Cycloaddition Reactions of an *o*-Quinoid 10-π-Electron System, 2*H*-Pyrrolo[3,4-*c*]pyridine

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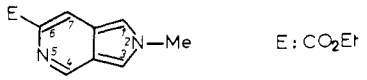
The cycloaddition reactions of ethyl 2-methyl-2*H*-pyrrolo[3,4-*c*]pyridine-6-carboxylate (1) with electron-deficient dienophiles have been investigated. While the reaction with an equimolar amount of diethyl acetylenedicarboxylate gives the 1:1 adduct **7** at room temperature, the 1:2 adducts **8a** and **8b** are obtained in equal amounts with an excess of dienophile. The stereochemistry of these 1:2 adducts is described. The reaction with *N*-phenylmaleimide is either endo or exo selective, depending on the reaction conditions. The competitive formation of the endo and exo isomers at 40 °C was measured by ^{1}H NMR. The kinetics of the endo–exo conversion at 40 °C indicate an external pathway for the isomerization.

Cycloadditions of dienophiles to the *o*-quinoid 10-π-electron isoindole system have been reported,[1] but little work has been done with the analogous pyrrolo[*c*]pyridines. 2-Methyl-2*H*-pyrrolo[3,4-*c*]pyridine has been prepared and shown to be a more stable ring system than the isoindoles.[2] This increased stability was attributed to resonance involving the pyridine nitrogen and to electron withdrawal by that nitrogen, which should make the pyrrole ring less susceptible to electrophilic attack—the probable cause of isoindole instability. Cycloaddition of dimethyl acetylenedicarboxylate (DMAC) to 2-methyl-2*H*-pyrrolo[3,4-*c*]pyridine has been reported to involve both the pyridine and pyrrole rings, giving the 1:3 adduct **6** in 9% yield.[3]

We have reported the preparation of ethyl 2-methyl-2*H*-pyrrolo[3,4-*c*]pyridine-6-carboxylate (1).[4] Its stability



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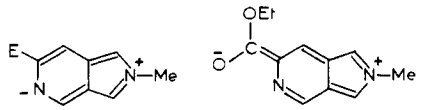
is comparable to that of 2-methyl-2*H*-pyrrolo[3,4-*c*]-pyridine and thus is more stable than 2-methylisoindole. We here report studies of the cycloadditions of the dienophiles diethyl acetylenedicarboxylate (DEAC) and *N*-phenylmaleimide (NPM) to **1**. We wished to compare the



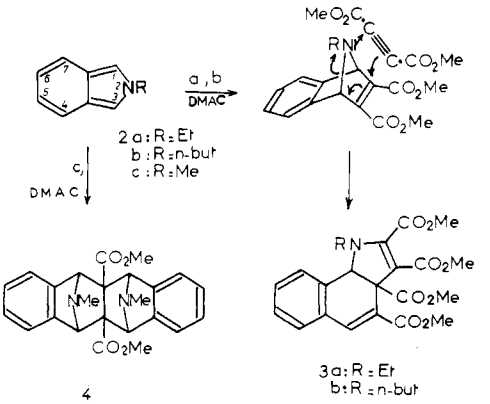
1a 1b

diene character of this *o*-quinoid system with the isoindoles and to investigate the participation of the substituted pyridine ring in these reactions.

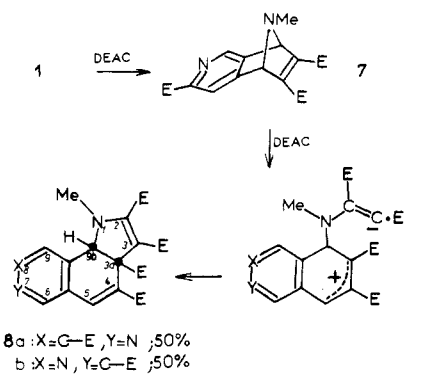
Results and Discussion

Cycloaddition Reactions of 1 with DEAC. Cycloadditions of DMAC to N-substituted isoindoles have been reported. *N*-Ethyl- and *N*-*n*-butylisoindoles (**2a,b**) gave the 1:2 adducts **3a** and **3b** (Scheme I); the intermediate 1:1 adducts were not isolated.[5] On the other hand, *N*-methylisoindole (**2c**) gave the 2:1 adduct **4**.[6]

