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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(2) Address all correspondence to C. B. Warren at the Monsanto Co., St. Louis, Mo. 63166.
(3) Recent monographs and reviews on chemical evolution and the origin of proteins include (a) S. W. Fox and K. Dose, "Molecular Evolution and the Origin of Life," W. H. Freeman, San Francisco, Calif., 1972; (b) C. Ponnamperuma, Ed., "Exobiology," American Elsevier, New York, N.Y., 1972; (c) R. M. Lemmon, *Chem. Rev.*, **70**, 95 (1970); (d) D. H. Kenyon and G. Steinman, "Biochemical Predestination," McGraw-Hill, New York, N.Y., 1969; (e) M. Calvin, "Chemical Evolution," Oxford University Press, New York, N.Y., 1969.
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A Synthetic Approach to the Skeleton of Histrionicotoxin[1]

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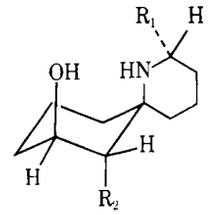
An approach to the ring skeleton of histrionicotoxin and dihydrohistrionicotoxin, involving the intramolecular oxidative cyclization of a nitrone moiety with an activated olefin, is described. The regiochemistry of the adduct is considered.

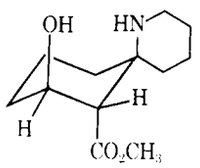
Histrionicotoxin and dihydrohistrionicotoxin (**1** and **2**, respectively), venoms isolated from the skins of certain Colombian frogs, are anticholinergic agents.[2a,b] These alkaloids are structurally intriguing in that they possess a spiro structure and may be the first examples of acetylenic and 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



1. $R_1 = CH_2C{=}CC{\equiv}CH$; $R_2 = C{=}CC{\equiv}CH$
2. $R_1 = CH_2CH_2CH{=}C{=}CH_2$; $R_2 = C{=}CC{\equiv}CH$
3. $R_1 = n\text{-}C_5H_{11}$; $R_2 = n\text{-}C_4H_9$
4. $R_1 = H$; $R_2 = CO_2CH_3$
5. $R_1 = H$; $R_2 = H$

toward the synthesis of spiro ester **7**, which offers promise as a key intermediate in the synthesis of the natural toxins. Compound **4** embodies the desired spiro skeletal system,



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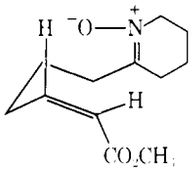
the proper stereochemical relationship between the hydroxyl and amine functions, and incorporates a functional group (*i.e.*, the ester moiety) of requisite stereochemistry capable, in principle, of chemical manipulation into the desired unsaturated side chain of the parent alkaloid. The introduction of the second side chain (*i.e.*, R_1 in **1–3**) appears conceivable as well.

Method of Attack. The use of nitrones in ring formation is well documented.[3,4] Moreover, it has been demonstrated recently that various alkaloidal systems can be approached by nitrone-induced cyclizations.[5,6] Thus, the cyclization of the nitrone ester **6** offers promise of producing the desired ring system **7** spontaneously. Hydrogenolysis of the nitro-



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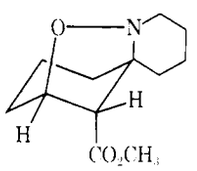

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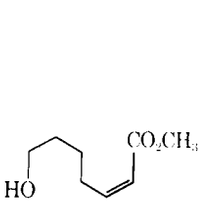
gen–oxygen bond of the isoxazolidine **7** would afford **4** directly. It is to be noted that the cis geometry about the double bond is essential to the introduction of an axial carbomethoxyl group. With these concepts in mind, we embarked on a synthesis of nitrone ester **6**.

The synthesis of the nitrone ester may be separated into three parts: (a) the preparation of the *cis*-α,β-unsaturated ester **8**; (b) the further elaboration of **8** into the keto ester **9**, and (c) the transformation of the hydroxyl group into the nitro functionality in **10**, the immediate presursor of nitrone **6**.



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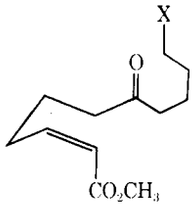
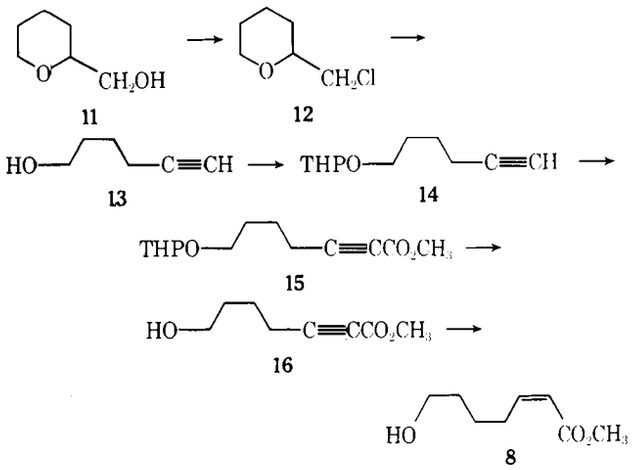


9, X = OH
10, X = NO_2

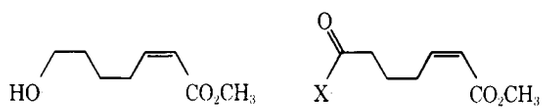
Methyl 7-Hydroxy-cis-2-heptenoate (8). Chlorination of 2-hydroxymethyltetrahydropyran (**11**) with thionyl chloride in pyridine[7] gave 2-hydroxymethyltetrahydropyran (**12**, Scheme I). Sodium amide in liquid ammonia[8] induced ring opening, and dehydrohalogenation afforded 5-hexyn-1-ol (**13**). The tetrahydropyranyl ether of **13** was acylated with methyl chloroformate, using *n*-butyllithium as base. The blocking group of the resulting ester, **15**, was removed with *p*-toluenesulfonic acid in anhydrous methanol. Reduction of **16** with Lindlar catalyst,[9] containing a small amount of quinoline, afforded methyl 7-hydroxy-*cis*-2-heptenoate (**8**) in 51% overall yield from **11**. This completed the first stage of our synthetic plan.

