(determined by GC) of 2-nonyl-5-(trifluoromethyl)furan and the starting material. A sample was purified by GC: ^{1}H NMR δ 0.6–2.0 n, 17 H, C_8H_{17}), 2.65 (t, 2 H, CH_2, J = 7 Hz), 6.0 (d, 1 H, H_3, $J_{3,4}$ = 4 Hz), 6.7 (m, 1 H, H_4); high-resolution mass spectrum, m/e 262.1543 (M^+; $C_{14}H_{21}F_3O$ requires 262.1542).

Similarly, 2-nonylthiophene (500 mg, 2.4 mmol) was trifluoromethylated for 26 h to afford after chromatography (hexane) 340 mg of a 70:25:5 mixture (determined by GC) of 2-nonyl-5-(trifluoromethyl)thiophene, starting material, and 3(4),5-bis-(trifluoromethyl)-2-nonylthiophene. A sample was purified by GC: ^{1}H NMR δ 0.6–2.0 (m, 17 H, C_8H_{17}), 2.82 (t, 2 H, CH_2, J = 7 Hz), 6.75 (m, 1 H, H_3), 7.25 (m, 1 H, H_4); high-resolution mass spectrum, m/e 278.1280 (M^+; ($C_{14}H_{21}F_3S$ requires 278.1245); ditrifluoromethylated derivative, high-resolution mass spectrum, m/e 346.1163 (M^+; $C_{15}H_{20}F_6S$ requires 346.1137).

Acknowledgment. We thank Mr. S. C. Ho and Mr. J. Ryan for the gas chromatographic analyses in the Montreal laboratories and Dr. H. J. Ramjit and Mr. R. Rhodes for the high-resolution mass spectra, which were run in the West Point laboratories.

Registry No. **4a**, 62541-43-9; **4b**, 62541-38-2; **4c**, 62541-40-6; **4d**, 62541-39-3; **4e**, 69624-13-1; **4f**, 62541-37-1; **4g**, 62541-42-8; **4h**, 86307-67-7; **4i**, 69624-14-2; **4j**, 86288-45-1; **4k**, 62541-68-8; **4l**, 62541-64-4; **4m**, 62541-56-4; **4n**, 62541-57-5; **4o**, 62541-55-3; **4p**, 86288-46-2; **4q**, 62541-58-6; **4r**, 86288-47-3; **4s**, 86288-48-4; **4t**, 86288-49-5; **4u**, 86288-50-8; **4v**, 62541-52-0; **4w**, 62541-51-9; **4x**, 86288-51-9; **4y**, 86288-52-0; **4z**, 86288-53-1; **4aa**, 62541-41-7; **4bb**, 62541-53-1; **4cc**, 62541-54-2; **4dd**, 86307-68-8; **4ee**, 62541-45-1; **4ff**, 62541-46-2; **4gg**, 62541-47-3; **4hh**, 62541-50-8; **4ii**, 62541-49-5; **4jj**, 62541-69-9; **4kk**, 86288-54-2; **4ll**, 69624-15-3; **4mm**, 69624-17-5; **4nn**, 86288-55-3; **4oo**, 62541-65-5; **6.1a**, 73259-61-7; **6.1b**, 66491-00-7; **6.1c**, 86307-69-9; **6.1d**, 86288-56-4; **6.1e**, 86288-57-5; **6.1g**, 86288-58-6; **6.1h**, 72791-94-7; **6.1i**, 86288-59-7; **6.1j**, 86288-60-0; **6.1k**, 86288-61-1; **6.2a**, 62541-29-1; **6.2b**, 66491-01-8; **6.2c**, 62569-72-6; **6.2d**, 86288-62-2; **6.2e**, 69624-08-4; **6.2f**, 62541-35-9; **6.2g**, 62541-32-6; **6.2i**, 69624-09-5; **6.2j**, 86288-63-3; **6.2k**, 86288-64-4; **6.3a**, 86288-65-5; **6.3b**, 66491-02-9; **6.3c**, 86288-66-6; **6.3d**, 86288-67-7; **6.3e**, 86288-68-8; **6.3f**, 62541-36-0; **6.3g**, 86288-69-9; **6.3i**, 86288-70-2; **6.3j**, 86288-71-3; **6.3k**, 86288-72-4; **11b**, 62541-66-6; **11c**·HCl, 62541-62-2; **12b**, 62541-67-7; **12c**, 62541-63-3; **14**, 86288-73-5; **19**, 86288-74-6; **19** methyl ester, 86288-75-7; **22**, 86288-76-8; CF_3I, 2314-97-8; 2-carbomethoxypyrrole, 1193-62-0; 2-carbomethoxy-4-cyanopyrrole, 937-18-8; 2-carbomethoxy-4-chloropyrrole, 1194-96-3; 2-carbomethoxy-4-bromopyrrole, 934-05-4; 2-carbomethoxy-4-nitropyrrole, 13138-74-4; 2-carbomethoxy-3,4,5-tribromopyrrole, 1198-67-0; phenethyl bromide, 103-63-9; phenethyl tosylate, 4455-09-8; 2-*p*-tolylethylamine, 3261-62-9; *p*-(methylthio)phenethyl mesylate, 86288-77-9; *p*-phthalimidophenethyl mesylate, 86288-78-0; methyl 2,5-dimethoxytetrahydrofuran-2-carboxylate, 39658-49-6; *N*-*trans*-styrylpyrrole-2-carboxylic acid, 34600-57-2; β-phenethyl isothiocyanate, 2257-09-2; 1-thio-3,4-dihydroisocarbostyryl, 6552-60-9; 3,4-dihydroisocarbostyryl, 1196-38-9; 7-nitro-3,4-dihydroisocarbostyryl, 22245-96-1; 2,7-dinitro-3,4-dihydroisocarbostyryl, 86288-79-1; 2,5-dimethoxytetrahydrofuran, 696-59-3; 7-amino-3,4-dihydroisocarbostyryl, 66491-03-0; 7-iodo-3,4-dihydroisocarbostyryl, 66491-04-1; valeryl chloride, 638-29-9; dimethylsulfamoyl chloride, 13360-57-1; thiocyanogen, 505-14-6; 2-thiocyanato-6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepin-11-one, 86288-80-4; 3-thiocyanato-6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepin-11-one, 86288-81-5; 2-(methylthio)-6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]-benzazepin-11-one, 86288-82-6; 3-(methylthio)-6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepin-11-one, 86288-83-7; trifluoromethanesulfenyl chloride, 421-17-0; 2-(chlorocarbonyl)-6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepin-11-one, 62541-48-4; *N*-benzylpyrrole, 2051-97-0; *N*-benzyl-2,5-bis(trifluoromethyl)pyrrole, 86288-84-8; *N*-benzyl-2-(trifluoromethyl)pyrrole, 86288-85-9; *N*-*p*-tolylpyrrole, 827-60-1; *N*-*p*-tolyl-2-(trifluoromethyl)pyrrole, 86288-86-0; *N*-(trimethylsilyl)indole, 17983-42-5; 2-(trifluoromethyl)indole, 51310-54-4; 3-(trifluoromethyl)indole, 51310-55-5; 2-nonylfuran, 68532-53-6; 2-nonyl-5-(trifluoromethyl)furan, 86288-87-1; 2-nonylthiophene, 57754-07-1; 2-nonyl-5-(trifluoromethyl)thiophene, 86288-88-2; bis(trifluoromethyl)-2-nonylthiophene, 86307-66-6.

Synthesis of 2-, 3-, and 9-Substituted 11-Oxo-11*H*-pyrrolo[2,1-*b*][3]benzazepines

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Syntheses of nuclear-substituted 11-oxo-11*H*-pyrrolo[2,1-*b*][3]benzazepines by three reaction sequences are described. The first and most successful route involves an internal Friedel–Craft cycliacylation of substituted *N*-(*Z*)-styrylpyrrole-2-carboxylic acids, the latter obtained via photoisomerization of the easily prepared *E* acids. The second path has as its key steps the cyclization of the acid chlorides of substituted *N*-(α,β-dichlorophenethyl)pyrrole-2-carboxylic acids followed by a chromous chloride reduction to generate the 5,6-double bond. Another route, employed with only limited success, involves cyclization of the acid chlorides of substituted *N*-(β-chlorophenethyl)pyrrole-2-carboxylic acids, followed by base-catalyzed elimination of HCl to form the 5,6-double bond. These substituted ketones are representatives of a novel tricyclic system and have been used for further elaboration into agents having muscle relaxant and other biological activities.