Scheme I



Scheme II



In the pyrrolo[*c*]pyridine series one can expect more complex reactions because 2-substituted pyridines are known to undergo cycloadditions with acetylenic diesters.[7] The orientation of such additions depends on the nature of the substituent; with an ester group, only a poor yield of trimethyl indolizine-1,2,3-tricarboxylate (**5**) is obtained.[8]

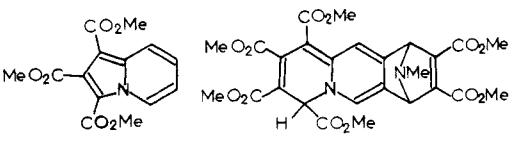


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Table I[a]

	formation of 7: k_1	formation of 8a and 8b: k_2
rate constants for second-order reaction (L mol^{-1} min^{-1}; temp 20 °C)	(6.0 ± 0.5)10^{-2}	(2.9 ± 0.2)10^{-4}

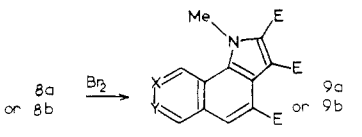
[a] Required conditions: [reagent] = [DEAC] = 0.4 mol L^{-1} (by ^{1}H NMR); solvent $CDCl_3$.

We have found that 1 reacts with DEAC at room temperature to give a quantitative yield of the 1:1 adduct 7 (Scheme II), the structure of which was determined from its ^{1}H NMR spectrum. Treatment of 7 with an excess of DEAC gave the isomeric 1:2 adducts **8a** and **8b** in equal amounts. However, heating a solution of **8a** and **8b** with more DEAC did not bring about cycloaddition to the pyridine ring. The isolation of the 1:1 adduct 7 shows that the pyridine ring stabilizes the bridged ring system, contrary to what has been observed in analogous benzene compounds.[5] The stability of 7 is indicated by comparison of its rate of formation with the rate of its reaction with DEAC (Table I).

The formation of 7 and of the 1:2 adducts **8a** and **8b** can be explained by analogy with the mechanism proposed by Kricka and Vernon for pyrroles[1b] and shown to be valid for the isoindoles.[5] The reaction involves a two-step mechanism via a zwitterionic intermediate (Scheme I). The isolation of **8a** and **8b** in equal amounts shows that the ring opening of 7 is not regioselective. We have established the structures of **8a** and **8b** by assigning their aromatic ^{1}H NMR peaks on the basis of the internal nuclear Overhauser effect (NOE). Saturation of the angular proton H_{9b} in **8a** and **8b** results in enhancements of 14% and 16%, respectively, of the signals of the neighboring aromatic protons H_9. The differences in the chemical shifts of these H_9 protons enabled us to identify the two isomers **8a** and **8b** unambiguously.

Cyclization of each zwitterionic intermediate can give two geometrical isomers, the ring junction being either cis or trans. Dreiding models of the cis and trans structures show that the angular ester group is not obstructed by the ester groups at the adjacent 3- and 4-positions. However, only the less rigid cis junction permits the proximity of the H_9 and H_{9b} protons that is indicated by the NOE. Moreover, each of **8a** and **8b** gives only a single spot by TLC. We therefore believe that only the cis isomer of each compound is formed.

Treatment of **8a** and **8b** with bromine converts them into the pyrroloisoquinolines **9a** and **9b** by loss of the



bridgehead ester group and hydrogen. The ^{1}H NMR spectra of these compounds show two pyridine proton signals at δ 9.20 and 9.40 for **9a** and at δ 8.70 and 10.09 for **9b**. The differences in these chemical shifts in each compound are attributed to deshielding of the H_9 protons by the *N*-methyl group; such an interaction is shown by Dreiding models.