Scheme I



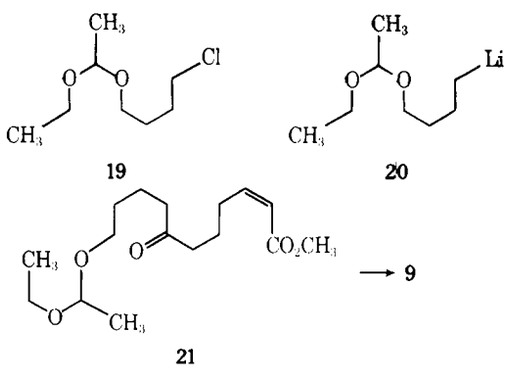
11 **12** **13** **14** **15** **16** **8**

Methyl 11-Nitro-7-keto-*cis*-undec-2-enoate (10). The second phase of the plan requires the conversion of the primary alcohol **8** into the acid chloride **18**, followed by the addition of a four-carbon segment by means of a lithium organocuprate.



8 **17**, X = OH; **18**, X = Cl

The organocopper reagent necessary for the chain extension was prepared from ethyl 4-chlorobutylacetaldehyde acetal (**19**) using the method of Eaton and coworkers,[10] followed by conversion of **19** into the organolithium reagent

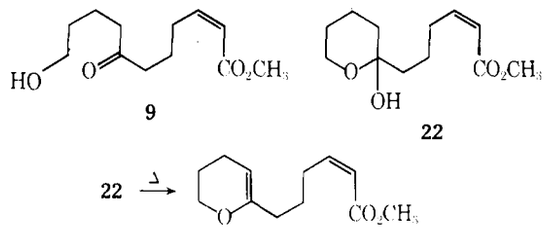


19 **20** **21** → **9**

20, using lithium wire containing 1% sodium. The organocopper reagent was then prepared by treatment of **20** with the copper complex derived from cuprous iodide and hexamethylphosphorus triamide in ether.[11] Addition of a precooled ether solution of the acid chloride **18**, prepared by stirring a benzene solution of the acid **17** with oxalyl chlo-

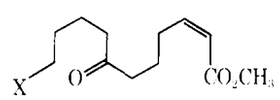
ride overnight at room temperature, to an ether solution of the organocopper reagent,[12] which was cooled to −78°, afforded the chain extended acetal **21**. The production of the keto alcohol **9** was accomplished by hydrolysis of the acetal using dilute hydrochloric acid in tetrahydrofuran.

Upon standing at room temperature, the keto ester **9** undergoes cyclization to the hemiketal **22**. This transformation was followed by the reduction in the intensity of the carbonyl absorption in the infrared region and a decrease in the intensity of the signal due to the methylene protons adjacent to the ketone function at δ 2.4 ppm in the nmr spectrum. Attempts to distill the keto ester resulted in dehydration to the dihydropyran **23**. Since the acyclic keto ester was required for our synthetic purposes, the mixture of isomers (*i.e.*, **9**, **22**, and **23**) was stirred in dilute aqueous acid for 30 min prior to further chemical transformation. The product was then extracted into methylene chloride, dried over anhydrous magnesium sulfate, and used directly.



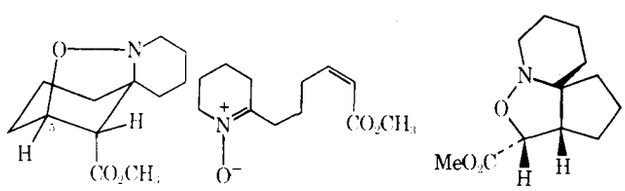
9 **22** **23**

The transformation of **9** into the nitro ketone **10** was straightforward. Treatment of **9** with triethylamine and methanesulfonyl chloride[13] in methylene chloride at 0° gave the corresponding methanesulfonate, **24a**. The bromide **24b** was obtained from **24a** using lithium bromide in acetone. Finally reaction of the bromide with sodium nitrite in dimethyl sulfoxide[14] gave **10**, and this completes the synthesis of the desired nitrone precursor.



24a, X = OMs
b, X = Br
10, X = NO_2

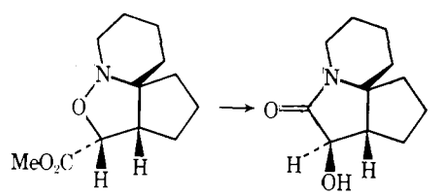
Nitrone Cyclization. It was suspected that the nitrone **6**, produced by reductive cyclization of the nitro ketone **10**, would spontaneously add to the intramolecularly situated α,β-unsaturated ester moiety, a good dipolarophilic unit.[3] Indeed, treatment of a solution of **10** in aqueous methanol with zinc and ammonium chloride gave no detectable sign of the nitrone **6**. The reaction did produce a basic product,



7 **6** **25**

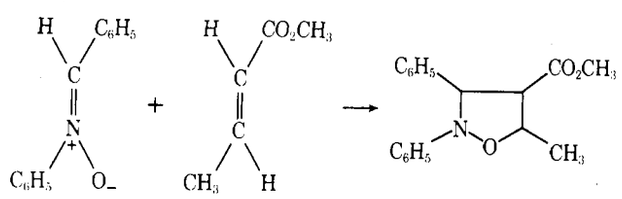
however, which exhibited no olefinic proton signals between 5.8 and 6.2 ppm, clearly suggesting that the nitrone had spontaneously cyclized as expected. Significantly, the pmr spectrum exhibited a doublet (J = 8.5 Hz) at 4.72 ppm. This signal is ascribed to the proton on the oxygen-bearing carbon of the isoxazolidine ring. The observed multiplicity would appear to rule out **7** as the major product of the reaction. Clearly, the proton on the 5 carbon of the isoxazolidine ring of **7** would be expected to be coupled to three other protons. Thus, the major product of the nitrone cyclization must be assigned the structure **25**.

