(22°). After evaporation of the solvent *in vacuo*, the residue was treated with benzene. The gray solid, which is insoluble to benzene, was found to be sufficiently pure DISN (68 mg): mp 163–165° dec (lit.[4] mp 165–166°).

Materials soluble to benzene were subjected to silica gel column chromatography. *p*-Chlorophenyl phenyl sulfide (0.60 g, 68% yield), which was contaminated by a small amount of *p,p'*-dichlorodiphenyl sulfide, and ClDISN (50 mg, 18% yield) were isolated from fractions eluted with benzene–*n*-hexane (3:2). Diphenyl sulfoxide (0.25 g, 30% yield) was obtained from fractions eluted with benzene–ethyl acetate (3:2). Furthermore, elution with benzene–ethyl acetate (1:1) gave additional 13 mg of DISN (38% total yield).

Reaction of Cl_2DISN with *N*-Benzyl-1,4-dihydronicotinamide. A solution of Cl_2DISN (0.35 g) in THF (10 ml) was cooled to −20° by a Dry Ice–CCl_4 bath. To this solution was added a solution of BNAH (0.86 g) in THF (30 ml). The solution was stirred for 30 min at −20° and crystals of BNA^+Cl^- (0.93 g, 94% yield) were filtered off. The solvent was evaporated *in vacuo* from the filtrate and the residue was purified by a column of silica gel. Elution with benzene–ethyl acetate (4:1) gave 94 mg of DISN (44% yield).

Reaction of Cl_2DISN with Sodium Borohydride. A mixture of Cl_2DISN (0.35 g) and $NaBH_4$ (0.16 g) in THF (30 ml) was stirred for 15 hr at room temperature. After usual work-up, 81% of Cl_2DISN used was recovered and no indication was obtained for the formation of DISN.

Reaction of Cl_2DISN with Olefins. A mixture of Cl_2DISN (0.35 g), Na_2CO_3 (0.42 g), and styrene (1.0 g) in benzene (10 ml) was kept at room temperature in a dark for 5 days. The residue remained after evaporation of the solvent *in vacuo* was subjected to column chromatography on silica gel, yielding 0.10 g of Cl_2DISN and pale yellow crystals, which was sublimed at 110° (1 Torr), giving white needles of 2,3-dicyano-5-phenylpyrazine (0.18 g, 63% yield): mp 164–165°; ir (Kbr) 3050, 2240, 1560, 1540, 1520, 1460, 1430, 1120, 794, 770, 693, and 510 cm^{-1}. *Anal.* Calcd for $C_{12}H_6N_4$: C, 69.89; H, 2.93; N, 27.17. Found: C, 69.84; H, 2.66; N, 27.00.

Similar reactions with β-methylstyrene and 2,3-dihydropyran gave **2b** and **2c** in 35 and 26% yields, respectively, after similar work-up described above.

Registry No.—**2a,** 52109-66-7; **2b,** 52109-67-8; **2c,** 52109-68-9; DAMN, 1187-42-4; DISN, 28321-79-1; Cl_2DISN, 33420-44-9; $(EtS)_2$DISN, 52109-69-0; $(MeS)_2$DISN, 52109-70-3; *tert*-butyl hypochlorite, 5923-22-8; ethanethiol, 75-08-1; 2-propanethiol, 75-33-2; benzenemethanethiol, 100-53-8; benzenethiol, 108-98-5; *p*-methoxybenzenethiol, 696-63-9; *p*-chlorobenzenethiol, 106-54-7; dimethyl sulfoxide, 67-68-5; diphenyl sulfide, 139-66-2; *N*-benzyl-1,4-dihydronicotinamide, 952-92-1; sodium borohydride, 16940-66-2; styrene, 100-42-5; β-methylstyrene, 637-50-3; 2,3-dihydropyran, 110-87-2.

Supplementary Material Available. Full ir, mass spectral, and elemental analyses data for compounds **2b, 2c,** and those listed in Table II as well as melting points of **2b** and **2c** will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-3373.