Cycloaddition Reactions of 1 with NPM. We have investigated the kinetics of the reaction of 1 with NPM, a less reactive dienophile than DEAC. The rates of formation of the endo and exo adducts were sufficiently different that we were able to study the mechanism of the endo–exo isomerization.

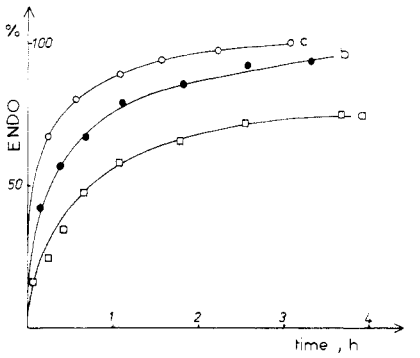
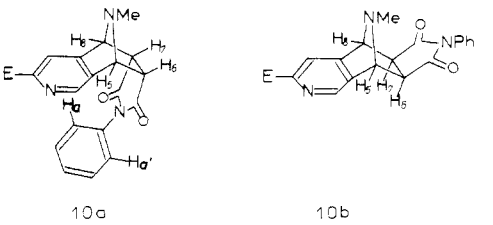


Figure 1. Formation of the endo isomer by using different [NPM]/[1] ratios: a, 1/1; b, 2/1; c, 3/1. These reactions were continued until the exo isomer appeared. Conditions: [1] = 0.39 mol L^{-1} at t = 0 min, solvent $CDCl_3$, temperature 20 °C.

There are two possible pathways for this cycloaddition reaction which depend on the interactions that affect the rigidity of the transition state, giving either endo (**10a**) or exo (**10b**) isomers. We have isolated both of these isomers.



10a 10b

We found that formation of the endo isomer was favored by short reaction times or low temperatures. However, selection of reaction conditions makes it possible to direct the reaction quantitatively to either isomer. Thus, when the reaction is carried out at 20 °C with a 3:1 ratio of NPM/1, the endo isomer was formed exclusively, as determined by ^{1}H NMR in $CDCl_3$ (Figure 1). On the other hand, only the exo isomer was formed when the reaction was run at 120 °C in xylene. Although the endo isomer is favored kinetically, longer reaction times or higher temperatures favor formation of the thermodynamically more stable exo isomer.[9]

The structures of the two stereoisomers were assigned on the basis of their ^{1}H NMR spectra. In the spectrum of the endo adduct **10a**, two aromatic protons appear far upfield as a broad band centered at δ 6.41, a spectral feature that has been observed in analogous compounds.[10] This chemical shift is attributed to the fact that both the protons H_a and $H_{a'}$ can come within the shielding zone of the pyridine ring because of rotation of the phenyl ring. The assigned stereochemistry of these isomers is confirmed by the coupling constants for H_7–H_8 and H_5–H_6. Both H_6 and H_7 in the exo adduct **10b** resonate as sharp singlets, whereas the corresponding protons in the endo adduct **10a** are broadened to AA′XX′ multiplets. Dreiding models indicate that the dihedral angles between H_5 and H_6 and between H_7 and H_8 in **10b** are close to 90° whereas these angles in **10a** are about 30°.

Endo–Exo Isomerization. Since the formation of the endo and exo configurations was quite stereoselective, it

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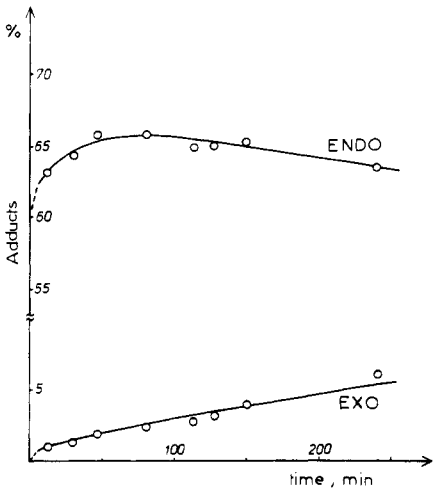