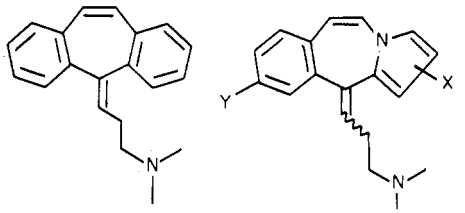
Introduction

The successful introduction[1,2] of cyclobenzaprine (1; 3-(5*H*-dibenzo[*a*,*d*]cyclohepten-5-ylidene)-*N*,*N*-dimethyl-1-propylamine) as a therapeutically useful skeletal muscle relaxant has stimulated efforts in these laboratories to discover novel structures with improved clinical efficacy. With use of the 5*H*-dibenzo[*a*,*d*]cycloheptene system as a lead, one of the target molecules selected was that in which one of the benzene rings of 1 was replaced by a pyrrole nucleus, affording the novel tricyclic system, pyrrolo[2,1-*b*][3]benzazepin-11-one 4 in which the pyrrole nitrogen is located at a bridgehead position. It was decided

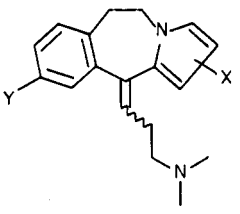
(1) Share, N. N.; McFarlane, C. S. *Neuropharmacology* **1975**, *14*, 675.
(2) De Lee, J. C.; Rockwood, C. A. *Curr. Ther. Res.* **1980**, *27*, 64.

0022-3263/83/1948-3234$01.50/0

to develop syntheses of both the fully unsaturated ketone **4** as well as of the 5,6-dihydro structure, **5**, with the ultimate objective being to prepare substituted derivatives of the general structures **2** and **3**, which possess the amine side chains essential for the desired pharmacologic effects. No fully unsaturated structures based on this ring system have yet been reported, although several partially saturated derivatives of this system appeared in the literature.[3-6] In

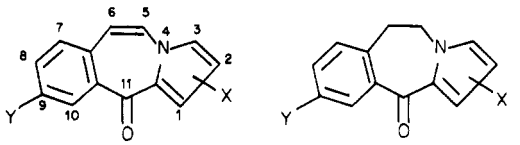


1 **2**



3

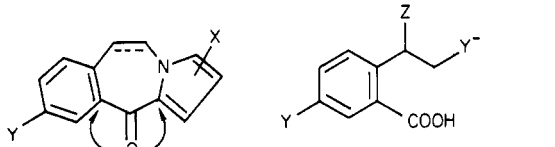
this paper there is described the chemistry leading to the synthesis of the ketones **4**. The preparation of the dihydro analogues **5**, the conversion of **4** and **5** to the cyclobenzaprine type analogues **2** and **3**, and their biological activities will be the subject of future papers.[15]



4 **5**

Retrosynthetic Strategy

For the synthesis of the parent as well as of nuclear-substituted 11-oxo-11*H*-pyrrolo[2,1-*b*][3]benzazepines **4**, several approaches were considered, all of which involved an internal Friedel–Crafts cycliacylation to form the seven-membered ring. This cyclization could proceed in either of two directions, path a or path b.



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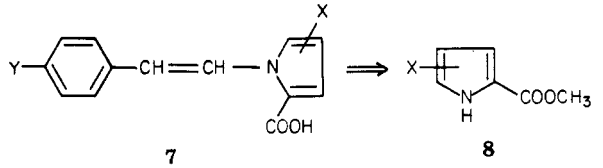
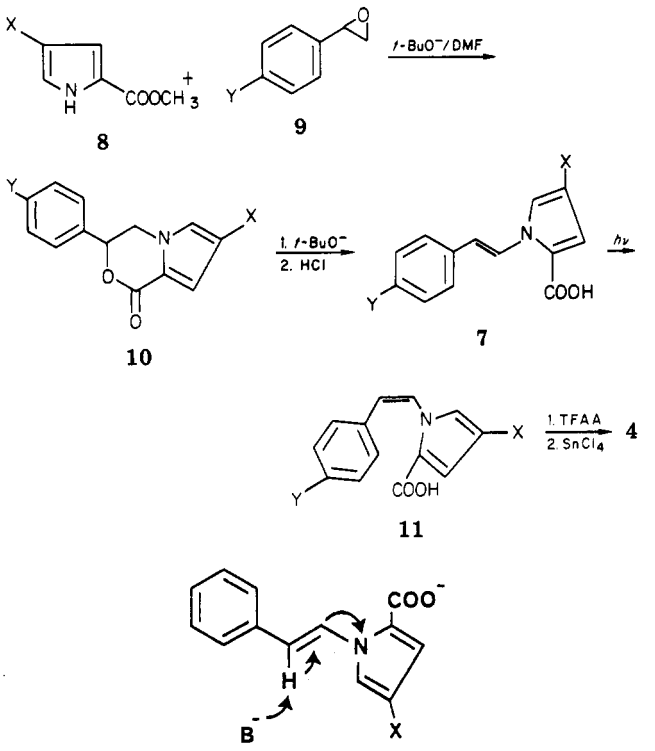


7 **8**

Path a requires an intermediate of type **6** wherein substituent Y′ can be readily converted to a pyrrole nucleus and substituent Z can be removed to afford the necessary double bond. Alternatively, cyclization b, toward the phenyl ring, appeared to be the method of choice. This route implies that *N*-styrylpyrrole carboxylic acids of type **7** are suitable intermediates for cyclization. Moreover, compounds of the type **7**, as well as their pyrrole precursors **8**, can be readily prepared by routes developed by Rokach et al.[7] and Bélanger,[8] respectively. The cycliacylation of **7**, or a saturated phenethyl analogue thereof, is a reasonable prospect provided that the substituent Y is not too deactivating at the meta position of the phenyl ring.

Scheme I



8 **9** **10** **7** **11**

Figure 1.

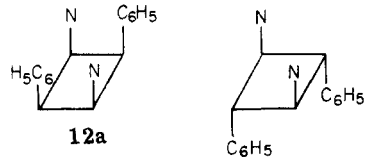
Results and Discussion

A. The most successful and generally applicable approach to ketones of the type **4** involved as the key step the photoisomerization of the *N*-(*E*)-styrylpyrrole-2-carboxylic acids **7** to the *Z* acids **11** (Scheme I). The *E* acids were prepared by reaction of a para-substituted styrene oxide with a 4-substituted pyrrole-2-carboxylate (**8**) in DMF at 100 °C in the presence of a catalytic amount of potassium *tert*-butoxide, a procedure that gave lactone **10** in excellent yield. When lactones **10** were treated with 1 equiv of potassium *tert*-butoxide, the *N*-(*E*)-styrylpyrrole-2-carboxylic acids **7** were obtained in very high yields after acidification. The ring opening is extremely rapid at room temperature. This two-step sequence to **7** is often superior to the one-step reaction previously reported by Rokach et al.[7] inasmuch as the latter reaction may often lead to poor recovery of product. The 4-substituted pyrrole-2-carboxylic acids, which are major contaminants of the one-step procedure, result from prolonged heating in the presence of strong base when the pyrrole ring has electron-withdrawing substituents in the 4-position. As a possible mechanism for this side reaction we suggest the removal of the benzylic proton from **7**, followed

(3) Huisgen, R.; Laschtuvka, E. *Chem. Ber.* **1960**, *93*, 65.
(4) Weinreb, S. M.; Averbach, J. *J. Am. Chem. Soc.* **1975**, *97*, 2503.
(5) Semmelhack, M. F.; Chong, B. P.; Stauffer, R. D.; Rogerson, T. D.; Chong, A.; Jones, L. D. *J. Am. Chem. Soc.* **1975**, *97*, 2507.
(6) Weinstein, B.; Craig, A. R. *J. Org. Chem.* **1976**, *41*, 875.
(7) Rokach, J.; Girard, Y.; Atkinson, J. G. *Can. J. Chem.* **1973**, *51*, 3765.
(8) Bélanger, P. *Tetrahedron Lett.* **1979**, 2505.

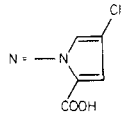
by the departure of the pyrrole anion (Figure 1). The phenylacetylene byproduct, however, could not be isolated, probably because of its instability under the reaction conditions.

