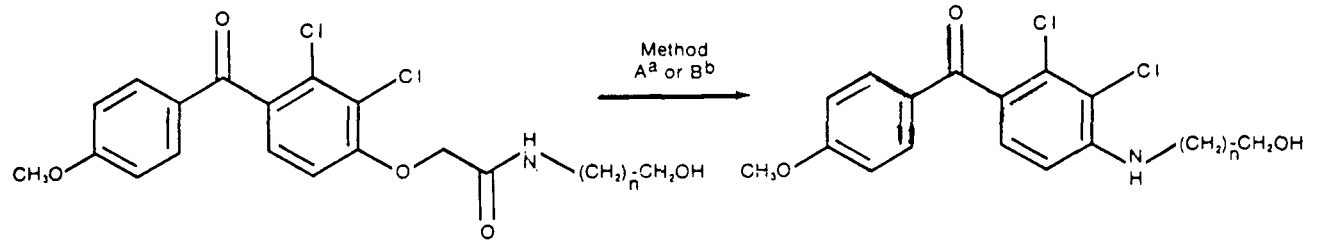


Table I. Smiles Rearrangement of *N*-(Hydroxyalkyl)-4-[(4-methoxybenzoyl)-2,3-dichlorophenoxy]acetamides



no.	*n*	method	yield,[c] %	mp, °C	time, min	temp, °C
1	1	A	66	113-114	10	−10
	1	B	71		30	0
2	2	A	59	111-112	15	0
	2	B	68		20	0
3	3	B	25	95-96	35	25
4	4	A			105	25

[a] Potassium hydride and dimethylformamide. [b] Potassium hydride and tetrahydrofuran-2.1 equiv of 18-crown-6. [c] The yields are isolated, and satisfactory spectral data and elemental analyses were obtained.

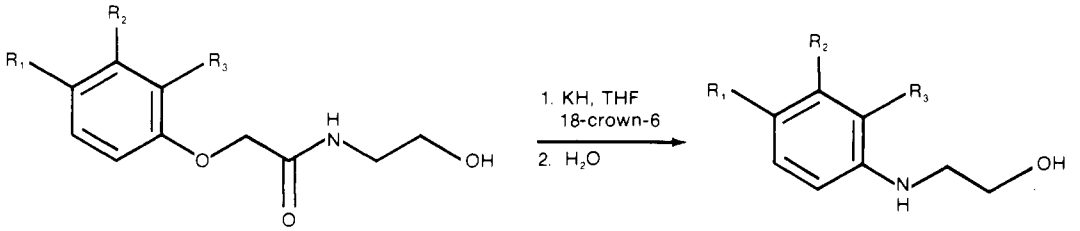
reaction of 3 with sodium hydride at room temperature, as judged by thin-layer chromatography, was ordered as follows: toluene < dichloromethane < tetrahydrofuran < dimethylformamide ≃ tetrahydrofuran–18-crown-6. When the rearrangement was performed in tetrahydrofuran at room temperature, the rate of the rearrangement was faster with potassium hydride than with sodium hydride. Lithium hydride produced no rearranged product. There was no appreciable rate difference when the soluble base potassium hexamethyldisilazide was used in place of potassium hydride. To test the need of a remote alkoxide anion for the rearrangement, amide 5 was allowed to react with 2.1 equiv of potassium hydride in dimethylformamide at ambient temperature. After 1 h the starting material had disappeared and the bicyclic amide 8 was isolated in 24% yield after flash chromatography to separate unidentified polar byproducts. Reaction of amide 3 with 2.1 equiv of potassium hydride in dimethylformamide at −10 °C for 10 min and subsequent addition of water gave rise to aniline 7 in 66% yield. Treatment of amide 4 under identical conditions gave only unreacted amide 4. Repeating the reaction of amide 4 with potassium hydride in dimethylformamide at −10 to 0 °C and then adding 1 equiv of tetrabutylammonium flouride in tetrahydrofuran gave the aniline 7 in 69% yield!

We next studied the effect of distance from the alkoxide anion to the amide anion. These results are summarized in Table I and show that the rearrangement of *N*-2-hydroxyethyl or *N*-3-hydroxypropyl amides (entry 1 and 2) proceeded in good yields. When the chain was extended to four (entry 3) or five carbon atoms (entry 4), the rate and the yield of hydroxy anilines dropped substantially. In the last example, no identifiable products were obtained.

Finally, the scope of the *N*-(2-hydroxyethyl)aniline synthesis was investigated by the reaction of a series of substituted *N*-(2-hydroxyethyl)(aryloxy)acetamides[5] with potassium hydride in tetrahydrofuran–18-crown-6 (Table II). As expected, electron-withdrawing substituents on the benzene ring facilitated the rate of the rearrangement and good yields of products were obtained (entries 1–4).