Figure 2. Formation of the endo and exo isomers **10a** and **10b**. Conditions: [1] = [NPM] = 0.5 mol L^{-1} at t = 0 min, solvent $CDCl_3$, temperature 40 °C.

was of interest to study the interconversion of these isomers. Two mechanisms have been proposed for the endo–exo isomerization:[11] (a) a mechanism that includes a retrodiene reaction with subsequent recombination of the kinetically free diene and dienophile, the external pathway, and (b) an intramolecular mechanism without the participation of kinetically free dissociation products, the internal pathway. Several methods,[12] particularly kinetic studies,[13] have been used to investigate this type of isomerization.

We followed the rates of formation of **10a** and **10b** from 1 by ^1H NMR at 40 °C, a temperature at which the relative concentrations of the two isomers could be followed easily. If the mechanism involves the external pathway, the formation of the endo and exo adducts should be competitive (see Figure 2), and the slopes d[endo]/dt and d[exo]/dt should have their highest values when the concentration of the addend is highest, i.e., at the beginning of the reaction. If the mechanism involves the internal pathway, d[endo]/dt should have its highest value at the beginning of the reaction, but d[exo]/dt should increase gradually and reach its highest value at a time corresponding to the maximum concentration of the endo adduct. Moreover, in a study of the decomposition of **10a** at 40 °C, the initial reaction was formation of 1 (Figure 3), and **10b** began to appear later. These data indicate an external pathway for this endo–exo isomerization at 40 °C.

Experimental Section

Melting points were measured with a Kofler hot-stage apparatus and were uncorrected. A Beckman IR 4250 spectrophotometer was used to obtain IR spectra in potassium bromide disks for solids. ^1H NMR spectra were taken with a Varian A-60 spectrometer with $(Me)_4Si$ as an internal standard; chemical shifts are expressed in δ values. Microanalyses were performed with a Technicon elemental analyzer. Mass spectra were measured with a JEOL B-100 (75 eV, 300 mA) spectrometer. Thin-layer chromatography (TLC) was performed on silica gel plates (Nano-Plates, SIL-20 UV_{254} Macherey-Nagel, 5 × 5 cm) with $CHCl_3$ as solvent.

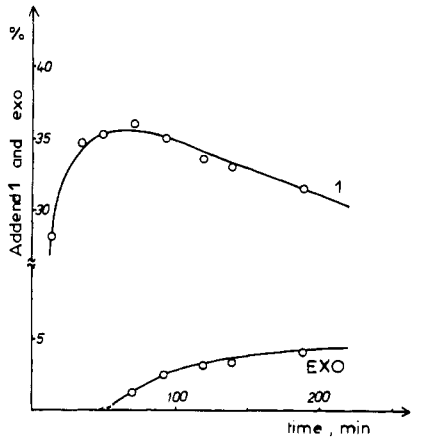

Figure 3. Decomposition of the endo isomer **10a**. Conditions: [**10a**] = 0.5 mol L^{-1} at t = 0 min, solvent $CDCl_3$, temperature 40 °C.

Ethyl 2-Methyl-2*H*-pyrrolo[3,4-*c*]pyridine-6-carboxylate (1). 1-Methyl-1*H*-pyrrole-3,4-dicarboxaldehyde[4] (0.27 g, 2 mmol), freshly prepared ethyl aminoacetate (0.31 g, 3 mmol) in ethanol (30 mL), and 3 drops of diethylamine were heated under reflux for 2 h. The solvent was removed under reduced pressure at room temperature. Sublimation of the crude product at 160 °C (1 mmHg) afforded compound 1: 0.27 g (67%); mp 111 °C; IR (KBr) 1700 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) 1.41 (t, 3, J = 7 Hz, CH_2CH_3), 4.01 (s, 3, NCH_3), 4.45 (q, 2, J = 7 Hz, CH_2CH_3), 7.21 (m, 1, aromatic), 7.30 (m, 1, aromatic), 8.32 (m, 1, H-7), 9.01 (m, 1, H-4).

Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.2; H, 5.7; N, 13.3.

Triethyl 5,8-Dihydro-9-methyl-5,8-epiiminoisoquinoline-3,6,7-tricarboxylate (7). A solution of DEAC (0.34 g, 2 mmol) and 1 (0.408 g, 2 mmol) in chloroform (15 mL) was stirred at room temperature for 12 h under a nitrogen atmosphere. Evaporation of the solvent gave a colored oil which was converted by column chromatography (neutral alumina, eluted with diethyl ether) to a colorless oil, a 1/1 adduct (7; 0.51 g, 68%). This attempted purification failed to produce an analytically pure sample: ^1H NMR ($CDCl_3$) 1.31 (t, 6, J = 7 Hz, 2 CH_2CH_3), 1.45 (t, 3, J = 7 Hz, CH_2CH_3), 4.26 (q, 4, J = 7 Hz, 2 CH_2CH_3), 4.48 (q, 2, J = 7 Hz, CH_2CH_3), 5.02 (s, 2, H_5 and H_8), 2.32 (s, 3, NCH_3), 8.16 (s, 1, H_4), 8.70 (s, 1, H_1).

Pentaethyl 3a,9b-Dihydro-1-methyl-1*H*-pyrrolo[2,3-*f*]-isoquinoline-2,3,3a,4,8-pentacarboxylate (8a) and Pentaethyl 3a,9b-Dihydro-1-methyl-1*H*-pyrrolo[3,2-*h*]isoquinoline-2,3,3a,4,7-pentacarboxylate (8b). Method A. From 1. Ethyl 2-methyl-2*H*-pyrrolo[3,4-*c*]pyridine-6-carboxylate (1; 0.512 g, 2.5 mmol) and DEAC (1.275 g, 7.5 mmol) were refluxed in xylene (30 mL) for 90 min. Evaporation of the solvent afforded a brown oil which was chromatographed [neutral alumina (5 g) eluted with the following: (1) petroleum ether (bp 45–60 °C), 0.5 L; (2) diethyl ether, 2 L]. Fraction 2 was evaporated to dryness to give a yellow gummy material (0.87 g). The ^1H NMR spectrum of this crude product indicated the presence of a 1:1 mixture of the adducts **8a,b**.

The above mixture was triturated with hot diethyl ether (10 mL) to provide on cooling a pale yellow solid pure isomer (**8a**; 0.33 g, 25%): mp 142–145 °C; IR (KBr) 1735, 1710 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) 1.10–1.60 (m, 15, 5 CH_2CH_3), 2.55 (s, 3, NCH_3), 4.00–4.70 (m, 10, 5 CH_2CH_3), 4.86 (s, 1, H_{9b}), 7.63 (s, 1, H_5), 8.00 (s, 1, H_9), 8.71 (s, 1, H_6); mass spectrum, m/e 544.

Anal. Calcd for $C_{27}H_{32}N_2O_{10}$: C, 59.55; H, 5.92; N, 5.14. Found: C, 59.0; H, 5.8; N, 5.0.

Evaporation of the mother liquor gave an oily residue (0.54 g) containing chiefly **8b**. Attempted purification of this quantity failed to produce pure compound **8b** (persistent contamination of this product with **8a**). A pure sample of **8b** (0.02 g from 0.08 g of starting material) was obtained by high-pressure liquid chromatography (silica gel, Waters, 10-μm packing, eluted with chloroform). TLC analysis of this sample showed only one spot corresponding to adduct **8b** (hygroscopic solid): mp 125–128 °C; IR (KBr) 1730, 1710 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) 1.10–1.65 (m, 15, 5 CH_2CH_3), 2.60 (s, 3, NCH_3), 4.00–4.75 (m, 10, 5 CH_2CH_3),

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4.97 (s, 1, H_{9b}), 7.58 (s, 1, H_5), 8.10 (s, 1, H_6), 8.66 (s, 1, H_9); mass spectrum, *m/e* 544.

