17β-OCOH). Anal. Calcd for $C_{19}H_{21}O_3I$: C, 53.52; H, 5.39. Found: C, 53.51; H, 5.29.

4-Iodo-1,3,5(10)-estratriene-3,17β-diol 17-formate (2i): mp 196–197 °C (MeOH); yield 43%; IR (KBr) 3400 (OH), 1700 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (3 H, s, 18-CH_3), 4.80 (1 H, t, J = 8 Hz, 17α-H), 6.80 (1 H, d, J = 9 Hz, 2-H), 7.23 (1 H, d, J = 9 Hz, 1-H), 8.13 (1 H, s, 17β-OCOH). Anal. Calcd for $C_{19}H_{21}O_3I$: C, 53.52; H, 5.39. Found: C, 53.52; H, 5.25.

2-Bromo-1,3,5(10)-estratriene-3,16α,17β-triol 16,17-diformate (3b): mp 187–188 °C (MeOH); yield 46%; IR (KBr) 3450 (OH), 1730 (C=O), 1710 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (3 H, s, 18-CH_3), 5.15 (1 H, d, J = 6 Hz, 17α-H), 5.32 (1 H, m, 16β-H), 6.73 (1 H, s, 4-H), 7.33 (1 H, s, 1-H), 8.03 and 8.13 (1 H, s, 16α- and 17β-OCOH). Anal. Calcd for $C_{20}H_{23}O_5Br$: C, 56.73; H, 5.43. Found: C, 56.77; H, 5.36.

4-Bromo-1,3,5(10)-estratriene-3,16α,17β-triol 16,17-diformate (3d): mp 222–224 °C (acetone); yield 42%; IR (KBr) 3450 (OH), 1730 (C=O), 1710 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (3 H, s, 18-CH_3), 5.15 (1 H, d, J = 6 Hz, 17α-H), 5.35 (1 H, m, 16β-H), 6.80 (1 H, d, J = 9 Hz, 2-H), 7.14 (1 H, d, J = 9 Hz, 1-H), 8.03 and 8.13 (1 H, s, 16α- and 17β-OCOH). Anal. Calcd for $C_{20}H_{23}O_5Br$: C, 56.73; H, 5.43. Found: C, 56.88; H, 5.62.

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A Retro-Diels–Alder Synthesis of 3-Pyrrolines

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In the course of our research in the design and synthesis of new antineoplastic agents, we required a method to prepare 1-methyl-3-pyrroline and related 3-pyrrolines. The reduction of pyrrole with zinc–acetic acid[1-3] or hydrochloric acid[4] gives 3-pyrroline contaminated with up to 35% of pyrrolidine.[5] A similar problem has been reported for the reduction of 1-methylpyrrole.[6] In addition to the mixture invariably obtained with this method, the scope is limited to simple 1- and 2-alkyl-3-pyrrolines.[7,8] We therefore undertook the development of a new synthesis of 3-pyrrolines.

The Diels–Alder Reaction has been used frequently as a method of protection for a double bond[9] or other functional group.[10-12] Modification can then be made on other functional groups, and the alkene can be regenerated in a thermal retro-Diels–Alder reaction. The synthesis of 1-methyl-3-pyrrole is given in Scheme I. Furan is pictured as the diene, but other dienes were also used and the results with several dienes are compared in Table I. The preparations of the Diels–Alder adducts and the subsequent reductions went cleanly. The final step, the retro-Diels–Alder reaction, proceeded in variable yield depending upon the diene used in the initial step and upon the thermolysis conditions.

Scheme I

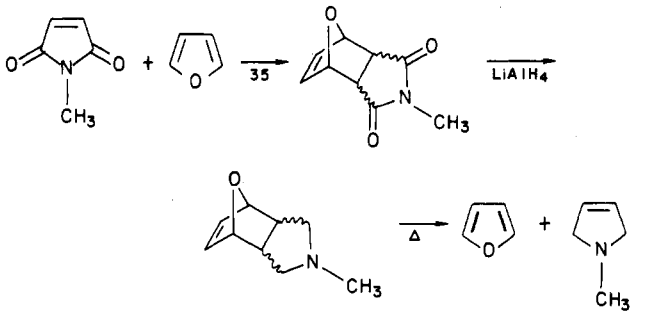

Table I. Synthesis of 1-Methyl-3-pyrroline

diene	% yield of Diels–Alder adduct	% yield of $LiAlH_4$ reduction	pyrolysis conditions temp., °C (method)[a]	pyrolysis % yield[b]
anthracene	93	83	500 (A)	*c*
furan	96	89	250 (A)	33
			300 (B)	0
			250–300 (C)	81[d]
cyclopentadiene	81	90	380–400 (C)	95[e]
dimethylanthracene	95	90	270	*f*

[a] Methods: A, adduct absorbed on sand and heated; B, adduct passed through a hot tube packed with glass beads; C, adduct dissolved in silicon oil and heated. [b] Yields were estimated by NMR. [c] The crude distillate contained a low yield of 1-methyl-3-pyrroline contaminated with an equivalent amount of 1-methylpyrrole. [d] Fractional distillation of the crude product gave pure 1-methyl-3-pyrroline in 60% isolated yield. [e] Fractional distillation of the crude product gave no pyrroline. [f] Pyrolysis not run on a preparative scale.