The photochemical step could be carried out equally well either in dilute alcohol solution or in a more concentrated MeCN–Et_3N solution. When performed in a MeCN suspension without Et_3N, extensive dimerization occurred. The dimer, a very insoluble, high-melting solid has been characterized by its NMR absorption at 4.90 ppm (t, J = 9 Hz) and at 6.43 ppm n(t, J = 9 Hz) assigned to cyclobutane protons. On the basis of this coupling constant and on the symmetry of these two absorptions, the structure is thought to be either **12a** or **12b**, with **12b** as the more likely possibility on the basis of analogy with the photodimerization of cinnamic acid in solution.[9]



12a

12b

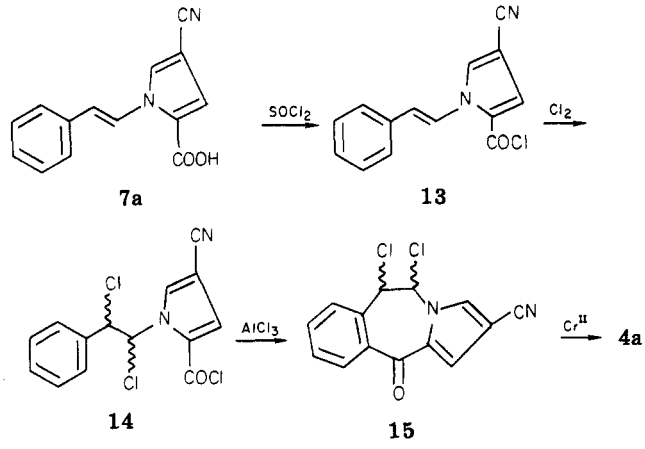


The photoisomerization that afforded good yields of **11** was easily monitored by NMR inasmuch as the coupling constants of the vinyl protons of the E-isomers **7** are 16 Hz but are only 9–10 Hz for the Z-isomers **11**. Also, on isomerization, the vinyl proton adjacent to the phenyl ring, at 8.4 ppm, is shifted upfield by about 1 ppm. The Z isomer was cyclized to the unsaturated tricyclic ketone **4** in good yield, using, sequentially, trifluoroacetic anhydride and stannic chloride in CH_2Cl_2 according to the method of Weinstein and Craig.[6] The cyclization of the corresponding acid chloride, catalyzed by the aluminum chloride, also worked equally well. Both entropic and electronic factors may be invoked to explain the facile cyclization observed in this series. The relative importance of either effect cannot be established with the data available.

This route to **4** is the one of choice and is general for N-styryl derivatives substituted either on the pyrrole or the benzene nucleus, provided the benzene ring is not deactivated.

B. Prior to the development of the method outlined in Scheme I, several other routes to **4** were examined, all of which involved path b type cycliacylations (vide supra). In these sequences the 5,6-double bond of **4** would, of necessity, be introduced after ring formation. For example, in principle, 11-oxo-5,6-dihydro-11H-pyrrolo[2,1-b][3]-benzazepines, **5**,[10] could be subjected to reagents known to be effective at introducing unsaturation into molecules. Attempted dehydrogenation of **5** (X = Y = H) with a variety of such reagents resulted in either extensive decomposition or no reaction at all.[11]

Scheme II



Scheme II describes an alternate approach in which an N-styrylpyrrolecarboxylic acid, **7a**, is a key intermediate. This approach, previously utilized in the corresponding dibenzo series,[12] makes use of 1,2-disubstituted phenethyl groups to provide access to the eventual 5,6-double bond. The conversion of E-acid **7a** to the acid chloride **13** was carried out with thionyl chloride or dichloromethyl methyl ether.[13] The crude acid chloride was treated at once with chlorine gas and the product, dichloro acid chloride **14**, was purified by rapid chromatography on silica gel. Cyclization of **14** with $AlCl_3$ afforded the dichloroketone **15**, from which the unsaturated ketone **4a** was obtained by a chromous ion reduction at the 5,6-position. The overall yield of this sequence was 25% from **8** (X = CN) and the styrene oxide **9** (Y = H). A limitation of this approach is that a deactivating substituent must be present in the pyrrole ring to avoid ring chlorination.

The first successful synthesis of a substituted 11-oxo-11H-pyrrolo[2,1-b]3]benzazepine was accomplished through the sequence outlined in Scheme III. The key step in this sequence involves an intermediate in which the benzyl position is substituted by a functional group capable of being converted to the requisite 5,6-double bond via a base-catalyzed elimination. Reaction of methyl 4-cyanopyrrole-2-carboxylate **8** (X = CN) with phenacyl bromide in DMF at 100 °C, using K_2CO_3 as base, gave an 85% yield of methyl N-phenacyl-4-cyanopyrrole-2-carboxylate (**16a**). The ester function was readily saponified to the corresponding sodium salt **17** (X = CN, Y = H), which was then reduced to the corresponding carbinol **18** (X = CN, Y = H) by sodium borohydride in ethanol. This salt, **18** (X = CN, Y = H), was converted to the chlorophenethyl acid chloride **20** (X = CN, Y = H) by way of the lactone **10a** in refluxing PCl_3–$POCl_3$. NMR and TLC evidence showed the formation of intermediate lactone **10a** from **18** (X = CN, Y = H) to be rapid. That **10a** is indeed an intermediate in the conversion has been confirmed by subjecting authentic lactone **10a** to these reaction conditions. Pure **10a** reacted slowly with refluxing PCl_5–$POCl_3$ to form **20** (X = CN, Y = H) with a reaction half-life of about 1 h at 110 °C. The $t_{1/2}$ for disappearance of **18** (X = CN, Y = H) is approximately 5 min at room temperature. Quenching the reaction of PCl_3–$POCl_3$ and **18** (X = CN, Y = H) after 30 min at room temperature led to a 78% yield of lactone **10a**.

Subsequently it was discovered that lactone **10a** could be prepared directly from **16a** by sodium borohydride

(9) Mustafa, A. *Chem. Rev.* **1952**, *51* 1.

(10) Girard, Y.; Atkinson, J. G.; Belanger, P. C.; Fuentes, J. J.; Rokach, J.; Rooney, C. S.; Remy, D. C.; Hunt, C. A., preceding paper in this issue.

(11) Palladium on charcoal in cymene, sulfur at 210 °C, or dichlorodicyanoquinone (DDQ) in cymene lead to no dehydrogenation. Starting material was recovered. Cerium nitrate in acetic acid, *tert*-amyl nitrite with either sodium ethoxide in EtOH or potassium *tert*-butoxide in DMF, selenium dioxide, chromium trioxide, tritylantimony hexafluoride, or lithium diisopropylamide, and DDQ gave mostly decomposition products. The use of NBS or bromine with irradiation gave low yields (less than 10%) of desired products.

(12) Slates, H. L.; Wendler, N. L. U.S. Patent 3 297 763; *Chem. Abstr.* **1967**, *66*, 65337.

(13) Ottenheijm, H. C. J.; De Man, H. H. M. *Synthesis* **1975**, 163.

Scheme III

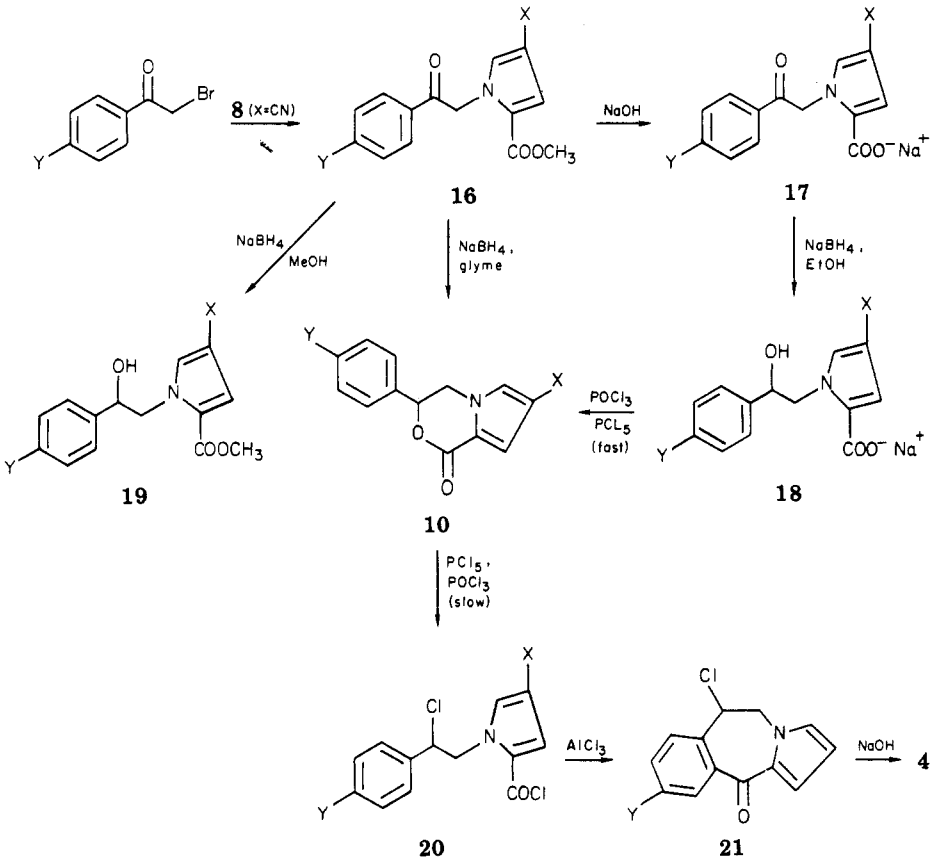
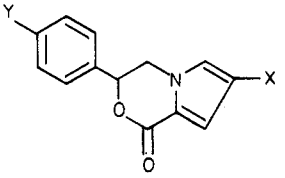