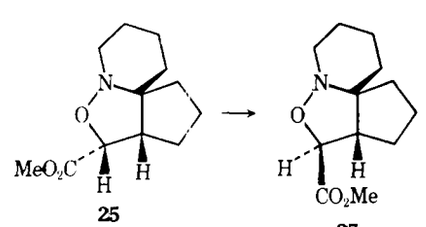
Chemical evidence for the structure **25** was obtained by cleavage of the nitrogen–oxygen bond with zinc and acetic acid.[4] Such treatment afforded a white solid which exhibits a carbonyl stretch at 5.95 μ and a hydroxyl band at 3.0 μ in the infrared spectrum. Further evidence for the hydroxy lactam structure **26** was obtained by examination of its pmr spectrum. The proton doublet due to the proton at the 5 position of the isoxazolidine ring shifted upfield from 4.72 (*i.e.*, in **25**) to 4.1 ppm. The smaller magnitude of the coupling (J = 5 Hz) indicates a trans coupling to a single proton, an expected consequence of the transformation. Mass spectral examination of adduct **25** and hydroxy lactam **26** indicates molecular ions at *m/e* 225 and 195, respectively.



25 **26**

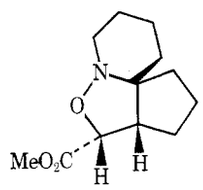
Since it now is apparent that the intramolecular cycloaddition did not proceed in the desired sense, one must reexamine the foundation upon which our initial expectations were based. A body of evidence[15-18] has accumulated which suggests that nitrones add to β-substituted α,β-unsaturated esters to give β-oxido ester adducts (*e.g.*, *vide infra* [16a]). This mode of addition would have produced the desired regioisomer **7** in the case in question. An explanation for the unexpected regiochemistry centers about the possibility that our initially derived adduct, **25**, is the product of kinetic control. Indeed, this adduct was formed spontaneously under very mild conditions (*vide supra*). There are examples where isoxazolidines, formed under kinetic conditions, can be converted to their thermodynamically favored counterparts;[15] however, refluxing a 1% solution of adduct **25** in toluene for 7 hr gave only a quantitative recovery of starting material. When adduct **25** was exposed to refluxing xylene for 30 hr, a new doublet appeared in the pmr spectrum at δ 4.18 ppm. The expected pattern for the proton at the 5 position of the isoxazolidine ring in **7** is a multiplet. Comparison of the coupling constant associated with the doublet at δ 4.72 ppm (J = 8.5 Hz) in adduct **25** with the doublet at δ 4.18 ppm (J = 6 Hz) in the thermally generated compound led to the conclusion that epimerization of the carbomethoxy group in **25** had occurred to give the isomeric adduct **27**, possibly *via* a base-catalyzed pathway. The marked similarity of the mass spectra of the adducts **25** and **27** is supportive of the structural assignment.





25 **27**

The predominant formation of **25**, and not **7**, from the nitrone cyclization might derive from the inherent relative stabilities of the ring systems involved. Examination of **25** and **7** suggests a piperidine ring common to both. If one focuses on the skeletal differences between the systems, it is clear that **25** possesses a *cis*-bicyclo[3.3.0]octyl skeleton, while **7** contains a bicyclo[3.2.1]octyl moiety. Clearly, if the



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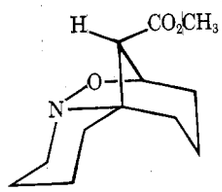

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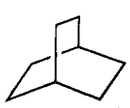
cis-bicyclo[3.3.0]octyl system is thermodynamically preferred, a reasonable rationale for the observed mode of cyclization would be available; however, Allinger and coworkers[19] have calculated an additional strain energy of *ca.* 4.7 kcal/mol in bicyclo[3.3.0]octane. This figure might be somewhat high[19] but does suggest that the [3.2.1] system should be at least somewhat more stable than its [3.3.0] counterpart. In addition, Schleyer and coworkers[20] have studied the thermodynamic properties of bicyclo[2.2.2]octane (**28**), bicyclo[3.3.0]octane (**29**), and bicyclo[3.2.1]octane (**30**). The isomers were equilibrated at temperatures



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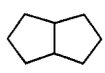

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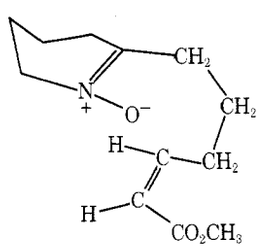
30

ranging from 23 to 72° and the product ratios determined. As the temperature increased, the amount of **29** increased at the expense of **28** and **30**, but even at 72°, the amount of **30** still predominated. Since thermodynamic considerations, albeit simplified, imply that appreciable amounts of **7** should be formed in the nitrone cyclization, the predominant formation of adduct **25** suggests the operation of some other factor.

It is quite possible that functionality and skeletal features not considered above may alter the relative adduct stabilities significantly; however, since the adducts are formed under conditions of apparent kinetic control, an examination of the relative transition state energies was undertaken using molecular models.

The transition states leading to the bicyclo[3.3.0]octyl system **25** and the bicyclo[3.2.1]octyl system **7** are depicted. An examination of the interactions apparent in these transition states discloses apparently serious steric interactions, indicated by the doubleheaded arrows in **32**, between the



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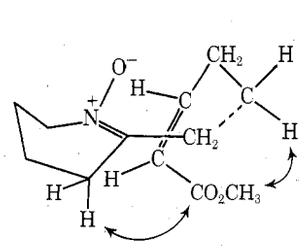

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carbomethoxy group and both C-3 of the nitrone and one of the side-chain methylene groups in the transition state leading to **7**. These interactions are absent in **31**. Thus, these steric interactions might outweigh an inherent preference for closure to the [3.2.1] system (*i.e.*, **7**).

We are testing this hypothesis by studying the cyclization of the olefin in which the ester group has been replaced by a hydrogen. Hopefully, such cyclization, where steric repulsions are minimized, would give **5** after hydrogenolysis.

Experimental Section

All melting points were determined on a Mel-Temp apparatus and are uncorrected. Infrared spectra were recorded on a Beckman IR-5a spectrophotometer and calibrated using the 6.238-μ band of polystyrene. Proton magnetic resonance spectra were obtained using a Jeol MH-100 or a Varian A-60 spectrometer using tetramethyl silane as the internal standard. Notations s, d, t, q, m, and b designate singlet, doublet, triplet, quartet, multiplet, and broad, respectively. Mass spectra were recorded on a Hitachi Perkin-Elmer RMU-6 spectrometer.