The best results were obtained when furan was used to prepare the adduct and the reduced adduct was pyrolyzed in a solution of silicon oil. The distillate from the reaction mixture consisted of a 1:1 mixture of furan and 1-methyl-3-pyrroline (60%). Thermolysis of the cyclopentadiene-protected material gave crude 1-methyl-3-pyrroline in ca. 95% yield, but attempts to purify 1-methyl-3-pyrroline by fractional distillation of the thermolysis product mixture led to extensive polymerization. No pyrroline was obtained. The adduct of 9,10-dimethylanthracene underwent thermolysis at a lower temperature than the adduct of anthracene. The high temperature required for the pyrolysis of the latter adduct resulted in the formation of a significant amount of *N*-methylpyrrole along with the desired 1-methyl-3-pyrroline.

The method was also used to synthesize *N*-phenyl-3-pyrroline. Thermolysis of the reduced adduct obtained from furan and *N*-phenylmaleimide gave the pure pyrroline in 83% yield. *N*-Phenyl-3-pyrroline had been previously synthesized in 35% yield from the reaction of aniline and *cis*-1,4-dichloro-2-butene.[14]

Functionalization of the α-position may be achieved by a Wittig reaction of the initial Diels–Alder adduct. The Wittig reaction of maleimide has been reported to give either mono- or disubstituted products depending on the condition employed.[15] Substitution at the β-position may

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also be envisioned since maleimides with activating substituents in the 3- or 4-position have been reported to undergo Diels-Alder reactions with cyclopentadiene.[16]

This route provides an efficient method of synthesizing pure 3-pyrrolines which were previously unattainable.

Experimental Section

General Methods. Melting points (uncorrected) were taken in open capillaries on a Hoover-Thomas Unimelt apparatus. NMR Spectra were determined for deuteriochloroform solutions containing ca. 1% tetramethylsilane as internal standard on Varian T60A and FT80 spectrometers. IR spectra were determined for KBr pellets with a Nicolet FT-IR infrared interferometer. Elemental analyses were performed by Atlantic Microlabs, Inc., Atlanta, GA.

***N*-Methyl-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboximide.** A stirred solution of *N*-methylmaleimide (4.44 g; 40 mmol) and furan (27.2 g; 400 mmol) in benzene (125 mL) was heated at reflux for 15 h. The reaction mixture was concentrated to dryness in vacuo and the pale yellow solid residue was crystallized from diethyl ether to give the adduct[13] (6.9 g; 96%) as white needles (a mixture of endo and exo isomers in a ratio of ca. 3:2): mp 138–141 °C; ^{1}H NMR δ 2.83 (s), 3.13 (s), 3.53 (m), 5.22 (s), 6.43 (s), 6.50 (s); IR 3013, 1690, 1439, 1381, 1293, 1134, 1018, 971 cm^{-1}. Anal. Calcd for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.45; H, 5.11; N, 7.80.

***N*-Phenyl-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboximide** was obtained in 71% yield as white plates (diethyl ether): mp 167–169 °C dec (lit.[17] mp 165.5 °C); ^{1}H NMR δ 3.00 (s, 2 H), 5.36 (m, 2 H), 6.53 (m, 2 H), 7.36 (m, 2 H); IR 3062, 3020, 1710, 1499, 1386, 1287, 1196, 1083, 1013, 872 cm^{-1}.

4-Methyl-4-aza-10-oxatricyclo[5.2.1.0^{2,6}]dec-8-ene. A solution of *N*-methyl-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboximide (6.5 g; 35 mmol) in dichloromethane (50 mL) was added dropwise to a stirred suspension of lithium aluminum hydride (3.99 g; 100 mmol) in anhydrous ether (100 mL). The mixture was stirred at 25 °C for 1 h and then carefully quenched with water. The salts were filtered and washed with chloroform (100 mL). The filtrate and chloroform washings were dried (sodium sulfate) and concentrated in vacuo. The yellow oily residue was distilled in vacuo to give the product (4.7 g; 89%) as a clear oil: bp 33–35 °C (0.05 torr); ^{1}H NMR δ 2.23 (s), 2.36 (s), 3.06 (m), 4.7 (s), 4.9 (m), 6.33 (s), 6.46 (s); IR 2950, 2781, 1456, 1252, 1146, 1013, 900 cm^{-1}. Anal. Calcd for $C_9H_{13}O_3 \cdot 0.75H_2O$: C, 65.63; H, 8.87; N, 8.50. Found: C, 65.71; H, 8.87; N, 8.48.