Table I. Substituted 3,4-Dihydro-1-oxo-3-phenyl-1*H*-pyrrolo[1,2-c]morpholine



compd	X	Y	mp, °C	% yield
10a	CN	H	183-184	88
10b	H	H	119-120	81
10c	Cl	H	150-151	83
10d	SCF_3	H	96-97	90
10e	3,4,5-Br_3	H	196-197	73
10f	H	Cl	113-114	77
10g	H	Br	153-154	73
10h	CN	Cl	200-201	81

reduction in glyme, thus obviating the need for separate saponification, reduction, and lactonization steps.

When the Friedel–Crafts cyclization of **20** (X = CN, Y = H) was carried out in tetrachloroethane at 140 °C for 3 min with aluminum chloride as catalyst (Huisgen's conditions[3]), extensive decomposition was observed. However, treatment of the crude reaction mixture with base followed by silica gel chromatography afforded a 6% yield of 2-cyano-11-oxo-11*H*-pyrrolo[2,1-*b*][3]benzazepine (**4a**). The Friedel–Crafts cyclization reaction gave rise to mixtures of the desired ketones **4** as well as to the precursors **21** in which elimination had not occurred. It was necessary, therefore, to treat the reaction mixture with base to complete the elimination. The low yield of this cyclization–elimination reaction is probably due to the inherent instability of intermediate **20** in the presence of $AlCl_3$ at high temperature.

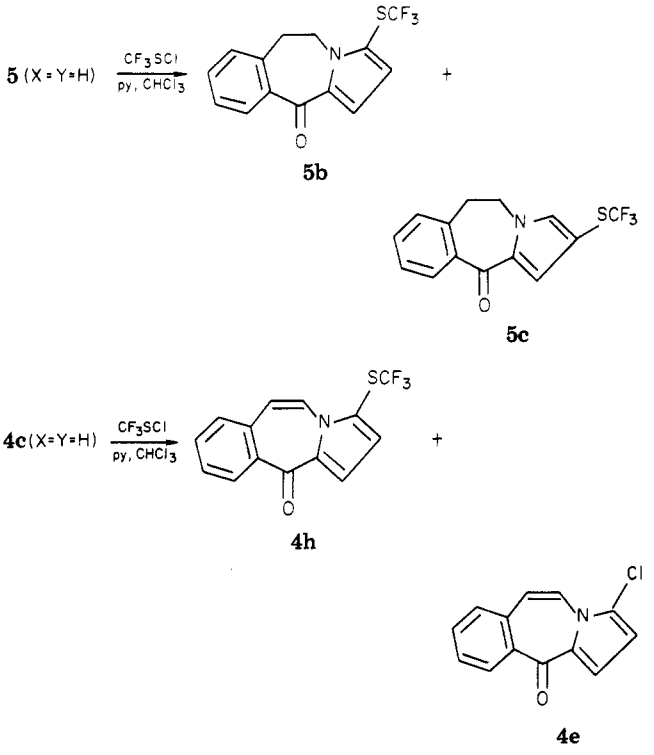
Electrophilic Substitution Reactions with 4 and Substituent Modifications. When **4c** was allowed to react with trifluoromethanesulfenyl chloride in a 1:1 mixture of pyridine–$CHCl_3$ at 50 °C for 2 h, only 3-substitution was observed, **4h** and **4e** being produced in a 3:1 ratio. This is in marked contrast with the behavior of the 5,6-dihydro analogue **5** (X = Y = H), which gave, under identical conditions, a 2:1 mixture of **5** (X = 2-SCF_3, Y = H) and **5** (X = 3-SCF_3, Y = H), respectively.[10] Thus it appears that in the 5,6-dehydro ketones **4** only the 3-position is reactive toward electrophiles, the double bond having a net deactivating effect toward position 2.

Reaction of **4j** with bis[(trifluoromethyl)thio]mercury and copper in HMPA permitted replacement of the 9-bromo substituent with a 9-(trifluoromethyl)thio group (**4i**). Likewise, reaction of **4j** with cuprous cyanide gave the 9-cyano derivative **4b**, which was hydrolyzed to the 9-carboxy derivative **4k**.

NMR Data for 4. A prominent feature in the NMR spectra of the tricyclic ketones **4** is the AB system for the two bridgehead protons located around 6.2 ppm for H_6 and around 7.2 ppm for H_5 with a coupling constant of 10 Hz.

Another characteristic of these ketones is the chemical shift of H_{10} located around 8.4 ppm. This deshielding effect, having a magnitude of about 1 ppm, is due to the position of H_{10} in the plane of the carbonyl. This effect results in an absorption that approximates a doublet of doublets with coupling constants of 9 and 2 Hz for ortho and meta coupling.

The position of the pyrrole protons are also characteristic and are easily assigned except for proton H_1, which normally is not observed, being deshielded considerably to a range where several other absorptions occur. The presence of substituents in position 2 gives rise to a doublet with a coupling constant of 2 Hz for H_3, normally located around 6.8 ppm. Substitutions at position 3 give rise to



a pattern where H_2 appears around 6.3 ppm as a doublet with a larger coupling constant of J_{AB} = 4 Hz.

Conclusion

Three synthetic routes are described that have permitted the preparation of both the parent ring system, as well as of nuclear-substituted derivatives, in the 11-oxo-11*H*-pyrrolo[2,1-*b*][3]benzazepine series. All three procedures are dependent on an internal Friedel–Craft cycliacylation step involving a carboxyl attached to the 2-position of a pyrrole ring and a benzene ring component of the pyrrole N-substituent. In the preferred procedure an *N*-(*Z*)-styrylpyrrole-2-carboxylic acid, available by photochemical isomerization of the readily available *E* acid, is utilized as the penultimate intermediate.

Experimental Section

Melting points were taken on a Thomas Hoover apparatus in open capillary tubes and are uncorrected. Ultraviolet spectra were determined with a 1-cm quartz cell in a Cary Model 11 spectrophotometer (95% EtOH solutions). Infrared spectra were recorded on a Perkin-Elmer 267 grating spectrophotometer. NMR spectral data were obtained on a Varian EM-360 or a Varian T-60 spectrometer in deuteriochloromorm unless indicated otherwise, using as internal standard tetramethylsilane (Me_4Si) for proton and fluorotrichloromethane for fluorine. Elemental analyses were performed by Dr. C. Daelllé, Montreal, by Galbraith Laboratories Inc., Knoxville, TN, and by Mr. K. B. Streeter and Associates in our West Point Laboratories.

***N*-(*E*)-Styryl-4-cyanopyrrole-2-carboxylic Acid (7a).** Following the procedure of Rokach et al.,[7] condensation of styrene oxide (36 g, 0.30 mol) and methyl 4-cyanopyrrole-2-carboxylate (8, X = CN; 48 g, 0.32 mol) yielded 68 g (96%) of compound **7a**: mp 191–194 °C dec; IR (KBr) 2235 (CN); 1690 cm^{-1} (COOH); NMR δ 6.67 (d, 1 H, J = 14 Hz, styryl proton), 7.30 (m, 6 H, aromatic protons and one pyrrole proton), 7.67 (d, 1 H, J = 2 Hz, pyrrole proton H_5), 8.27 (d, 1 H, J = 14 Hz, styryl proton).

Anal. Calcd for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.75. Found: C, 70.34; H, 4.14; N, 11.67.