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Synthesis of α-Cyanoglycine *N*-Carboxyanhydride and α-Cyanoglycine[1]

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Received July 25, 1974

α-Cyanoglycine *N*-carboxyanhydride (**4**), a new, monomeric precursor of poly-α-cyanoglycine (**2**) required for chemical evolution studies, was synthesized from ethyl α-cyanoglycine (**6a**) by the following sequence of reactions, rather than by standard procedures from the highly labile amino acid, α-cyanoglycine (**5**). Compound **6a** was converted to its *N*-benzyloxycarbonyl (CBZ) derivative by treatment with benzyl chloroformate in refluxing ethyl acetate and then was selectively hydrolyzed with aqueous KOH to *N*-CBZ-α-cyanoglycine (**7b**). A slight change in the reaction conditions to KOH in 50% acetone–water brought about hydrolysis of both the ester and the nitrile groups and yielded *N*-CBZ-aminomalonic acid. Compound **7a** reacted with trifluoroacetic anhydride to produce α-cyanoglycine *N*-carboxyanhydride (**4**), which with a large excess of water gave α-cyanoglycine (**5**).

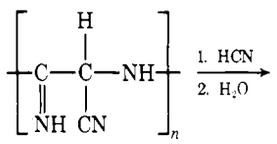
During the past 2 decades, extensive research on the origin of life[3] has led to the widespread belief that the prebiological formation of primitive proteins occurred in two stages, α-amino acid synthesis initiated by the action of high energy from natural sources on the components of a reducing atmosphere followed by polycondensation of the accumulated monomers in the oceans or on land. A critical examination of the evidence for the second step suggests, however, that the inherent thermodynamic barrier to spontaneous polymerization of α-amino acids has been overcome only when specific environments have been invoked (anhydrous locales, high-temperature milieu, or acidic bodies of water, for example) that are not characteristic of a young, developing planet. This objection does not apply to an alternative route for protein abiogenesis that has been proposed[4] for the direct synthesis of heteropolypeptides from hydrogen cyanide and water without the intervening formation of α-amino acids.

Table I
Nmr Spectra of *N*-CBZ-α-cyanoglycine Derivatives[a,b]

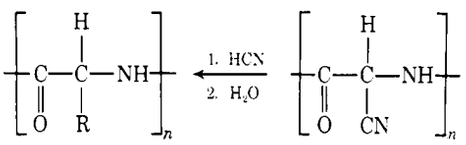
Positions of hydrogens	Compounds 7a	7b	7c	8
COOH		13.53 s		
>NH	8.65 bd[c] (J = 8.0 Hz)	8.65 bd (J = 8.0 Hz)	*e*	8.03 bd (J = 8.0 Hz)
C_6H_5	7.38 s	7.37 s	7.40 s	7.37 s
NH_2				6.62 bs[d]
>CH	5.72 d (J = 8.0 Hz)	5.62 d (J = 8.0 Hz)	4.70 d (J = 6.5 Hz)	5.62 d (J = 8.0 Hz)
CH_2	5.15 s	5.20 s	5.15 s	5.20 s
CH_2CH_3	4.23 qt 1.12 tr			

[a] In dimethyl-d_6 sulfoxide. [b] All chemical shifts in ppm from tetramethylsilane. [c] Broadened doublet. [d] Broadened singlet. [e] No peak observed.

According to this hypothesis a low-energy pathway exists for the spontaneous polymerization of hydrogen cyanide to polyaminomalononitrile (**1**). Successive reactions of hydrogen cyanide with the activated nitrile groups of **1** then yield heteropolyamidines that become converted by water to heteropolypeptides (**2**) possessing side chains of today's proteins. To demonstrate the feasibility of the postulated

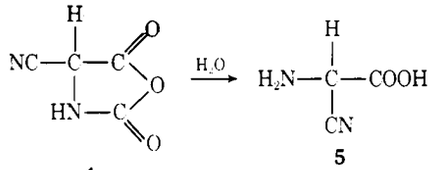


1



2 3

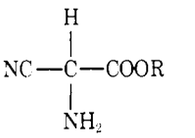
conversion of homopolymer **1** to heteropolymer **2** one would like to synthesize polymer **1** unambiguously and then show that it can be modified to polymer **2** by treatment with hydrogen cyanide and water. On the other hand, using the tools of amine acid chemistry, one can synthesize poly-α-cyanoglycine (**3**),[4c,e] a polyamide analog of polyamidine **1** that should be readily obtainable in a pure state by controlled polymerization of α-cyanoglycine *N*-carboxyanhydride (**4**). We report here the first synthesis of **4** and its hydrolysis to α-cyanoglycine (**5**), a highly reactive amino acid hitherto[5] obtained only by enzymatic deacylation of acetoamidocyanoacetic acid. Future papers will report the second part of this work (polymerization of *N*-carboxyanhydride **4** to polyamide **3** and subsequent reaction of



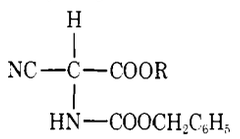
4 5

compound **3** with hydrogen cyanide and water to yield heteropolypeptides).[4c,e]

A key intermediate in the synthesis of α-cyanoglycine (**5**) was ethyl aminocyanoacetate (**6a**), readily prepared by nitrosation[6] of ethyl cyanoacetate followed by reduction with mercury amalgam.[7] Methyl aminocyanoacetate (**6b**) was prepared by the same route from methyl cyanoacetate. Both cyanoacetates **6a** and **6b** form stable salts with *p*-toluenesulfonic acid[7b] but not with hydrogen chloride.