2-(Chloromethyl)tetrahydropyran (12). An adaptation of the procedure used by Brooks[7a] to prepare tetrahydrofurfuryl chloride was used to prepare **12**. To a mixture of 103 g (0.888 mol) of tetrahydropyran-2-methanol (**11**) and 150 ml (1.09 mol) of freshly distilled pyridine was added 76.0 ml (1.06 mol) of freshly distilled thionyl chloride at a rate to maintain a reaction temperature of 40–45°. When the addition was complete, the mixture was heated for 8 hr at 45° by means of an oil bath. The resulting heavy brown oil was washed with ether (6 × 150 ml) and each time the ether was decanted. The combined ether solution was washed with water (4 × 75 ml), saturated aqueous sodium bicarbonate (3 × 75 ml), and saturated aqueous sodium chloride (2 × 75 ml). The ether solution was dried over anhydrous magnesium sulfate, and ether was removed at reduced pressure. Distillation of the residue gave 79 g (66% yield) of the chloride **12** as a colorless liquid: bp 55.0–55.5° (6 mm) [lit.[7b] 53–54° (12 mm)].

5-Hexyn-1-ol (13). An adaptation of the procedure used by Whiting[8] to prepare 4-pentyn-1-ol was used to prepared 5-hexyn-1-ol (**13**). Sodium amide was prepared by the addition of 35.9 g (1.52 mol) of freshly cut sodium to 600 ml of anhydrous liquid ammonia, containing 0.3 g of ferric nitrate nonahydrate. When the addition was complete, stirring was continued for 30 min. To the gray suspension of sodium amide was added dropwise 48.1 g (0.360 mol) of 2-(chloromethyl)tetrahydropyran (**12**). When the addition was complete, stirring was continued for 3 hr. Gradually, 80 g (1.5 mol) of ammonium chloride was added at a rate to allow a controllable neutralization of the base. The ammonia was allowed to evaporate overnight. The residual oily solid was extracted with a Soxhlet extractor with ether for 24 hr. The ether solution was dried over anhydrous magnesium sulfate, and the ether was removed at reduced pressure. Distillation of the residue gave 30.3 g (86% yield) of the alcohol **13** as a colorless liquid: bp 53° (1.2 mm) [lit.[21] bp 82° (20 mm)].

Tetrahydropyranyl Ether of 5-Hexyn-1-ol (14). To a mixture of 39.5 g (0.402 mol) of 5-hexyn-1-ol (**13**) and 1 ml of concentrated hydrochloric acid, cooled in an ice bath, was added 40.0 g (0.476 mol) of dihydropyran. When the addition was complete, stirring was continued at room temperature overnight. The solution was poured into 200 ml of saturated aqueous sodium bicarbonate, and the organic layer was separated. The aqueous layer was extracted with ether (3 × 100 ml). The combined extracts were dried over anhydrous magnesium sulfate, and the ether was removed at reduced pressure. Distillation of the residue gave 72.2 g (98% yield) of the tetrahydropyranyl ether **14** as a colorless liquid: bp 60–65° (0.2 mm); ir (neat) 8.95 (s), 9.3 (s), and 9.65 μ (s); nmr ($CDCl_3$) δ 1.3–2.0 (m, 10), 1.95 (t, 1, J = 2.5 Hz), 2.2 (m, 2), 3.5 (m, 2), 3.8 (m, 2), and 4.6 ppm (broad singlet, 1).

Methyl 7-Hydroxy-2-heptynoate (16). To a solution of 70.5 g (0.387 mol) of the tetrahydropyranyl ether **14** in 500 ml of freshly distilled tetrahydrofuran which was cooled to −78° was added 176 ml (0.412 mol) of a 2.34 M hexane solution of n-butyllithium. When the addition was complete, stirring was continued at −78° for 30 min. By means of a Dry Ice cooled addition funnel, the tetrahydrofuran solution, just prepared, was added over 4 hr to a solution of 62 ml (0.80 mol) of freshly distilled methyl chloroformate, in 500 ml of tetrahydrofuran which was cooled to −78°. When the addition was complete, the resulting mixture was stirred at −78° for 1 hr. The tetrahydrofuran solution, without warming, was siphoned into 1.6 l. of saturated aqueous sodium bicarbonate. The organic layer was separated, and the aqueous layer was extracted with ether (3 × 100 ml). The combined organic extracts were dried over anhydrous magnesium sulfate, and the solvent was removed at reduced pressure, to give the crude ester **15**.

To a solution of the crude ester **15**, in 500 ml of anhydrous methanol, was added 0.5 g of *p*-toluenesulfonic acid, and the resulting mixture was stirred overnight at room temperature. The acid was neutralized by the addition of 2 ml of triethylamine, and the methanol was removed at reduced pressure. The residue was taken up in 300 ml of methylene chloride and washed with 2% aqueous hydrochloric acid (2 × 100 ml) and saturated aqueous sodium bicarbonate (2 × 100 ml). The methlene chloride solution was dried over anhydrous magnesium sulfate, and the methylene chloride was removed at reduced pressure. Distillation of the residual oil gave 56.4 g (93% yield) of ester **16** as a light yellow oil: bp 90–95° (0.15 mm); ir (neat) 2.95 (m), 4.45 (s), 4.83 (s), 7.95 (s), and 9.3 μ (m); nmr ($CDCl_3$) δ 1.68 (m, 4), 2.4 (m, 2), 3.2 (broad singlet, 1) 3.65 (m, 2), and 3.75 ppm (s, 3); mass spectrum (M+) *m/e* 156.

Methyl 7-Hydroxy-*cis*-hept-2-enoate (8). A mixture of 54.0 g (0.346 mol) of methyl 7-hydroxy-2-heptynoate (**16**), 200 ml of absolute methanol, 0.4 g of Lindlar catalyst,[9] and 12 drops of quinoline was hydrogenated in a Parr apparatus at 14 psi until the hydrogen up-take ceased. The catalyst was removed by filtration, and the methanol was removed at reduced pressure. The residue was dissolved in 300 ml of methylene chloride and washed with cold 5% aqueous hydrochloric acid (1 × 30 ml) and saturated aqueous sodium bicarbonate (1 × 50 ml). The methylene chloride solution was dried over anhydrous magnesium sulfate, and the methylene chloride was removed at reduced pressure. Distillation of the residue gave 45.8 g (84% yield) of the ester **8** as a colorless oil: bp 74–78° (0.15 mm); ir (neat) 2.9 (s), 5.8 (s), 6.1 (m), 7.8 (s), 8.35 (s), 9.4 (s), 9.75 (s), and 12.2 μ (m); nmr ($CDCl_3$) δ 1.6 (m, 4), 2.7 (m, 2), 2.9 (broad singlet, 1), 3.7 (m, 2), 3.75 (s, 3), 5.8 (d, 1, J = 12 Hz), and 6.3 (doublet of triplets, 1, J = 8, 12 Hz); mass spectrum (M − H_2O *m/e* 140.

Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.29; H, 8.78.

4-Chloro-1-butanol. Using the procedure of Starr and Hixon,[22] 4-chloro-1-butanol was prepared in 26% yield as a clear liquid: bp 58–60° (2 mm) [lit.[22] 70–71° (7 mm)].

Ethyl-4-chlorobutylacetaldehyde Acetal (19). Modification of Eaton's procedure[10] was necessary to prepare ethyl-4-chlorobutylacetaldehyde acetal (**19**). To a mixture of 70 g (0.65 mol) of 4-chloro-1-butanol, which had been washed with saturated aqueous sodium bicarbonate and dried over anhydrous potassium carbonate, and 250 ml (2.6 mol) of ethyl vinyl ether was added 1.5 ml of trifluoroacetic acid. The resulting solution was stirred in an ice bath for 4 hr and stored in a refrigerator overnight. The trifluoroacetic acid was neutralized by the addition of 7 ml of triethylamine, and the excess ethyl vinyl ether was removed at reduced pressure. The residue was dissolved in 150 ml of ether and washed with water (1 × 100 ml). The ether solution was dried over anyhdrous magnesium sulfate, and the ether was removed at reduced pressure. Distillation of the residue gave 101 g (86% yield) of acetal **19** as a colorless liquid: bp 37–39° (0.1 mm); ir (neat) 8.8 (s), 9.15 (s), 9.4 (s), and 15.5 μ (m); nmr ($CDCl_3$) δ 1.18 (t, 3, J = 6 Hz), 1.38 (d, 3, J = 6 Hz), 1.8 (m, 4), 3.55 (m, 4), and 4.7 ppm (q, 1, J = 6 Hz).

Ethyl-4-lithiobutylacetaldehyde Acetal (20). To a vigorously stirred suspension of 215 cm (1.33 mol) of freshly washed lithium 1% sodium alloy wire cut into 0.5 cm lengths, in 600 ml of anhydrous ether, was added 2 ml of 1,2-dibromoethane, to clean the surface of the lithium metal. The suspension was cooled to −18° and 98 g (0.4 mol) of ethyl-4-chlorobutylacetaldehyde acetal (**19**) was added dropwise over 2 hr. When the addition was complete, stirring was continued at −18° for 2 hr. The precipitate was allowed to settle for 20 min, and the ether solution was filtered through a sintered glass disk by a positive pressure of argon. The solution was stored at −30° in a freezer. Immediately before use, the concentration of the organolithium was determined using the procedure of Watson and Eastham.[3]

A 2.0-ml aliquot of the ether solution was added to water. The aqueous solution was saturated with sodium chloride and extracted with ether (4 × 25 ml). The combined ether extracts were dried over anhydrous magnesium sulfate, and the ether was removed at reduced pressure to give a colorless liquid characterized as the ethylbutylacetaldehyde acetal: nmr ($CDCl_3$) δ 0.9 (t, 3, J = 6 Hz), 1.2 (t, 3, J = 6 Hz), 1.25 (d, 3, J = 6 Hz), 1.5 (m, 4), 3.5 (m, 4), and 4.7 ppm (q, 1, , J = 6 Hz).

Methyl 6-Carboxy-*cis*-hex-2-enoate (17). To a solution of 45.3 g (286 mmol) of methyl 7-hydroxy-*cis*-hept-2-enoate (**8**), in 473 ml of acetone, was added 400 ml of an aqueous solution of 65 g (650 mmol) of chromium trioxide and 49 ml of concentrated sulfuric acid, prepared by the procedure of Meinwald[24] over 1.5 hr. When the addition was complete, stirring was continued at room temperature for 1.5 hr. The excess chromic acid was destroyed by the addition of a saturated aqueous solution of sodium bisulfite, until the orange color was discharged. The organic layer was separated, and the aqueous layer was extracted with ether (3 × 150 ml). The combined organic extracts were washed with saturated aqueous sodium bicarbonate (3 × 150 ml). The aqueous solution was acidified with concentrated hydrochloric acid and extracted with ether. The ether extracts were dried over anhydrous magnesium sulfate, and the ether was removed at reduced pressure, to give 33.8 g (69% yield) of the acid **17** as a light yellow oil; ir (neat) 3.0 (s), 5.85 (s), 6.1 (m), 8.4 (s), and 12.2 μ (w); nmr ($CDCl_3$) δ 1.78 (m, 2), 2.4 (t, 2, J = 8 Hz), 2.7 (m, 2), 3.6 (s, 3), 5.9 (d, 1, J = 12 Hz), 6.15 (doublet of triplets, 1, J = 8 and 12 Hz), and 11.2 ppm (broad singlet, 1).

Methyl 7-Chloro-7-keto-*cis*-hept-2-enoate (18). To a solution of 33.7 g (0.196 mol) of methyl 6-carboxy-*cis*-hex-2-enoate (**17**), in 400 ml of dry benzene, was added 27.0 ml (0.305 mol) of freshly distilled oxalyl chloride. The resulting solution was stirred overnight at room temperature. The benzene was removed at reduced pressure (40 mm). Two 50-ml protions of dry benzene were added then removed at reduced pressure to ensure that no traces of oxalyl chloride remained. Without further purification, the acid chloride **18** was used in the next step: ir (neat) 5.55 (s), 5.85 (s), 61. (w), 8.3 (s), and 12.25 μ (w).

To a small sample of the acid chloride **18** was added methanol. The methanol was removed at reduced pressure to give a light yellow diester: nmr ($CDCl_3$) δ 1.7 (quintet, 2, J = 7 Hz), 21. (m, 2), 2.5 (m, 2), 3.05 (s, 3), 3.10 (s, 3), 5.5 (d, 1, J = 12 Hz), and 5.9 ppm (doublet of triplets, 1, J = 8, 12 Hz).

Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.96; H, 7.90.

Methyl 11-Hydroxy-7-keto-*cis*-undec-2-enoate (9). An adaptation of the Posner[12] procedure was used to prepare ketone **9.** To a suspension of 40 g (0.21 mol) of purified cuprous iodide[25] and 350 ml of anhydrous ether was added 78.0 ml (0.425 mmol) of hexamethylphosphorus triamide.[26] The resulting solution was stirred at room temperature for 30 min and was then cooled to −78°. To the cooled solution was added 450 ml (0.42 mol) of a 0.92 *M* ether solution of the organolithium reagent **20.** The resulting yellow solution was warmed to −50° and stirred for 2 hr. The solution was recooled to −78° and, by means of a Dry Ice cooled dropping funnel, was added to an ether solution of acid chloride **18,** which had just been prepared from 0.190 mol of **17.** When the addition was complete, stirring was continued at −78° for 30 min. The excess copper reagent was quenched by the addition of 45 ml of anhydrous methanol, warming to −30°, and siphoning the ether solution into 1.0 l. of saturated aqueous ammonium chloride. The ether layer was separated and added to 1.0 l. of cold 2% aqueous sulfuric acid. This produced a fluffy white precipitate. The solid was filtered through Celite, and the ether layer was separated from the filtrate. The ether solution was washed with saturated aqueous sodium bicarbonate (2 × 150 ml). The ether solution was dried over anhydrous magnesium sulfate, and the ether was removed at reduced pressure, to give crude ketone **21** as a yellow oil.

Water was added to a solution of the crude ketone **21** in 300 ml of tetrahydrofuran until the first sign of turbidity, then 6 drops of concentrated hydrochloric acid were introduced. The solution was stirred at room temperature for 4 hr. The tetrahydrofuran was removed at reduced pressure, and the hydrochloric acid was neutralized with solid sodium bicarbonate. The aqueous solution was extracted with methylene chloride (1 × 300 ml). The methylene chloride solution was dried over anhydrous magnesium sulfate, and the methylene chloride was removed at reduced pressure, to give 36.3 g of keto alcohol **9** in an 83.5% yield from acid **17:** ir (neat) 2.9 (m), 5.8 (s), 6.1 (w), 8.3 (s), 8.5 (s), and 12.2 μ (w); nmr ($CDCl_3$) δ 1.6 (m, 6), 2.4 (m, 4), 2.6 (m, 2), 3.2 (broad singlet, 1), 3.6 (m, 2), 3.7 (s, 3), 4.7 (d, 1, J = 12 Hz), and 6.1 ppm (doublet of triplets, 1, J = 8, 12 Hz); mass spectrum (M − H_2O) *m/e* 210.

A sample of **9** was collected from a gas chromatograph, using a 2 ft, 0.5 in. diameter column, packed with 15% silicone rubber on 60–80 mesh Chromasorb W, and heated to 180°, for elemental analysis. The results of the elemental analysis were far from being accurate. By nmr spectroscopy the predominant component of the collected material was the dihydropyran **23:** nmr ($CDCl_3$) δ 1.4–2.2 (m, 8), 2.7 (m, 2), 3.7 (s, 3), 4.0 (t, 1, J = 5 Hz), 4.55 (t, 1, J = 4 Hz), 5.8 (d, 1, J = 12 Hz), and 6.2 ppm (doublet of triplets, 1, J = 8, 12 Hz).

Methyl 11-Hydroxy-7-keto-*cis*-undec-2-enoate Methanesulfonate (24a). Using the procedure of Crossland[13] the methane-

sulfonate **24a** was prepared. To a solution of 35.8 g (0.157 mol) of the alcohol **9** and 40 ml (0.29 mol) of freshly distilled triethylamine, in 500 ml of methylene chloride which was cooled to −15°, was added dropwise 14.5 ml (0.191 mole) of freshly distilled methanesulfonyl chloride. When the addition was complete, stirring was continued at −15° for 30 min. The methylene chloride solution was washed with cold water (2 × 150 ml), saturated aqueous sodium bicarbonate (2 × 150 ml), and saturated aqueous sodium chloride (2 × 150 ml). The methylene chloride solution was dried over anhydrous magnesium sulfate, and the methylene chloride was removed at reduced pressure, to give 41.6 g (87% yield) of the methanesulfonate **24a** as a red oil: ir (neat) 5.8 (s), 6.1 (w), 7.4 (m), 8.35 (s), 8.5 (s), and 12.2 μ (w); nmr ($CDCl_3$) δ 1.3–2.0 (m, 6), 2.3–2.8 (m, 6), 3.05 (s, 3), 3.7 (s, 3), 4.3 (t, 2, J = 6 Hz), 4.9 (d, 1, J = 12 Hz), and 6.3 ppm (doublet of triplets, 1, J = 8, 12 Hz).

Methyl 11-Bromo-7-keto-*cis*-undec-2-enoate (24b). A mixture of 41.0 g (134 mmol) of the methanesulfonate **24a** and 60 g (690 mol) of -anhydrous lithium bromide, in 500 ml of acetone, was refluxed overnight. The solid was removed by filtration, and the acetone was removed at reduced pressure. The residue was taken up in 250 ml of methylene chloride and washed with water (2 × 150 ml). The methylene chloride solution was dried over anhydrous magnesium sulfate, and the methylene chloride was removed at reduced pressure to give 37.7 g (97% yield) of the bromide **24b** as an orange oil: ir (neat) 5.8 (s), 6.1 (w), 8.3 (s), 8.5 (s), and 12.2 μ (w); nmr ($CDCl_3$) δ 1.4–2.0 (m, 6), 2.2–2.8 (m, 6), 3.4 (t, 2, J = 6 Hz), 3.7 (s, 3), 5.8 (d, 1, J = 12 Hz), and 6.2 ppm (doublet of triplets, 1, J = 8, 12 Hz).