General Procedure for the Preparation of Ketones 4a according to Scheme I. 7-Cyano-3,4-dihydro-1-oxo-3-phenyl-1*H*-pyrrolo[1,2-*c*]morpholine (10a). A mixture of methyl 4-cyanopyrrole-2-carboxylate (8, X = CN; Y = H; 1.5 g, 10 mmol), styrene oxide **9** (Y = H; 1.5 g, 12.5 mmol), and potassium *tert*-butoxide (115 mg, 1 mmol) in 15 mL of DMF was heated at 100 °C for 18 h. The mixture was poured into H_2O and the crystalline solid was removed by filtration, washed with H_2O, and air-dried to yield 2.1 g of crude **10a**: mp 176–178 °C. Recrystallization from MeOH raised the melting point to 184 °C: IR (KBr) 2235 (CN), 1730 (C=O) cm^{-1}; NMR δ 4.52 (m, 2 H, CH_2), 5.93 (m, 1 H, CH), 7.47 (s, 6 H, aromatic and pyrrole H_5), 7.93 (d, J = 2 Hz, 1 H, pyrrole H_3).

Anal. Calcd for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.51; H, 4.23; N, 11.64.

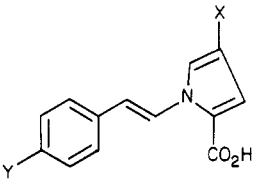
The analogues **10b–h**, which were prepared by this route, are listed in Table I.

***N*-(*E*)-Styryl-4-cyanopyrrole-2-carboxylic Acid (7a).** To lactone **10a** (278 mg, 1 mmol) in 1 mL of DMF was added at room temperature potassium *tert*-butoxide (125 mg, 1.1 mmol). After stirring 15 min, the mixture was poured into H_2O and acidified with 6 N HCl. The solid was filtered, washed with H_2O, and air-dried to yield 267 mg (96%) of **7a**, mp 192–194 °C, after recrystallization from MeOH. It was identical with the acid obtained previously by the method of Rokach et al.[7]

The *E*-acids **7b–i**, which were also prepared by one of these two methods, are listed in Table II.

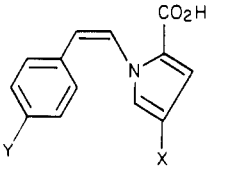
***N*-(4-Bromo-(*Z*)-styryl)pyrrole-2-carboxylic Acid (11e).** A 0.025 M solution of *N*-(4-bromo-(*E*)-styryl)pyrrole-2-carboxylic acid (**7h**; 25.6 g, 0.088 mol) in 95% EtOH (350 mL) was irradiated under nitrogen with a 450-W Hanovia lamp through a Vycor filter. Progress of the photoisomerization was monitored by NMR or UV, and when the reaction had progressed to at least 80% completion (4–5 h), the solution was concentrated in vacuo to a slurry of approximately $^1/_{20}$ original volume. After cooling in an ice bath the suspension was filtered, affording 20.2 g (78%) of crude **11e**, mp 166–172 °C, suitable for the subsequent cyclization. An analytical sample was prepared by recrystallization from MeOH: mp 189–190 °C; IR (KBr) 1655 (CO) cm^{-1}; NMR δ 6.07–6.23 (m,

Table II. Substituted *N*-(*E*)-Styrylpyrrole-2-carboxylic Acids



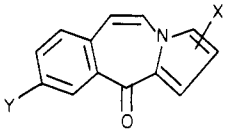
compd	X	Y	mp, °C	% yield
7a	CN	H	192–194	96
7b	H	H	183–184	84
7c	Cl	H	168–170	87
7d	SCF_3	H	191–193	88
7e	3,4,5-Br_3	H	199–201	96
7f	Br	H	150–152	79
7g	H	Cl	193–195	87
7h	H	Br	198–199	98
7i	CN	Cl	225–227	79

Table III. Substituted *N*-(*Z*)-Styrylpyrrole-2-carboxylic Acids



compd	X	Y	mp, °C	% yield
11a	CN	H	193–195	94
11b	H	H	124–125	83
11c	Cl	H	161–163	79
11d	SCF_3	H	96–98	98
11e	H	Br	189–190	78
11f	CN	Cl	193–196	86
11g	H	Cl	178–179	96

Table IV. Substituted 11-Oxo-5*H*-pyrrolo[2,1-*b*][3]benzazepine



compd	X	Y	mp, °C	% yield
4a	2-CN	H	190-191	67
4b[a]	H	9-CN	237-241	100
4c	H	H	113-114	75
4d	2-Cl	H	139-141	63
4e[b]	3-Cl	H	108-110	28
4f	H	9-Cl	188-190	70
4g	2-SCF_3	H	147-148	61
4h[b]	3-SCF_3	H	137-138	47
4i[c]	H	9-SCF_3	158-159	82
4j	H	9-Br	210-214	60
4k[d]	H	9-COOH	340-344	86
4l	2-CN	9-Cl	303-307	67

[a] Prepared from 4j. [b] Prepared from 4c. [c] Prepared from 4j. [d] Prepared from 4b.

1 H, pyrrole), 6.39 (d, 1 H, J = 9 Hz, *cis*-vinyl), 6.66–7.60 (m, 6 H, pyrrole, phenyl), 7.22 (d, 1 H, J = 9 Hz, *cis*-vinyl), 12.40 (s, 1 H, COOH).

Anal. Calcd for $C_{13}H_{10}BrNO_2$: C, 53.44; H, 3.45; N, 4.80; Br, 27.35. Found: C, 53.21; H, 3.37; N, 4.73; Br, 27.18.

Using the above procedure, the *Z*-acids **11b–g** listed in Table III were prepared.

9-Bromo-11-oxo-11*H*-pyrrolo[2,1-*b*][3]benzazepine (4j). A suspension of 10.0 g (0.034 mol) of the *Z*-acid **11e** in 100 mL of dry CH_2Cl_2 was stirred under a nitrogen atmosphere at 0 °C while being treated with 9.6 mL (0.068 mol) of trifluoroacetic anhydride. After 3 min the resulting solution was treated dropwise with 12.0 mL (0.1 mol) of dry stannic chloride and the mixture was then allowed to come to 20–25 °C over several hours. The solution was poured into a mixture of 400 mL each of $CHCl_3$ and H_2O, and the resulting emulsion was filtered through Celite. After several washes of the filter cake with $CHCl_3$, the combined filtrates were separated, and the $CHCl_3$ phase was washed successively with H_2O and dilute aqueous NH_4Cl solution. The $CHCl_3$ solution was concentrated in vacuo to a volume of about 50 mL and was subsequently chromatographed over silica gel, eluting with $CHCl_3$. The pale yellow product fractions were combined and evaporated to give 5.6 g (60%) of **4j** as a bright yellow solid, TLC homomgeneous ($CHCl_3$), mp 211–214 °C dec. One recrystallization from EtOAc gave pure **4j**: mp 210–214 °C dec; IR (KBr) 1660 (C=O), 1585, 1540 cm^{-1}; NMR (Me_2SO-d_6) δ 6.56 (d, 1 H, J = 10 Hz, H_5), 6.80 (t, 1, J = 4 Hz, H_2 pyrrole), 7.53–8.10 (m, 5 H, H_1, H_3, H_6, H_7, H_8), 8.56 (d, 1 H, J = 2 Hz, H_{10}).

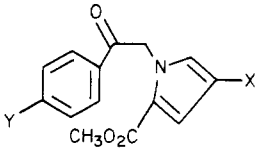
Anal. Calcd for $C_{13}H_8BrNO$: C, 56.96; H, 2.94; Br, 29.15; N, 5.10. Found: C, 56.99; H, 3.16; Br, 28.99; N, 4.82.

The tricyclic ketones **4f** and **4g** were prepared by using the above procedure and are listed in Table IV.

2-Cyano-11-oxo-11*H*-pyrrolo[2,1-*b*][3]benzazepine (4a). To *N*-(*Z*)-styryl-4-cyanopyrrole-2-carboxylic acid (**11a**; 29 g, 0.1 mol) in CH_2Cl_2 (200 mL) was added dichloromethyl methyl ether (25 mL). Reflux was maintained until all acid had dissolved. The dark brown solution was evaporated to dryness to yield a dark oil corresponding to the acid chloride by IR. Without further characterization, the oil was dissolved in CH_2Cl_2 (200 mL). The solution was cooled to 0 °C by an ice bath and $AlCl_3$ (20 g, 0.15 mol) was added in small portions. After stirring for 30 min, the mixture was poured on ice, extracted three times with $CHCl_3$, washed with H_2O, and dried ($MgSO_4$). The residue was adsorbed on silica gel (1 kg) and was eluted with benzene/EtOAc (1:1, v/v) to afford 17.1 g (67%) of **4a**: mp 190–191 °C; IR (KBr) 2220, 1670 (C=O) cm^{-1}; NMR δ 6.37 (d, 1 H, J = 10 Hz, H_5), 7.13 (d, 1 H, J = 10 Hz, H_6), 7.60 (m, 5 H, pyrrole and aromatic protons), 8.50 (m, 1 H, H_{10}).