6a, R = C_2H_5
b, R = CH_3



7a, R = CH_2CH_3
b, R = H
c, R = K

All attempts to synthesize α-cyanoglycine in one step by hydrolysis of ethyl ester **6a** or methyl ester **6b** were unsuccessful; only black, intractable polymer was obtained. This result prompted the development of a synthesis of α-cyanoglycine-NCA (**4**) and of α-cyanoglycine (**5**) by the following series of reactions: (a) conversion of compound **6a** to its *N*-benzyloxycarbonyl (*N*-CBZ) derivative **7a**, (b) hydrolysis of ester **7a** to acid **7b**, (c) conversion of acid **7b** to *N*-carboxyanhydride **4**, and (d) conversion of anhydride **4** to α-cyanoglycine (**5**). The lability of compounds **6a**, **7a**, and **7b** to base and to nucleophilic reagents (*e.g.*, chloride ion) brought about the development of new methods for carrying out these synthetic steps.

Ethyl *N*-CBZ-α-Cyanoglycine (7a). Use of standard Schotten-Bauman procedures[8] (base + acid chloride + amino acid) to acylate ethyl ester **6a** with benzyl chloroformate gave very poor yields (less than 5%) of *N*-CBZ derivative **7a**. However, a direct acylation of **6a** with benzyl chloroformate in refluxing ethyl acetate produced the desired compound in better than 80% yield.[9]

***N*-CBZ-α-Cyanoglycine (7b).** The selectivity of the hydrolysis of ethyl ester **7a** was controlled by the solvent. With aqueous 0.25 *N* KOH **7a** was converted to **7b** in better than 90% yield. With the same concentration of KOH in 50% (v/v) acetone–water the ester and the nitrile functions were both hydrolyzed and *N*-CBZ-aminomalonamic acid (**8**) was obtained in 85% yield. Malonamic acid **8**, on the other hand, was converted back to nitrile **7b** by treatment with dicyclohexylcarbodiimide in dimethylformamide.[10] The nmr spectra of compounds **7a**, **7b**, **7c**, and **8** are presented in Table I.

The selectivity of the hydrolysis reaction appears to be related to the solubility of ester **7a** in the two hydrolysis solvent systems. Ethyl ester **7a** is soluble in acetone–water and insoluble in water. Addition of KOH to the water causes **7a** to dissolve, and nmr analysis of the solution (0.25 *N*

KOD in D_2O) shows that the methine and imine protons on ester **7a** have exchanged with deuterium. Thus ionization of **7a**, concomitant with its dissolution in water, appears to account for the selectivity of the reaction.

α-Cyanoglycine-NCA. The conversion of *N*-CBZ-α-amino acids to α-amino acid *N*-carboxyanhydrides (Leuchs' anhydrides, NCAs) is a well-worked out process.[11] The general method is to convert the CBZ-α-amino acid to its acid chloride or bromide, which then cyclizes either spontaneously or with gentle heating. However, all attempts to convert compound **7b** to α-cyanoglycine-NCA by the acid chloride route were unsuccessful, since *N*-CBZ acid **7b** formed an acid chloride that, while stable at room temperature, slowly polymerized at 45° in anhydrous methyl acetate. One possible reason for this result is that chloride ion was reacting with α-cyanoglycine-NCA to produce polymer. At any rate, this concept suggested the use of trifluoroacetic anhydride (TFAA) as the condensing reagent, since the literature provides evidence that mixed anhydrides formed from TFAA are more reactive than corresponding acid chlorides[12] and that the trifluoroacetate leaving group is a poorer nucleophile than chloride ion.[13]

Addition of trifluoroacetic anhydride to a suspension of *N*-CBZ amino acid **7b** in benzene produced the desired result. The amino acid immediately went into solution, and 30 sec later α-cyanoglycine-NCA appeared in better than 90% yield as a white precipitate with spectral (nmr, ir) and elemental analysis consistent with the structure of α-cyanoglycine-NCA. Benzyl trifluoroacetate, the by-product of the reaction, was isolated and identified by comparison of its glpc retention time and ir spectrum with those of an authentic sample.