(5) The *N*-(2-hydroxyethyl)(aryloxy)acetamides were prepared by the reaction of 1-substituted (aryloxy)acetic acids with 1.2 equiv of *N,N*-carbonyldiimidazole at room temperature in tetrahydrofuran for 30 min and subsequent addition of 1.2 equiv of ethanolamine at −50 °C. Purification by flash chromatography afforded 63% to 83% yields of the secondary amides.

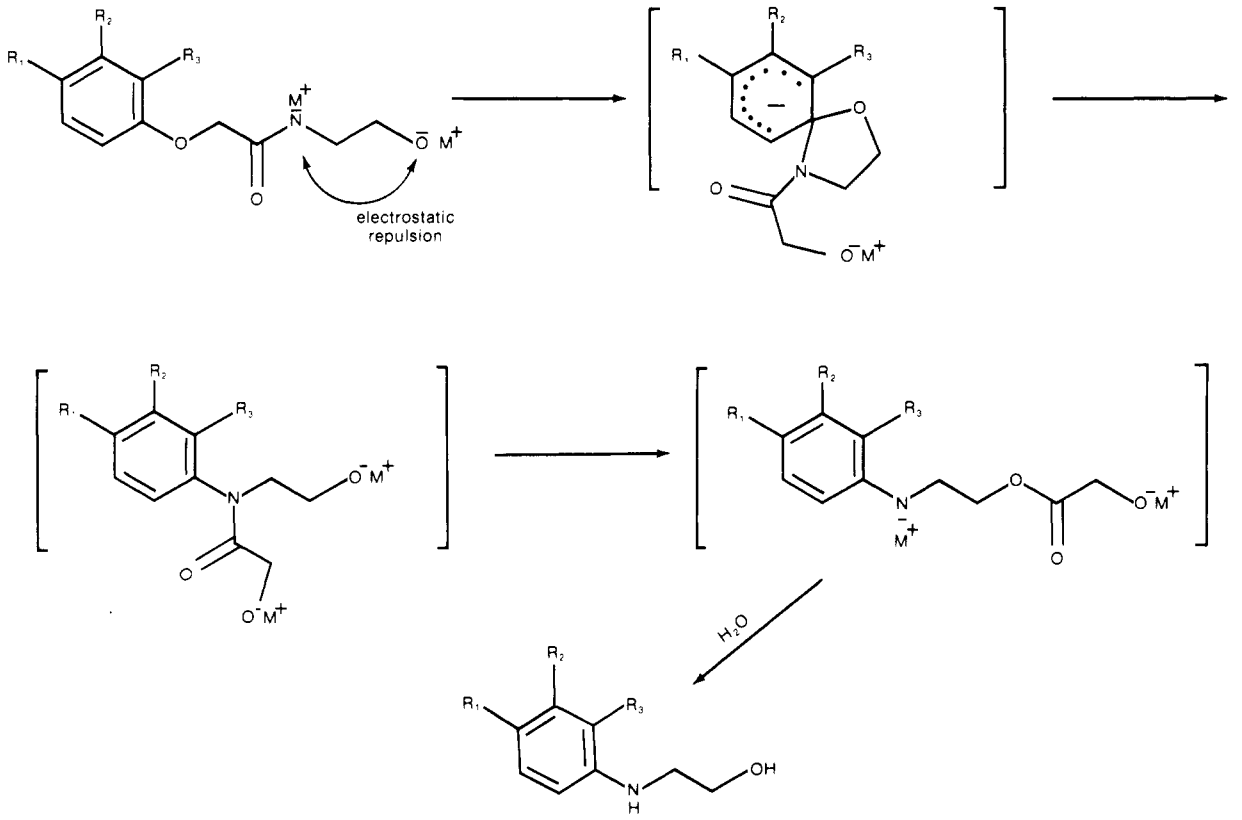
Table II. Smiles Rearrangement of Substituted *N*-(2-Hydroxyethyl)(aryloxy)acetamides



no.	R_1	R_2	R_3	yield,[a] %	mp, °C	time, h	temp, °C
1	NO_2	H	H	63	109-111	1	−40 to −30
2	H	Cl	Cl	63	76-77	1	−20 to 0
3	Cl	H	H	50	79-80	18.5	20
4	H	H	Br	39	oil	0.1	20
5	H	H	H	21	oil	20	45 to 50
6	CH_3	H	H	28	oil	40	50 to 55
7	CH_3O	H	H	35	48-49	19	90

[a] The yields are isolated, and satisfactory spectral data and elemental analyses were obtained.