Anal. Calcd for $C_{14}H_8N_2O$: C, 74.99; H, 3.87; N, 13.45. Found: C, 74.88; H, 3.82; N, 13.39.

Table V. Substituted Methyl *N*-Phenacylpyrrole-2-carboxylates



compd	X	Y	mp, °C	% yield
16a	CN	H	172-173	84
16b	H	H	105-106	73
16c	Cl	H	130-131	86
16d	SCF_3	H	121-122	84
16e	3,4,5-Br_3	H	199-200	93
16f	H	Cl	135-136	70
16g	H	Br	147-148	75
16h	CN	Cl	170-171	80

The tricyclic ketones **4c**, **4d**, **4f**, and **4l** were prepared by using the above procedure and are listed in Table IV.

Preparation of 4a Using the Procedure of Scheme II. *N*-(*E*)-Styryl-4-cyano-2-(chlorocarbonyl)pyrrole (13). A mixture of *N*-((*E*)-styryl)-4-cyanopyrrole-2-carboxylic acid (**7a**; 12 g, 50 mmol) suspended in thionyl chloride (20 mL) was refluxed until dissolution occurred. The excess thionyl chloride was removed under vacuum and the residue was dissolved in 20% Et_2O/hexane (50 mL). The solution was placed in the refrigerator for several hours. Filtration afforded 11.6 g (91%) of acid chloride **13**: mp 116–118 °C; IR (KBr) 2235 (CN), 1750 (CO) cm^{-1}; NMR δ 6.77 (d, 1 H, J = 14 Hz, vinyl proton), 7.37 (s, 5 H, aromatic protonse, 7.57 (s, 1 H, pyrrole proton, H_5), 7.77 (s, 1 H, pyrrole proton, H_3), 7.93 (d, 1 H, J = 14 Hz, vinyl proton).

Anal. Calcd for $C_{14}H_9N_2OCl$: C, 65.51; H, 3.53; N, 10.91; Cl, 13.81. Found: C, 65.27; H, 3.33; N, 10.67; Cl, 14.04.

***N*-(1,2-Dichlorophenethyl)-4-cyano-2-(chlorocarbonyl)-pyrrole (14).** *N*-(*E*)-Styryl-4-cyano-2-(chlorocarbonyl)pyrrole (**13**; 11.6 g, 0.455 mol) was dissolved in $CHCl_3$ (100 mL) and chlorine was bubbled through the solution. The reaction was monitored by NMR. The volatiles were removed under vacuum, yielding 14.6 g (98%) of compound **14** as a yellow oil, homogeneous by TLC: IR (film) 2240, 1730, 1745 (C=O) cm^{-1}; NMR δ 5.27 (d, 1 H, J = 4 Hz, CHCl β to nitrogen), 7.10 (d, 1 H, J = 4 Hz, CHCl α to nitrogen), 7.33 (s, 5 H, aromatic protons), 7.47 (d, 1 H, J = 2 Hz, pyrrole proton H_5), 7.93 (d, 1 H, J = 2 Hz, pyrrole proton H_3).

This intermediate was used as such for the next step.

2-Cyano-5,6-dichloro-11-oxo-5,6-dihydro-11*H*-pyrrolo[2,1-*b*][3]benzazepine (15). To *N*-(1,2-dichlorophenethyl)-4-cyano-2-(chlorocarbonyl)pyrrole (**14**; 3.3 g, 10 mmol) in refluxing dichloroethane (50 mL) was added rapidly $AlCl_3$ (5 g, 3.75 mmol). The mixture was refluxed for 5 min and then was poured on ice. After extraction with $CHCl_3$, the organic layer was washed with H_2O, dried (Na_2SO_4), and concentrated under vacuum. The residue was adsorbed on a column of 300 g of silica gel and eluted with a mixture of benzene/EtOAc (1:1) to yield 1.77 g (60%) of **15**: mp 237–238 °C; IR (KBr) 2230 (CN), 1632 (C=O) cm^{-1}; NMR δ 5.87 (d, 1 H, J = 5 Hz, CHCl β to nitrogen), 7.20 (d, 1 H, J = 5 Hz, CHCl α to nitrogen), 7.70 (m, 6 H, aromatic protons), 8.23 (m, 1 H, H_{10}).

Anal. Calcd for $C_{14}H_8Cl_2N_2O$: C, 57.76; H, 2.77; Cl, 24.36; N, 9.62. Found: C, 57.44; H, 2.51; Cl, 24.76; N, 9.80.

2-Cyano-11-oxo-11*H*-pyrrolo[2,1-*b*][3]benzazepine (4a). Chromium (1.5 g, 28.8 mmol) was dissolved in a mixture of H_2O (30 mL) and concentrated HCl (10 mL) under nitrogen. To the dark blue solution of chromous chloride was added 2-cyano-5,6-dichloro-11-oxo-5,6-dihydro-11*H*-pyrrolo[2,1-*b*][3]benzazepine (**15**; 4.2 g, 14.4 mmol) dissolved in acetone (50 mL). The reaction temperature was maintained at 80 °C. The reaction was over at the end of the addition. The solid was filtered, washed well with H_2O, and air-dried to give 2.3 g (70%) of **4a**, mp 190–191 °C, identical with the sample prepared according to Scheme I.

General Procedure for the Preparation of Ketones 4 according to Scheme III. Methyl *N*-Phenacyl-4-cyanopyrrole-2-carboxylate (16a) (Table V). Phenacyl bromide (2.7

g, 13.6 mmol) was added to a mixture of methyl 4-cyanopyrrole-2-carboxylate (2.0 g, 13.3 mmol) and K_2CO_3 (2.7 g) in DMF (15 mL). After stirring at room temperature for 30 min, the reaction mixture was poured into H_2O. The solid was filtered, washed with H_2O, and air-dried to yield crude **16a**, which, after recrystallization from MeOH, had mp 169–172 °C; IR (KBr) 2230 (CN), 1720 (COO), 1695 (CO) cm^{-1}; NMR δ 3.70 (s, 3 H, methoxy), 5.73 (s, 2 H, methylene protons), 7.20 (s, 2 H, pyrrole H_3 and H_5), 7.53 (m, 3 H, meta and para aromatic protons), 7.93 (m, 2 H, ortho aromatic protons).

Anal. Calcd for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.51; N, 10.44. Found: C, 66.97; H, 4.55; N, 10.28.

7-Cyano-3,4-dihydro-1-oxo-3-phenyl-1*H*-pyrrolo[1,2-*c*]morpholine (10a). Sodium borohydride (0.4 g, 10 mmol) was added to methyl *N*-phenacyl-4-cyanopyrrole-2-carboxylate (**16a**; 2.7 g, 10 mmol) in anhydrous dimethoxyethane (15 mL). The reaction mixture was stirred at room temperature for 30 min. It was then poured into H_2O and extracted with Et_2O. The organic layer was washed with H_2O, dried (Na_2SO_4), and concentrated in vacuo. The residue was triturated in 50 mL of Et_2O and **10a** (0.62 g, 26%) was obtained on filtration. Recrystallization from MeOH gave mp 183–184 °C. Compound **10a** was found to be identical with the material prepared from the condensation of **8** (X = CN, Y = H) with styrene oxide **9** (Y = H) in the presence of a catalytic amount of potassium *tert*-butoxide (Scheme I). Alternatively, the morpholines **10** may be prepared from **16** via **17** and **18** as described below.