Method B. From 7. A solution of adduct 7 (0.187 g, 0.5 mmol) and DEAC (0.34 g, 2 mmol) in xylene (5 mL) was refluxed under nitrogen for 90 min. After evaporation of the xylene under reduced pressure, the crude product was treated as in method A and gave adducts **8a** and **8b** in the same proportion and with identical yields.

Tetraethyl 1-Methyl-1*H*-pyrrolo[2,3-*f*]isoquinoline-2,3,4,8-tetracarboxylate (9a). Bromine (0.50 g, 3.10 mmol) was added to a suspension of **8a** (0.272 g, 0.5 mmol) in methanol (5 mL) at room temperature. The mixture became a clear solution and was stirred at room temperature for 12 h. The solvent and excess bromine were removed under reduced pressure, and the residue was triturated with aqueous sodium hydroxide (2%, 10 mL) to provide a white precipitate (0.11 g after drying, 47%). Recrystallization from diethyl ether gave an analytical sample of **9a**: mp 135–136 °C; IR (KBr) 1725, 1705 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) 1.25–1.70 (m, 12, 4 CH_2CH_3), 4.25–4.80 (m, 8, 4 CH_2CH_3), 4.55 (s, 3, NCH_3), 8.25 (s, 1, H_5), 9.20 (s, 1, aromatic), 9.40 (s, 1, aromatic).

Anal. Calcd for $C_{24}H_{26}N_2O_8$: C, 61.27; H, 5.57; N, 5.95. Found: C, 60.9; H, 5.7; N, 5.8.

Tetraethyl 1-Methyl-1*H*-pyrrolo[3,2-*h*]isoquinoline-2,3,4,7-tetracarboxylate (9b). Bromine (0.50 g, 3.10 mmol) and **8b** (0.27 g, containing about 10% **8a**) in methanol (5 mL) were stirred at room temperature for 12 h. The solution was treated as above to give a white solid (**9b**; 0.13 g, 55% crude product contaminated with 10% **9a**). Recrystallization of this material from diethyl ether (0.104 g) and then purification by high-pressure liquid chromatography (silica gel, Waters, 10-μm packing, eluted with chloroform) gave an analytically pure sample of **9b**: mp 118–122 °C; IR (KBr) 1725, 1715 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) 1.30–1.70 (m, 12, 4 CH_2CH_3), 4.25–4.80 (m, 11, 4 CH_2CH_3 and NCH_3), 8.17 (s, 1, H_5), 8.70 (s, 1, H_6), 10.09 (s, 1, H_9).

Anal. Calcd for $C_{24}H_{26}N_2O_8$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.3; H, 5.8; N, 6.2.

Endo Adduct of Ethyl 2-Methyl-2*H*-pyrrolo[3,4-*c*]-pyridine-6-carboxylate (1) with *N*-Phenylmaleimide. A solution of 0.102 g (0.5 mmol) of 1 and 0.259 g (1.5 mmol) of *N*-phenylmaleimide in 10 mL of chloroform was stirred at room temperature for 4 h. Removal of all solvent under high vacuum left a residue which was washed carefully with diethyl ether to give 0.15 g (79%) of the endo isomer: mp 135–140 °C dec; IR (KBr) 1710, 1765 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) 1.42 (t, 3, J = 7 Hz, CH_2CH_3), 2.14 (s, 3, NCH_3), 3.90–4.05 (m, 2, α to carbonyl), 4.48 (q, 2, J = 7 Hz, CH_2CH_3), 4.65–4.85 (m, 2, bridgehead), 6.30–6.55 (m, 2, H_a and $H_{a'}$), 7.15–7.40 (m, 3, aromatic), 8.12 (s, 1, H_4), 8.75 (s, 1, H_1).

Anal. Calcd for $C_{21}H_{19}N_3O_4$: C, 66.83; H, 5.07; N, 11.13. Found: C, 66.8; H, 5.0; N, 11.4.