Reaction of α-cyanoglycine-NCA with methanolic HCl followed by reaction with trifluoroacetic anhydride produced a volatile *N*-trifluoroacetyl methyl ester derivative (**9**) of α-cyanoglycine. This compound was identical (same retention time on two different glpc columns) with that obtained by trifluoroacetylation of the *p*-toluenesulfonate salt of methyl ester **6b**.

α-Cyanoglycine (5). Reaction of α-cyanoglycine-NCA with a large excess of water followed by lyophilization of the resulting clear solution gave a white powder, with elemental analysis and ir spectrum consistent with structure **5**. A chemical proof of structure was provided by conversion of **5** to its *N*-trifluoroacetyl methyl ester derivative by treatment first with trifluoroacetic anhydride to form a mixed anhydride followed by addition of methanol to form the methyl ester. This derivative had the same retention time on two different glpc columns as the compound obtained by trifluoroacetylation of the *p*-toluenesulfonate salt of methyl ester **6b**.

Experimental Section

General. Melting points are uncorrected; nmr spectra were obtained with a Varian A60; infrared spectra were obtained with a Beckman IR4; microanalyses were carried out by Galbraith Laboratories, Knoxville, Tenn. A Varian Aerograph 2100 dual-column gas chromatograph equipped with flame ionization detectors was used in the single column made for gas chromatographic analyses. The signal from the chromatograph was fed to an Infotronics CRS-104 digital integrator and then to a Varian Aerograph Model 30 recorder. The chromatograph was fitted with two 1.9 m × 2 mm i.d. glass U columns, one packed with OV 17 (1%) on 80–100 mesh HP Chromosorb G (OV 17 column) and the other with ethylene glycol adipate on 80–100 mesh acid-washed, heat-treated Chromosorb W (EGA column). EGA packing was purchased from Regis Chemical Co. (Code No. 201033). General gas chromatographic conditions were as follows: nitrogen carrier gas flow, 20 ml/min; H_2 flow, 30 ml/min; air flow, 350 ml/min; detector temperature, 230°; injector temperature, 170°. Derivatization reactions were carried out in 16 × 75 mm screw-capped test tubes fitted with Teflon-lined caps (Corning 9826, A. H. Thomas Co.). A Lab-Line Temp-Blok (A. H. Thomas Co.), which was heated with a Thermolyne, Model HP-A1G15B hot plate (Fisher Scientific Co.), was used to heat the derivatization tubes.

Ethyl (6a) and Methyl Aminocyanoacetate (6b). Methyl and ethyl cyanoacetate were converted to oximino derivatives by the method of Parker[6] and then reduced to amines by the method of Ferris and Orgel.[7a,b] Overall yields for each compound ranged from 48 to 55%. Both amines rapidly polymerized at room temperature but were stable at −70°.

The reduction of ethyloximinocyanoacetate by aluminum amalgam was conveniently followed by gas chromatography. The reaction mixture (3 ml) was filtered through a sintered glass filter. Trifluoroacetic anhydride, 0.5 ml, and 1.0 ml of the filtrate were placed into a derivatization tube and heated to 65° for 5 min. This solution (1 μl) was injected onto the OV 17 column: column oven temperature, 50 to 200° at 40/min; retention times ethyloximinocyanoacetate, 6.9 min; ethyl aminocyanoacetate (**6a**), 12.5 min.

Methyl aminocyanoacetate–*p*-toluenesulfonate salt was prepared by the method of Ferris and Orgel[7a,b] in 50% yield: mp 174–176° (dec); ir (KBr) 2875, 2240 (weak), 1775, and 1195 cm^{-1}; nmr (DMSO-d_6) δ 8.77 (broad singlet, 3, NH_3^+), 7.28 (quartet, 4, CH_3–C_6H_4–SO_2^-), 5.96 (s, 1, CH–CN), 3.88 (s, 3, $COOCH_3$), 2.32 (s, 3, CH_3–CH_6H_4–).

Anal. Calcd for $C_{11}H_{14}N_2O_5S$: C, 46.15; H, 4.93; N, 9.78; O, 29.94. Found: C, 45.97; H, 5.00; N, 9.64; O, 28.07.