Sodium *N*-Phenacyl-4-cyanopyrrole-2-carboxylate (17, X = CN, Y = H). Methyl *N*-phenacyl-4-cyanopyrrole-2-carboxylate (**16a**; 5.3 g, 20 mmol) and NaOH (0.8 g, 20 mmol) in EtOH (15 mL) were stirred at reflux for 30 min. The salt **17** (X = CN, Y = H; 4.7 g, 87%), which crystallized out, was filtered, washed with cold EtOH, and air-dried: IR (KBr) 2225 (CN), 1700 (CO), 1570 (COO^-) cm^{-1}; NMR (D_2O + TSP) δ 5.73 (s, 2 H, CH_2CO, almost completely exchanged by D_2O), 7.03 (d, 1 H, J = 2 Hz, pyrrole H_5), 7.33 (d, 1 H, J = 2 Hz, pyrrole H_3), 7.60 (m, 3 H, meta and para aromatic protons), 7.93 (m, 2 H, ortho aromatic protons).

Anal. Calcd for $C_{14}H_9N_2O_3Na$: C, 60.87; H, 3.28; N, 10.14. Found: C, 60.53; H, 3.52; N, 10.00.

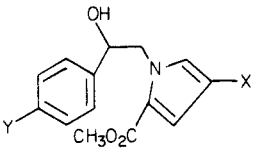
Sodium *N*-(2-Hydroxyphenethyl)-4-cyanopyrrole-2-carboxylate (18, X = CN, Y = H). To sodium *N*-phenacyl-4-cyanopyrrole-2-carboxylate (**17**, X = CN, Y = H; 2.76 g, 10 mmol) in H_2O (5 mL) and EtOH (5 mL) was added $NaBH_4$ (0.2 g, 5 5 mmol). Stirring at room temperature was maintained for 15 min. The mixture was evaporated to dryness and the residue was taken up in EtOH. The insolubles were filtered, washed with Et_2O, and air-dried to yield 2.76 g (100%) of sodium salt **18** (X = CN, Y = H): IR (KBr) 2225 (CN), 1590 (COO^-) cm^{-1}; NMR (D_2O + TSP) δ 4.47 (m, 2 H, CH_2), 5.00 (m, 1 H, J = 5 Hz, CHO), 6.93 (d, 1 H, pyrrole H_5, J = 2 Hz), 7.17 (d, 1 H, J = 2 Hz, pyrrole H_3), 7.30 (s, 5 H, aromatic protons).

This material was used directly for the next step.

7-Cyano-3,4-dihydro-1-oxo-3-phenyl-1*H*-pyrrolo[1,2-*c*]morpholine (10a). A mixture of sodium *N*-(2-hydroxyphenethyl)-4-cyanopyrrole-2-carboxylate (**18**; 270 mg, 1 mmol) and PCl_5 (0.5 g, 2.4 mmol) in $POCl_3$ (3 mL) was stirred at room temperature for 30 min. The reaction mixture was poured into ice, stirred for 10 min, and extracted with $CHCl_3$. The organic layer was washed with H_2O, dried (Na_2SO_4), and concentrated in vacuo. The residue, taken up in MeOH, yielded 196 mg (78%) of lactone **10a**, mp 181–183 °C, found to be identical with the material prepared from the condensation of **8** (X = CN, Y = H) with styrene oxide **9** (Y = H) in the presence of a catalytic amount of potassium *tert*-butoxide (Scheme I).

***N*-(2-Chlorophenethyl)-4-cyano-2-(chlorocarbonyl)pyrrole (20, X = CN, Y = H).** A mixture of sodium *N*-(2-hydroxyphenethyl)-4-cyanopyrrole-2-carboxylate (**18**, X = CN, Y = H; 2.96 g, 11 mmol) and PCl_5 (5 g, 24 mmol) in $POCl_3$ (20 mL) was stirred at reflux for 18 h. The volatiles were removed under vacuum, and the residue was extracted with CH_2Cl_2 (3 × 30 mL). The extracts were filtered rapidly through a short silica gel column to yield 2.4 g (75%) of acid chloride **20** (X = CN, Y = H; 2.4 g, 75%): mp 115–116 °C; IR (KBr) 1745 (C=O), 2225 (CN) cm^{-1}; NMR δ 4.45 (m, 2 H, CH_2), 5.13 (t, 1 H, CHCl, J = 5 Hz), 6.93 (d, 1 H, pyrrole H_5, J = 2 Hz), 7.23 (d, 1 H, J = 2 Hz, pyrrole H_3), 7.37 (s, 5 H, aromatic protons).

Table VI. Substituted Methyl *N*-1-Phenethylpyrrole-2-carboxylates



compd	X	Y	mp, °C	% yield
19a	CN	H	121–122	77
19b	H	H	74–75	72
19c	H	Br	99–100	70
19d	H	Cl	104–105	70
19e	CN	Cl	144–146	97

Anal. Calcd for $C_{14}H_{10}N_2OCl_2$: C, 57.36; H, 3.44; N, 9.56; Cl, 24.19. Found: C, 56.98; H, 3.19; N, 9.38; Cl, 24.41.

2-Cyano-11-oxo-11*H*-pyrrolo[2,1-*b*][3]benzazepine (4a). To *N*-(2-chlorophenethyl)-4-cyano-2-chlorocarbonyl pyrrole (**20**, X = CN, Y = H; 0.54 g, 1.85 mmol) in CCl_4 (3 mL) was added $AlCl_3$ (1 g, 7.5 mmol). After heating in an oil bath at 140 °C for 3 min, the mixture was poured onto ice, extracted three times with CH_2Cl_2, washed with H_2O, and dried (Na_2SO_4). On evaporation, a mixture of **4a** and 2-cyano-11-oxo-6-chloro-5,6-dihydro-11*H*-pyrrolo[2,1-*b*][3]benzazepine (**21**; X = CN, Y = H; 292 mg) was recovered. This mixture was treated with an ethanolic sodium hydroxide solution (30 mL, 1 N) for 30 min at room temperature. The volatiles were evaporated under vacuum. H_2O (20 mL) was added and the mixture was extracted with CH_2Cl_2, washed with H_2O, and dried (Na_2SO_4). Preparative TLC, using as eluent benzene–EtOAc (3:1, v/v), yielded 24 mg of pure **4a**, mp 190–191 °C, identical with the material prepared according to Scheme I.

Methyl *N*-(2-Hydroxyphenethyl)-4-cyanopyrrole-2-carboxylate (19a) (Table VI). To methyl *N*-phenacyl-4-cyanopyrrole-2-carboxylate (100 mg, 0.37 mmol) in MeOH (5 mL) was added $NaBH_4$ (40 mg, 1.06 mmol). After being stirred at room temperature for 15 min, the mixture was poured into H_2O and extracted with EtOAc. The extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo to give **19a** as a crystalline solid: mp 121–122 °C (from MeOH); IR (KBr) 3480 (OH), 2240 (CN), 1710 (COO) cm^{-1}; NMR δ 3.83 (s, 3 H,), 4.20 (d of d, 1 H, J = 8, 14 Hz), 4.77 (d of d, 1 H, J = 4, 14 Hz), 5.00 (d of d, 1 H, J = 4, 8 Hz), 7.17 (d, 1 H, J = 2 Hz, pyrrole H_5), 7.27 (d, 1 H, 2 Hz, pyrrole H_3), 7.37 (s, 5 H, aromatic protons).

Anal. Calcd for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.22; N, 10.36. Found: C, 66.82; H, 5.34; N, 9.97.

Nuclear Substitution Reactions of Ketones 4. 9-[(Trifluoromethyl)thio]-11-oxo-11*H*-pyrrolo[2,1-*b*][3]benzazepine (4i). A mixture of 9-bromo-11-oxo-5*H*-pyrrolo[2,1-*b*][3]benzazepine (**4j**; 8.0 g 0.029 mol), bis[(trifluomethyl)thio]mercury[14] (35.0 g, 0.087 mol), Cu (electrolytic dust; 17.9 g, 0.281 mol), and HMPA (75 mL) was stirred under nitrogen at 150 °C for 2 h. The reaction was cooled in an ice bath prior to treatment with Et_2O (100 mL) and 3% NaOH (75 mL). After stirring for 1 h, the mixture was filtered through Celite, the filtrate was separated, and the product was extracted into Et_2O by the standard procedure. The Et_2O phase was dried ($MgSO_4$) and filtered, and the solvent was evaporated. Trituration of the sticky brown residue from the Et_2O solution with EtOH gave 7.0 g (82%) of **4i**, mp 155–159 °C, TLC homogeneous (C_6H_6). An analytical sample was obtained by recrystallization from MeCN: mp 158–159 °C; ^{19}F NMR δ 41.3 (SCF_3).

Anal. Calcd for $C_{14}H_8F_3NOS$: C, 56.95; H, 2.73; F, 19.30; N, 4.74; S, 10.86. Found: C, 56.78; H, 2.59; F, 19.28; N, 4.51; S, 11.07.