Scheme II



Compounds with electron-donating groups (entries 6 and 7) and the parent compound (entry 5) gave lower yields of hydroxy anilines and slower rates of rearrangement.

In conclusion, it has been found that *N*-(2-hydroxyethyl)(aryloxy)acetamides undergo a rapid and exothermic rearrangement when exposed to potassium hydride in dissociating media. The rearrangement of these hydroxy amides is much faster than simple primary amides or *n*-alkyl secondary amides. This rate enhancement was produced by two factors. First, the rate increased as anions became more ionic due to solvent and counterion effects. Second, the rate increased even more when the alkoxide was closer to the amide anion. These two factors demonstrated that the coulombic repulsion between the alkoxide and amide anions must be the driving force for the rearrangement. The dianion relieved the electrostatic interaction by delocalizing the amide anion into the benzene ring. The overall effect produced a higher ground-state free energy of dianion starting material relative to the increased transition-state dianion free energy and thereby lowered the energy of activation (Scheme II). Thus, we have unveiled a useful variant of the Smiles rearrangement that allows ready access to *N*-(2-hydroxyethyl)anilines from the corresponding (aryloxy)acetic acids. Furthermore, the concept of accelerating anionic rearrangements by neighboring alkoxide anions is unique and should find utility in other anionic rearrangements. We are currently applying this process to the synthesis of biologically active compounds.

Acknowledgment. We thank Professor Peter Beak at the University of Illinois Champaign-Urbana for valuable discussions during the course of this work.

Registry No. 1, 62966-99-8; 1 ethyl ester, 87762-02-5; 1 imidazole derivative, 87762-03-6; 2, 87762-04-7; 3, 87762-05-8; 4, 87762-06-9; 5, 87762-07-0; 6, 87762-08-1; 7, 87762-09-2; 7 hydroxy

acetate, 87762-10-5; 8, 87762-11-6; *N*-(3-hydroxypropyl)-4-[(4-methoxybenzoyl)-2,3-dichlorophenoxy]acetamide, 87762-12-7; *N*-(4-hydroxybutyl)-4-[(4-methoxybenzoyl)-2,3-dichlorophenoxy]acetamide, 87762-13-8; *N*-(5-hydroxylpentyl)-4-[(4-methoxybenzoyl)-2,3-dichlorophenoxy]acetamide, 87762-14-9; *N*-(2-hydroxyethyl)-2-(4-nitrophenoxy)acetamide, 52547-52-1; 2-(2,3-dichlorophenoxy)-*N*-(2-hydroxyethyl)acetamide, 87762-15-0; 2-(4-chlorophenoxy)-*N*-(2-hydroxyethyl)acetamide, 7462-17-1; 2-(2-bromophenoxy)-*N*-(2-hydroxyethyl)acetamide, 87762-16-1; *N*-(2-hydroxyethyl)-2-phenoxyacetamide, 6326-87-0; *N*-(2-hydroxyethyl)-2-(4-methylphenoxy)acetamide, 66889-71-2; *N*-(2-hydroxyethyl)-2-(4-methoxyphenoxy)acetamide, 51816-48-9; 3-[[4-(4-methoxybenzoyl)-2,3-dichlorophenyl]amino]propanol, 87762-17-2; 4-[[4-(methoxybenzoyl)-2,3-dichlorophenyl]amino]-butanol, 87762-18-3; 2-[(4-nitrophenyl)amino]ethanol, 1965-54-4; 2-[(2,3-dichlorophenyl)amino]ethanol, 87762-19-4; 2-[(4-chlorophenyl)amino]ethanol, 2933-81-5; 2-[(2-bromophenyl)amino]-ethanol, 87762-20-7; 2-(phenylamino)ethanol, 122-98-5; 2-[(4-methylphenyl)amino]ethanol, 2933-74-6; 2-[(4-methoxyphenyl)-amino]ethanol, 2933-77-9; (4-nitrophenoxy)acetic acid, 1798-11-4; (2,3-dichlorophenoxy)acetic acid, 2976-74-1; (4-chlorophenoxy)-acetic acid, 122-88-3; (2-bromophenoxy)acetic acid, 1879-56-7; phenoxyacetic acid, 122-59-8; (4-methylphenoxy)acetic acid, 940-64-7; (4-methoxyphenoxy)acetic acid, 1877-75-4; ethanolamine, 141-43-5; *n*-butylamine, 109-73-9; sodium hydride, 7646-69-7; toluene, 108-88-3; dichloromethane, 75-09-2; tetrahydrofuran, 109-99-9; dimethylforamide, 68-12-2; 18-crown-6, 17455-13-9; potassium hydride, 7693-26-7.