Ethyl *N*-Benzyloxycarbonyl-α-cyanoglycine (7a). Ethyl aminocyanoacetate (**6a**, 13.6 g, 0.106 mol) was added to 100 ml of ethyl acetate which contained 21.1 g (0.124 mol) of benzyl chloroformate. The reaction mixture was stirred for 10 min at room temperature and then refluxed for 2.5 hr. Norit-A (1 g) was added to the reaction mixture, which was then filtered, and the solvent was stripped off *in vacuo*. The resulting yellow residue, washed with 100 ml of ether and recrystallized from benzene, gave 23.5 g (85% yield) of **7a**, mp 113–114.5°.

***N*-Benzyloxycarbonyl-α-cyanoglycine (7b).** Ethyl *N*-benzyloxycarbonyl-α-cyanoglycine (**7a**, 13 g, 50 mmol) was stirred with 210 ml of 0.25 *N* KOH for 2.5 hr. The resulting yellow solution was acidified with 116 ml of 2 *N* H_2SO_4 and then extracted with four 100-ml portions of ether. The ether extracts were dried over $MgSO_4$ and then concentrated under reduced pressure to an oil, which was diluted with 50 ml of methylene chloride and stripped to dryness again. The resulting white residue was recrystallized from methylene chloride to yield 10.7 g (45.7 mmol, 91% yield) of **7b**. An analytical sample was prepared by a further recrystallization from methylene chloride, mp 103–105° (dec).

Anal. Calcd for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.30; N, 11.95. Found: C, 56.44; H, 4.25; N, 11.76.

***N*-Benzyloxycarbonylaminomalonamic Acid (8).** Ethyl *N*-CBZ-α-cyanoglycine (**7b**, 5.2 g, 20 mmol) was dissolved in 50 ml of acetone and added to 50 ml of 0.50 *M* KOH. The solution was stirred for 3 hr at room temperature, and the acetone was stripped off *in vacuo*. The aqueous portion of the solution was extracted with two 20-ml portions of methylene chloride, acidified to pH 1.0 with sulfuric acid, and extracted with five 20-ml portions of ether. The ether extract was dried over magnesium sulfate and the ether was then stripped off to give a yellow residue, which was washed with pentane and finally methylene chloride to yield 4.3 g (85%) of a white powder, mp 85–87° (dec). The nmr spectrum is presented in Table I.

Anal. Calcd for $C_{11}H_{12}N_2O_5$: C, 52.38; H, 4.80; N, 11.1. Found: C, 52.10; H, 4.86; N, 10.90.

α-Cyanoglycine *N*-Carboxyanhydride (4). All procedures were carried out in an N_2-filled drybox. Benzene and pentane were dried over molecular sieves (Linde 4A). All glassware was heated to 130° for 1 hr prior to use. To a rapidly stirred suspension of *N*-benzyloxycarbonyl-α-cyanoglycine (**7b**, 7.17 g, 30.7 mmol) in 250 ml of benzene was added 7.7 g (37 mmol) of trifluoroacetic anhydride. The resulting mixture was stirred at room temperature (21°) for 30 min, during which time **7b** went into solution and a white precipitate appeared. The reaction mixture was diluted with 200 ml of pentane and filtered through a fritted glass filter; the precipitate was washed with 25 ml of chloroform and 25 ml of pentane: yield, 3.41 g (27.5 mmol, 90%); mp 110–114° (dec); ir (KBr) 2340 cm^{-1} (–C≡N), 1870 and 1790 cm^{-1} (–C(=O)–O–C(=O)–); nmr (acetone-d_6) δ 8.9 (broad singlet, 1, HN<), 6.05 (d, 1, J = 1.75 Hz, HC–CN).

Anal. Calcd for $C_4H_2N_2O_3$: C, 38.10; H, 1.60; N, 22.22; O, 38.07. Found: C, 38.32; H, 1.71; N, 22.38; O, 38.85.

α-Cyanoglycine (5). α-Cyanoglycine *N*-carboxyanhydride (**4**,

1.24 g, 10 mmol) was dissolved into 50 ml of dioxane which had been distilled from lithium aluminum hydride. This solution was placed into an addition funnel and added dropwise to 180 ml of vigorously stirred water. During the addition process a slow stream of nitrogen was passed through the addition funnel to prevent premature reaction of the anhydride with water vapor. After addition was complete the material was stirred for an additional 1 hr and freeze-dried to yield 746 mg (75% yield) of a white powder, mp 101–103° (dec).