(14) Remy, D. C.; Rittle, K. E.; Hunt, C. A.; Freedman, M. B. *J. Org. Chem.* **1976**, *41*, 1644.

(15) **Note Added in Proof**: The utilization of a number of these ketones for certain medicinal chemical purposes has now been described: (a) Remy, D. C.; Britcher, S. F.; Anderson, P. S.; Bélanger, P. C.; Girard, Y.; Clineschmidt, B. V. *J. Med. Chem.* **1982**, *25*, 231. (b) Remy, D. C.; Britcher, S. F.; King, S. W.; Anderson, P. S.; Hunt, C. A.; Randall, W. C.; Bélanger, P.; Atkinson, J. G.; Girard, Y.; Rooney, C. S.; Fuentes, J. J.; Totaro, J. A.; Robinson, J. L.; Risely, E. A.; Williams, M. *Ibid.* **1983**, *26*, 974.

9-Cyano-11-oxo-11*H*-pyrrolo[2,1-*b*][3]benzazepine (4b). A mixture of 9-bromo-11-oxo-11*H*-pyrrolo[2,1-*b*][3]benzazepine (**4j**; 5.0 g, 0.018 mol), CuCN (3.2 g, 0.036 mol), and dry DMF (25 mL) was stirred at reflux for 3 h, cooled to 35 °C, and then treated with CH_2Cl_2 (50 mL), H_2O (100 mL), and NaCN (2 g). After stirring at ambient temperature for 4 h, the layers were separated, and the product was isolated by means of a CH_2Cl_2 extraction. The crude orange solid, 4.0 g (100%), mp 237–241 °C dec, was triturated with hot EtOAc to produce analytically pure **4b**: mp 239–242 °C dec; IR (Nujol) 2222 (CN) cm^{-1}.

Anal. Calcd for $C_{14}H_8N_2O$: C, 76,35; H, 3.66; N, 12.72. Found: C, 76.15; H, 3.66; N, 12.90.

3-Chloro- and 3-[(Trifluoromethyl)thio]-11-oxo-11*H*-pyrrolo[2,1-*b*][3]benzazepine (4e and 4h). To a solution of 11-oxo-11*H*-pyrrolo[2,1-*b*][3]benzazepine (**4c**; 2.5 g, 12.8 mmol) in $CHCl_3$ (50 mL) and pyridine (10 mL) was added a $CHCl_3$ solution containing trifluoromethanesulfenyl chloride (5 g, 36.6 mmol). The resulting mixture was heated at 50 °C for 24 h. It was then poured into H_2O and the organic phase was separated. The aqueous phase was further extracted twice with CH_2Cl_2. The organic fractions were combined, washed with H_2O, dried (Na_2SO_4), and concentrated in vacuo to give a residue, which was chromatographed on a silica gel column. Elution with Et_2O–hexane (1:1) gave 3-[(trifluoromethyl)thio]-11-oxo-11*H*-pyrrolo-[2,1-*b*][3]benzazepine (**4h**): mp 137–138 °C; IR (KBr) 1665, 1610, 1590, 1140 cm^{-1}; NMR δ 6.30 (d, 1 H, J = 10 Hz, H_6), 6.93 (d, 1 H, J = 4 Hz, H_2), 7.30–7.50 (m, 4 H, H_6, H_7, H_8, H_1), 7.73 (d, 1 H, J = 10 Hz, H_5), 8.43 (m, 1 H, H_{10}).

Anal. Calcd for $C_{14}H_8F_3NOS$: C, 56.94; H, 2.73; N, 4.87; S, 10.86; F, 18.95. Found: C, 56.48; H, 2.70; N, 4.87; S, 11.04; F, 19.44.

A second fraction gave 3-chloro-11-oxo-11*H*-pyrrolo[2,1-*b*]-[3]benzazepine (**4e**; 0.9 g): mp 108–110 °C; IR (KBr) 1660, 1610, 1585 cm^{-1}; NMR δ 6.18 (d, 1 H, J = 10 Hz, H_6), 6.43 (d, 1 H, J = 4 Hz, H_2), 7.1–7.4 (m, 4 H, H_7, H_8, H_9, H_1), 8.43 (m, 1 H, H_{10}).

Anal. Calcd for $C_{13}H_8ClNO$: C, 67.99; H, 3.51; N, 6.10; Cl, 15.44. Found: C, 68.13; H, 3.53; N, 5.98; Cl, 15.58.

9-Carboxy-11-oxo-11*H*-pyrrolo[2,1-*b*][3]benzazepine (4k). A solution of 2.0 g (0.009 mol) of nitrile **4b** in a mixture comprised of 24 mL of H_2O (24 mL), 95% EtOH (12 mL), and KOH (6 g) was refluxed for 2 h and poured into 300 mL of H_2O. The aqueous solution was extracted with a 1:1 mixture of Et_2O/EtOAc and then carefully acidified with glacial HOAc. The bright yellow solid that precipitated was collected and washed with H_2O to give 1.8 g (86%) of **4k**, mp 328–344 °C dec. An analytical sample was obtained by recrystallization from MeCN: mp 340–344 °C dec; IR (KBr) 1610 (ketone CO), 1660–1690 (br, acid CO) cm^{-1}; neutralization equivalent calcd 239.2, found 245.1 (+2.5%); mass spectrum, m/e 239 (M^+), 222 (M^+ – OH).

Anal. Calcd for $C_{14}H_9NO_4$: C, 70.29; H, 3.79; N, 5.86. Found: C, 69.52; H, 3.89; N, 5.55.

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Registry No. **4a**, 62541-73-5; **4b**, 65561-06-0; **4c**, 62541-74-6; **4d**, 86288-89-3; **4e**, 86288-90-6; **4f**, 69624-21-1; **4g**, 70539-01-4; **4h**, 65561-30-0; **4i**, 69624-22-2; **4j**, 62541-75-7; **4k**, 65606-24-8; **4l**, 69624-23-3; **5** (X = Y = H), 62541-43-9; **7a**, 65561-21-9; **7b**, 34600-57-2; **7c**, 86288-91-7; **7d**, 86288-92-8; **7e**, 86288-93-9; **7f**, 86288-94-0; **7g**, 86288-95-1; **7h**, 86288-96-2; **7i**, 86288-97-3; **8** (X = CN), 937-18-8; **8** (X = H), 1193-62-0; **8** (X = Cl), 1194-96-3; **8** (X = SCF_3), 62541-34-8; **8** (X = 3,4,5-Br_3), 1198-67-0; **8** (X = Br), 934-05-4; **9** (X = H), 96-09-3; **9** (X = Cl), 2788-86-5; **9** (X = Br), 32017-76-8; **10a**, 65561-26-4; **10b**, 35566-71-3; **10c**, 86288-98-4; **10d**, 86288-99-5; **10e**, 86289-00-1; **10f**, 86289-01-2; **10g**, 86289-02-3; **10h**, 86289-03-4; **11a**, 65561-22-0; **11a** acid chloride, 86289-04-5; **11b**, 34600-56-1; **11b** acid chloride, 86289-05-6; **11c**, 86289-06-7; **11c** acid chloride, 86289-07-8; **11d**, 86289-08-9; **11e**, 69624-19-7; **11f**, 69624-20-0; **11f** acid chloride, 86307-70-2; **11g**, 69624-18-6; **11g** acid chloride, 86289-09-0; **13**, 65561-23-1; **14**, 65561-24-2; **15**, 62541-78-0; **16a**, 62541-79-1; **16b**, 86289-10-3; **16c**, 86289-11-4; **16d**, 86289-12-5; **16e**, 86289-13-6; **16f**, 86289-14-7; **16g**, 86289-15-8; **16h**, 86307-71-3; **17** (X = CN; Y = H), 86289-16-9; **18** (X = CN; Y = H), 86289-17-0; **19a**, 86289-18-1; **19b**, 35566-72-4; **19c**, 86289-19-2; **19d**, 86289-20-5; **19e**, 86289-21-6; **20** (X = CN; Y = H), 62541-80-4; **21** (X = CN; Y = H), 86289-22-7; phenacyl bromide, 70-11-1; *p*-chlorophenacyl bromide, 536-38-9; *p*-bromophenacyl bromide, 99-73-0; trifluoromethanesulfenyl chloride, 421-17-0.

Supplementary Material Available: IR, NMR, and elemental analysis data for compounds **16**, **7**, **11**, **4**, **10**, and **19** (6 pages). Ordering information is given on any current masthead page.