Methyl 11-Nitro-7-keto-*cis*-undec-2-enoate (10). Using the procedure of Kornblum,[14] the nitro compound **24c** was prepared. To a solution of 31 g (0.52 mol) of dry urea and 27 g (0.39 mol) of dry sodium nitrite, in 170 ml of freshly distilled dimethyl sulfoxide, was added dropwise 37.0 g (0.127 mol) of bromide **24b.** When the addition was complete, stirring was continued for 4 hr. The dimethyl sulfoxide solution was poured into 2 l. of ice–water and continuously extracted with ether for 24 hr. The ether solution was washed with water (2 × 100 ml) and dried over anhydrous magnesium sulfate, and the ether was removed at reduced pressure. The residue contained a mixture of the nitrite ester of alcohol **9,** the methyl ester of acid **17,** and the nitro compound **24c** which was determined by its nmr spectrum. Heating the mixture to 60° (0.03 mm) for 12 hr removed all of the nitrite ester and most of the methyl ester. The resulting orange oil (25.6 g) contained 85% of the nitro compound and 15% of the methyl ester of the acid **17,** which was determined by the integration of the methyl ester singlet at δ 3.6 ppm relative to the triplet at δ 4.4 ppm, characterized as the methylene protons adjacent to the nitro group in **10:** ir (neat) 5.8 (s), 6.1 (w), 6.4 (s), 8.3 (s), 8.5 (s), and 12.2 δ (w); nmr ($CDCl_3$) δ 1.2–2.0 (m, 6), 2.1–2.7 (m, 6), 3.7 (s, 3), 4.4 (t, 2, J = 6 Hz), 5.9 (d, 1, J = 12 Hz), and 6.3 ppm (doublet of triplets, 1, J = 8, 12 Hz).

Attempted separation of a small portion of the mixture for elemental analysis by preparative layer chromatography, using silic gel as absorbent, and a 75:25 mixture of methylene chloride and hexane as elutents, failed.

Methyl Octahydro-1*H*-cyclopent[3,4]isoxazolo[2,3-*a*]pyridine-*endo*-4-carboxylate (25). To a solution of 1.23 g (4.76 mmol) of the nitro compound (**10**) obtained in the previous experiment, in 70 ml of 25% aqueous methanol containing 0.38 g (7.1 mmol) of ammonium chloride, was added 2.0 g of freshly activated zinc dust. The suspension was stirred at room temperature for 4.5 hr. The zinc salts were removed by filtration and washed with hot 50% aqueous methanol (2 × 50 ml). The methanol was removed at reduced pressure. The aqueous solution was saturated with solid sodium chloride and extracted with methylene chloride (5 × 50 ml). The methylene chloride solution was washed with 10% aqueous hydrochloric acid (3 × 20 ml) and dried over anhydrous magnesium sulfate, and the methylene chloride was removed at reduced pressure, to give 0.357 g of a neutral yellow oil. The aqueous solution was basified with solid sodium bicarbonate, saturated with solid sodium chloride, and extracted with methylene chloride (5 × 30 ml). The methylene chloride solution was dried over anhydrous magnesium sulfate, and the methylene chloride was removed at reduced pressure, to give 0.62 g (51% yield) of adduct **25** as a light yellow oil: ir (neat) 5.7 (s), 6.95 (m), 8.35 (s), and 9.4 μ (m); nmr spectrum ($CDCl_3$) 1.1–2.1 (m, 12), 2.7–3.4 (m, 3), 3.72 (s, 3), 4.72 ppm (d, 1, J = 8.5 Hz); mass spectrum (70 ev) m/e (rel intensity) 225 (24), 182 (6), 167 (12), 166 (100), 138 (27), 124 (28), 113 (53), 97 (11).

The methiodide of adduct **25** was prepared by the addition of 1.0 ml (16 mmol) of methyl iodide to a small amount of the adduct **25.** The resulting solid was recrystallized from ethanol–ether to give a hydroscopic white solid, mp 167–168°. Even though a small sample of the methiodide was dried at 80° (0.05 mm) for 12 hr, the results of the elemental analysis suggested that the white solid contained water.

Octahydro-7-hydrocyclopent[*i*]indolizin-6(7*H*)-one (26). To a solution of 0.306 g (1.36 mmol) of adduct **25,** in 5 ml of 50% aqueous acetic acid, was added 1.0 g (15 mmol) of zinc dust. The mixture was heated at 70° for 24 hr. The remaining zinc metal was removed by filtration and washed with hot water (*ca.* 70°). The filtrate was basified with solid sodium carbonate, saturated with solid sodium chloride, and continuously extracted with methylene chloride for 24 hr. The methylene chloride solution was dried over anhydrous magnesium sulfate, and the methylene chloride was removed at reduced pressure. Recrystallization of the resulting solid from hexane–ether gave 0.207 g (78% yield) of a white solid: mp 99–100°; ir (KBr) 3.0 (s), 5.95 (s), and 6.9 μ (s); nmr ($CDCl_3$) 1.2–D.1 (m, 12), 2.00 (m, 1), 2.74 (bt, 2, J = 7 Hz), 4.1 (d, 1, J = 5 Hz), 5.3 ppm (bs, 1); mass spectrum (70 ev) m/e (rel intensity) 195 (51), 167 (13), 166 (75), 153 (87), 152 (100), 138 (30), 125 (32), 124 (14).

Anal. Calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.38; H, 8.77; N, 7.07.

Attempted Isomerization of Methyl Octahydro-1*H*-cyclopent[3,4]isoxazolo[2,3-*a*]pyridine-*endo*-4-carboxylate (25). Trial A. A solution of 184 mg (0.815 mmol) of the adduct **25,** in 50 ml of toluene, was refluxed under a constant stream of argon for 7 hr. The toluene solution was cooled and extracted with cold 10% aqueous hydrochloric acid (3 × 25 ml). The aqueous solution was basified with solid sodium bicarbonate, saturated with solid sodium chloride, and extracted with methylene chloride (4 × 25 ml). The methylene chloride solution was dried over anhydrous magnesium sulfate, and the methylene chloride was removed at reduced pressure to give 134 mg of a light yellow oil whose nmr spectrum was identical with that of the starting material **25.**

Trial B. A solution of 0.30 g (1.3 mmol) of adduct **25,** in 60 ml of xylene, was refluxed under a constant stream of argon for 8 hr. The reaction product was isolated as in trial A to give 0.28 g of a yellow oil. The nmr spectrum of the yellow oil appeared identical with the starting material except for a small shoulder on the methyl ester singlet at δ 3.75 ppm.