***N*-Phenyl-4-aza-10-oxatricyclo[5.2.1.0^{2,6}]dec-8-ene** was prepared in 88% yield as a crude yellow powder: mp 119–121 °C; ^{1}H NMR δ 2.53 (m), 3.00 (m), 4.76 (m), 6.36 (s), 6.93 (m), 7.16 (m); IR 2964, 1597, 1506, 1365, 1210, 1153, 991, 907 cm^{-1}.

1-Methyl-3-pyrroline. A solution of 4-methyl-4-aza-10-oxatricyclo[5.2.1.0^{2,6}]dec-8-ene (4.53 g; 30 mmol) in silicon oil [50 mL; bp >140 °C (0.002 torr)] was placed in a 100-mL round-bottom flask equipped with a short-path distillation apparatus and a gas bubbler. The receiver was cooled to −78 °C. The solution was heated to 250–300 °C for 2 h under an argon purge. The crude distillate (3.7 g), a 1:1 mixture of furan and 1-methyl-3-pyrroline, was fractionally distilled to give 1-methyl-3-pyrroline (1.5 g; 60%): bp 75–77 °C; mp of HCl salt 185–187 °C; ^{1}H NMR δ 2.5 (s, 3 H), 3.47 (s, 4 H), 5.77 (s, 2 H). Anal. Calcd for $C_5H_9N \cdot HCl \cdot 0.5H_2O$: C, 46.70; H, 8.62; N, 10.89; Cl, 27.57. Found: C, 46.61; H, 8.65; N, 10.84; Cl, 27.68.

1-Phenyl-3-pyrroline. Method A. A suspension of 4-phenyl-4-aza-oxatricyclo[5.2.1.0^{2,6}]dec-8-ene (2.13 g; 10 mmol) and silicon oil [50 mL, bp >140 °C (0.002 torr)] was placed in a 100-mL round-bottom flask equipped with a short-path distillation apparatus and a gas bubbler. The condenser was heated to 80 °C and the receiver cooled to −78 °C. The suspension was heated to 250–300 °C for 2 h at 60 torr under a bleed of argon. The distillate, which collected as a yellow solid, was chromatographed (silica gel eluted with dichloromethane) to give a white powder that was crystallized from methanol, yielding 1-phenyl-3-pyrroline as white flakes (1.2 g; 83%), mp 99–101 °C.

Method B. A solution of *cis*-1,4-dichloro-2-butene (2.5 g; 20 mmol), aniline (5.5 g; 60 mmol), and benzene (25 mL) was stirred at reflux for 2 h. The reaction mixture was cooled to 25 °C and washed with water (2 × 50 mL). The organic solution was dried (sodium sulfate) and concentrated under reduced pressure to give a red gum that was crystallized from methanol to yield 1-phenyl-3-pyrroline as white flakes (1.01 g, 35%): mp 99–101 °C (lit.[14] mp 101–102 °C); ^{1}H NMR ($CDCl_3$/Me_4Si) δ 4.03 (s, 4 H), 5.86 (s, 2 H), 6.36–7.40 (complex m, 5 H); IR (KBr) 3041, 2964, 1632, 1597, 1513, 1393, 1189, 998, 745 cm^{-1}.

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Mechanism of Singlet Oxygen Addition to Conjugated Butadienes.[1] Solvent Effects on the Formation of a 1,4-Diradical. The 1,4-Diradical/1,4-Zwitterion Dichotomy

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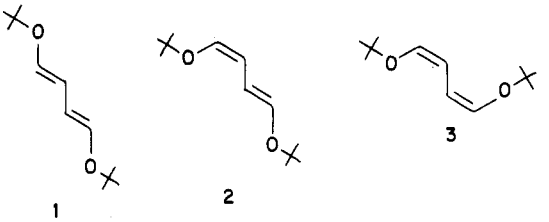
A more detailed examination[1] of solvent effects on the addition of singlet oxygen to isomeric dienes 1–3[2] has



uncovered a very revealing isomerization that implicates diradical intermediates on the energy surface for the formation of dioxetanes. These results corroborate our earlier suggestion[1] of competing concerted and stepwise dioxetane production and most importantly, from a synthetic viewpoint, demonstrate that careful consideration must be given to the proper choice of solvent for singlet oxygen diene reactions.

The photooxidations of dienes 1–3 were accomplished by irradiation of dilute solutions of each diene in the presence of a sensitizer at −78 °C (see the Experimental Section). The low temperatures were required to prevent decomposition of the sensitive dioxetane products (Chart I). The dilute solutions were necessary in order to prevent substrate dye interactions which compromised the configurational integreties of the dienes. Control reactions in both acetone-d_6 and THF-d_8 under the identical conditions utilized for the photooxidations except under an inert atmosphere (acetone-d_6–nitrogen; THF-d_8–argon) verified that less than 5% isomerization of any of the three dienes could occur. Under these carefully controlled conditions integrations of the proton NMR spectra of the reaction mixtures allowed quantitation of the product distributions as a function of solvent.[3] These data, which

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