Anal. Calcd for $C_3H_4N_2O_2$: C, 36.01; N, 4.03; N, 27.99. Found: C, 36.03; H, 3.99; N, 27.73.

Recrystallization was carried out by dissolution of 500 mg of the freeze-dried residue in 10 ml of H_2O. The aqueous solution was acidified to pH 2 with HCl, treated with charcoal at room temperature for ~2 min, filtered, and cooled in an ice bath, and 30 ml of absolute ethanol was added to initiate crystallization. The crystals were washed with ethanol and then ether; 210 mg (47% yield) of material were obtained: mp 126.5° (dec) (lit.[5,6] mp 121.5°); ir (KBr) 2980 cm^{-1} (NH_3^+), 2264 (CN), 2020 (NH_3^+), 1660 (COO^-), 1620 (NH_3^+), 1590 (NH_3^+), 1360 (COO^-), 485 (NH_3^+).

Anal. Calcd for $C_3H_4N_2O_2$: C, 36.01; H, 4.03; N, 27.99. Found: C, 35.34; H, 4.19; N, 27.27.

Elemental analyses suggest that recrystallization increases and sharpens the melting point (possibly by removing traces of aminoacetonitrile, which could otherwise initiate base-catalyzed decomposition of the molecule) but does not increase the purity of the material.

Chemical Proof of Structure of α-Cyanoglycine (5) and α-Cyanoglycine-NCA (4). (a) Formation of *N*-Trifluoroacetyl Methyl Ester Derivatives. Methyl aminocyanoacetate–*p*-toluene sulfonate salt (20 mg) was added to 1 ml of 25% (v/v) trifluoroacetic anhydride in methylene chloride in a 16 × 75 mm screw-capped test tube and heated at 45° for 30 min.

α-Cyanoglycine-NCA (**4**), 20 mg, and 12.5 *N* methanolic HCl (1.0 ml) were placed into a 16 × 75 mm screw-capped test tube and heated to 45° for 5 min. Volatile reagents were stripped off with a stream of nitrogen, 1 ml of 25% (v/v) trifluoroacetic anhydride was added to the residue, and the mixture was heated to 45° for 30 min.

α-Cyanoglycine (**5**), 10 mg (0.1 mmol), was added to 2 ml of 25% trifluoroacetic anhydride (1.7 *M*) in a screw-capped test tube. The material was heated to 40° for 30 min and cooled to room temperature. Methyl alcohol (140 μl, 3.34 mmol) was cautiously added to the reaction mixture.

(b) Gas chromatographic Procedure. Samples (1 μl) of each solution and a 1-μl sample of a mixture of all three samples were injected onto the OV 17 and the EGA columns. Only one peak (better than 90% of total peak area) was observed on the EGA column. On the OV 17 column peak for *p*-toluenesulfonyl trifluoroacetate and a peak for methyl *N*-trifluoroacetyl-α-cyanoglycine were observed. Conditions for the EGA column were as follows: column oven, 90 to 210° at 4°/min; retention time methyl *N*-TFA-α-CN-Gly, 13.0 min; conditions for the OV 17 column: column oven, 80 to 220° at 4°/min; retention time *p*-toluenesulfonyl trifluoroacetate, 2.0 min; methyl *N*-TFA-α-CN-Gly, 4.2 min.

Registry No.—**4**, 52486-66-5; **5**, 6232-21-9; **7a**, 3878-13-5; **7b**, 52486-67-6; **7c**, 52486-68-7; **8**, 52486-69-8; methyl aminocyanoacetate–*p*-toluenesulfonate salt, 52486-71-2.

References and Notes

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A Synthetic Approach to the Skeleton of Histrionicotoxin[1]

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Received June 28, 1974

An approach to the ring skeleton of histrionicotoxin and dihydrohistrionicotoxin, involving the intramolecular oxidative cyclization of a nitrone moiety with an activated olefin, is described. The regiochemistry of the adduct is considered.

Histrionicotoxin and dihydrohistrionicotoxin (**1** and **2**, respectively), venoms isolated from the skins of certain Colombian frogs, are anticholinergic agents.[2a,b] These alkaloids are structurally intriguing in that they possess a spiro structure and may be the first examples of acetylenic and allenic moieties appearing in animal kingdom derived natural products.[2c] That the biological activity is not intimately associated with the unsaturated linkages is evidenced by the fact that perhydrohistrionicotoxin (**3**) retains activity.[2b]

It is clear that these alkaloids provide an unusual synthetic challenge. Our initial efforts have been directed