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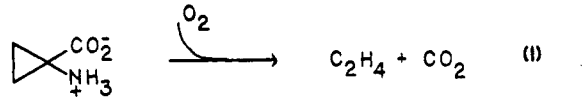
Received July 11, 1983

Ethylene Biosynthesis. 1. A Model for Two Reactive Intermediates

Summary: Two reactive intermediates, 1-carboxycyclopropylnitrene and 1-carboxycyclopropylnitrenium, have been demonstrated as competent intermediates for the biosynthetic conversion of 1-aminocyclopropanecarboxylic acid to ethylene.

Sir: The 1979 report of Adams and Yang[1] that 1-aminocyclopropanecarboxylic acid (ACC, 1) is the immediate biosynthetic precursor to the plant hormone ethylene solved a long-standing problem in plant physiology[2] (eq 1). It has generated many new questions about the



(1)

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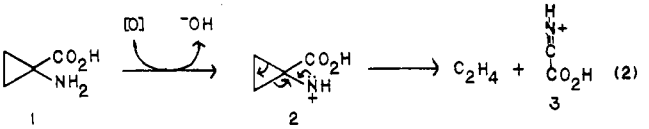
chemistry involved, however, few of which have thus far been answered. Research in this area is hampered by the fact that the enzyme responsible for ethylene biosynthesis (EFE, ethylene-forming enzyme) is associated with the cell membrane and does not survive breakage of the cell wall.[3] It is well established through in vivo studies that the EFE requires oxygen and is inhibited by free-radical scavengers,[1,3] metal chelators,[4] reducing agents,[3] and white light.[5]

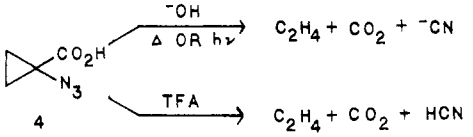
Several proposals have been made for the chemistry behind ethylene biosynthesis. Yang[1] proposed the nucleophilic opening of the cyclopropane ring at the fully substituted carbon by hydrogen peroxide. Lurssen[6] postulated the NADH-mediated reduction of a CoA-ester-ACC-pyridoxal Schiff base followed by a fragmentation; this hypothesis remains unsupported by evidence for any of these cofactors in the EFE. Baldwin[7] proposed covalent bonding between ACC and the EFE, oxidative decarboxylation to a cyclopropanone imine, and extrusion of ethylene. This yields an isonitrile, which is hydrolyzed to formate. Finally, Yang made another proposal[8] involving oxidation of ACC by hydrogen peroxide to yield a nitrenium ion (2). He then proposed fragmentation of this ion to ethylene and cyanoformate conjugate acid 3 (eq 2).



(2)

In order to evaluate the merits of the last mechanistic proposal, we have examined the nitrenium ion proposed by Yang as well as nitrene intermediates for ethylene biosynthesis. The latter were investigated because we were uncertain of the state of protonation of 2 at pH 6, the pH maximum for ethylene biosynthesis.

The decomposition of 1-azidocyclopropanecarboxylic acid[9] (4, AzCC) was conducted thermally, photochemically,



and under acid catalysis. The thermal (125 °C, aqueous KOH) and photochemical (9:1 EtOH/H_2O, 450-W Hanovia lamp, Vycor filter, sensitized and unsensitized) reactions in a 10-mM basic solution, representing the nitrene intermediate, yield ethylene, carbon dioxide, and cyanide ion. The chemical yield of each component under a given set of conditions is the same, 25% in the former and 75% in the latter. This was determined by gas chromatography[10]

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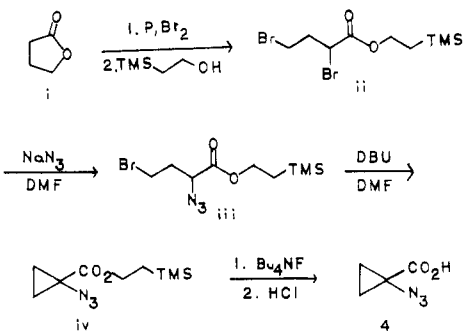
(9) Prepared in 47% overall yield by a modification of the procedure found in: DuBois, G. E.; Crosby, G. A.; McGarraugh, G. V.; Ng, S. Y.-W.; Stephenson, R. A.; Wang, P. C.; Wingard, R. E. *J. Org. Chem.* **1982**, *47*,



1319.
(10) Ethylene and CO_2 were identified and quantified by using an 80% Porapak N/20% Porapak Q 6 ft × 1/8 in. column, operated at 35 °C and using a thermal conductivity detector.

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