Trial C. A solution of 0.265 g (1.18 mmol) of the adduct **25,** in 70 ml of xylene, was refluxed under a constant stream of argon for 30 hr. The reaction product was isolated as in trial A to give 0.222 g of a brown oil. The nmr spectrum of the brown oil showed the appearance of a distinguishable doublet at δ 4.1 ppm. The mixture was separated by preparative layer chromatography, using silica gel as the adsorbent and a 50:50 mixture of hexane and methylene chloride as elutents, to give two fractions. The major component gave 126 mg of a light yellow oil whose nmr and ir spectra were identical with those of starting material **25.** The minor component gave 30 mg of a light yellow oil which was assigned the structure methyl octahydro-1*H*-cyclopent[3,4]isoxazolo[2,3-*a*]pyridine-*exo*-4-carboxylate (**27**): ir (neat) 5.7 (s), 6.95 (m), 7.9 (m), and 8.15 μ (s); nmr ($CDCl_3$) 1.1–2.0 (m, 12), 2.70 (m, 1), 3.17 (m, 2), 3.89 (s, 3), 4.18 (d, 1, J = 6 Hz); mass spectrum (70 ev) m/e (rel intensity) 225 (14), 187 (18), 166 (34), 138 (21), 124 (100), 113 (42), 97 (9).

Registry No.—**8,** 52500-23-9; **9,** 52571-11-6; **10,** 52500-24-0; **11,** 100-72-1; **12,** 18420-41-2; **13,** 928-90-5; **14,** 1720-37-2; **15,** 52500-25-1; **16,** 52500-26-2; **17,** 52500-27-3; **18,** 52500-28-4; **19,** 52500-29-5; **20,** 52500-30-8; **21,** 52500-31-9; **24a,** 52500-32-0; **24b,** 52500-33-1; **25,** 52611-61-7; **25** methiodide, 52555-45-0; **26,** 52500-34-2; **27,** 52500-35-3; 4-chloro-1-butanol, 928-51-8; methyl 6-carbomethoxy-*cis*-hex-2-enoate, 52500-36-4.

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Total Synthesis of β-Lactam Antibiotics. VI. 3-Arylcephalosporins[1]

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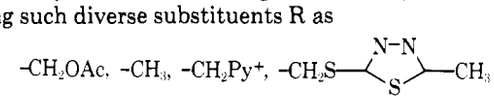
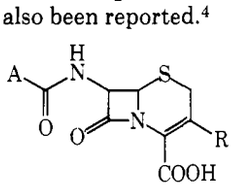
The total synthesis of *dl*-3-phenyl-, 3-*p*-carbomethoxyphenyl-, and 3-(4-thiazolyl)-7β-(2-thienyl)acetamidodecephalosporanic acids **12a–c** is described.

Cephalosporins **1** are a class of semisynthetic antibiotics that are being increasingly used because of their breadth of spectrum, potency, acid stability, and high degree of tolerance by man. In recent years an intensive worldwide effort has been made to obtain modified cephalosporins with improved properties.[2] Variations at the 3 position have been particularly fruitful, resulting in clinically useful drugs having such diverse substituents R as

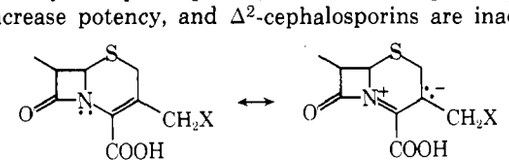


Many other modifications have also been reported, the vast majority of which have $-CH_2X$ as the 3 substituent,[2,3] although R = H has also been reported.[4]



1

It is believed that resonance of type **2** plays a role in the bioactivity of cephalosporins, since electronegative groups X increase potency, and Δ^2-cephalosporins are inactive.[2]



2

However, the activity of 3-methylcephems such as cephalexin (X = H) shows that X^- does not have to depart during the bioactive event. Furthermore, a theoretical study also concluded that during thiolation of cephalosporins at the β-lactam carbonyl, negative charge tends to accumulate at C-3 but that the CH_2–X bond does not break.[5]

For these reasons it seemed worthwhile to prepare cephems bearing aromatic rings directly attached to C-3. At the inception of this project, there was no known way to do this by partial synthesis.[6] However, the total synthesis recently developed in these laboratories[7] has the capability of great variation in the 3 substituent, and this route (Scheme I) was therefore chosen for the preparation of 3-aryl cephems.

The alkylation of thioamide **3**[7] with phenacyl chloride and cyclization of **4a** to the thiazine **5a** were best done sequentially, with isolation of **4a.** When more than 1 equiv of K_2CO_3 was used with phenacyl chloride as had previously been done with 1-chloro-3-acetoxy-2-propanone,[7] extensive decomposition occurred. Phenacyl bromide could be used in place of the chloride, but in addition to **4a** it gave an isomer, presumably trans. Both isomers were stable to interconversion in refluxing $CDCl_3$.

Many conditions were tried for the cyclization of **4a** to **5a,** including K_2CO_3–acetone,[7] $KHCO_3$–acetone, Et_3N–$CHCl_3$, PhLi–THF, NaH–THF, LDA–THF, and NaH–glyme. Of these, the latter gave the cleanest product and was used in all subsequent work.

Cycloaddition of azidoacetyl chloride to **5a** gave cephem **6a,** sometimes containing the Δ^2 isomer, which was formed from **6a** with catalysis by triethylamine. The isomers were separable by chromatography, but with care the problem was avoidable altogether.

The stereochemistry of **6a** was established as trans by the coupling constant of 1.5 Hz for H-6 and H-7, in accord with previous observations[7] as well as our own subsequent examples. Since all naturally occurring cephalosporins and penicillins have cis stereochemistry, and trans compounds are inactive, it was necessary to epimerize the 7 substituent. This could not be done by simple equilibration because the trans isomers are generally the more stable ones, and so our procedure based upon steric approach control was used.[8] Azidocephem **6a** was reduced to amine **7a,** which was converted to its Schiff base **8a** with *p*-nitrobenzaldehyde. Formation of the 7 anion with phenyllithium, activation with DMF, and then acidification under kinetically controlled conditions, which occurs preferentially from the less hindered side, provided the cis Schiff base **9a** with the natural configuration at C-7, along with recovered **8a,** in a 2:1 ratio.