Exo Adduct of Ethyl 2-Methyl-2*H*-pyrrolo[3,4-*c*]-pyridine-6-carboxylate (1) with *N*-Phenylmaleimide. A mixture of 0.102 g (0.5 mmol) of 1, 0.174 g (1 mmol) of *N*-phenylmaleimide, and 10 mL of xylene was heated at 120 °C for 20 min. The reaction mixture was evaporated to dryness, and the residue was washed carefully with diethyl ether to give 0.13 g (68%) of exo isomer: mp 190–195 °C dec; IR (KBr) 1710, 1770 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) 1.45 (t, 3, J = 7 Hz, CH_2CH_3), 2.01 (s, 3, NCH_3), 2.91 (s, 2, α to carbonyl), 4.48 (q, 2, J = 7 Hz, CH_2CH_3), 4.63 (s, 1, bridgehead), 4.66 (s, 1, bridgehead), 7.36 (m, 5, aromatic), 8.16 (s, 1, H_4), 8.75 (s, 1, H_1).

Anal. Calcd for $C_{21}H_{19}N_3O_4$: C, 66.83; N, 5.07; N, 11.13. Found: C, 66.7; H, 5.0; N, 11.4.

Registry No. 1, 51110-69-1; 7, 76190-36-8; **8a**, 76190-37-9; **8b**, 76206-84-3; **9a**, 76190-38-0; **9b**, 76190-39-1; **10a**, 76190-40-4; **10b**, 76248-16-3; 1-methyl-1*H*-pyrrole-3,4-dicarboxaldehyde, 51110-65-7; ethyl aminoacetate, 459-73-4; diethyl acetylenedicarboxylate, 762-21-0; *N*-phenylmaleimide, 941-69-5.

Total Synthesis of *dl*-Ancistrofuran: A Study of Cyclic Ether Formation

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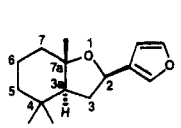
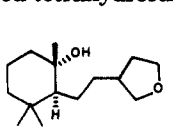
A six-step synthesis of *dl*-ancistrofuran (1) and its C-2 epimer (**31**) which involves a mercuric ion initiated diene cyclization of homogeranic acid to give lactone **16** and the phenylselenenyl chloride induced cyclization of alkylidene lactone **19** has been achieved. Also of interest are the zinc chloride assisted aldol condensation of **17** with α-(phenylthio)-γ-butyrolactone enolate anion to generate **29** and the use of ene adducts of **27** as substrates for cyclization to tetrahydrofurans **25** and **26**.

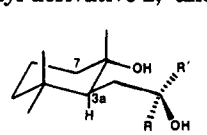
Ancistrofuran (1) is the major component in the defensive secretion of the termite *Ancistrotermes cavithorax* soldier.[1] The compound was assigned its constitution on the basis of spectroscopic analysis;[1] the relative configuration at C_{3a} and C_{7a} was deduced from NMR solvent shift studies on the reduced tetrahydrofuranyl derivative **2**,[2] and the configuration at C_2 was suggested on the basis of chemical studies carried out during the course of the first total synthesis of the molecule.[2] In that work only one of the diastereomeric pair of diols **3a** and **3b** could be cyclized upon treatment with 1 equiv of *p*-toluenesulfonyl chloride in pyridine. The product was identical with natural ancistrofuran. It was argued that "steric compression exists between the furan and ring hydrogens at [C_7] and [C_{3a}] in the conformation required for cyclization of (the monotosylate of) the isomer [**3b**]^2." Therefore, it was concluded that ancistrofuran must have the furan ring cis to the C_{7a} methyl group.



1



2



3a R = H R' = 3-furanyl

3b R' = H R = "

In the course of another synthetic project in our laboratory we had prepared diene **4** by the sequence outlined

(1) Baker, R.; Briner, P. H.; Evans, D. A. *J. Chem. Soc., Chem. Commun.* 1978, 410.

(2) Baker, R; Briner, P. H.; Evans, D. A. *J. Chem. Soc., Chem. Commun.* 1978, 981.

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