(S)-(−)-2-(1-Ethoxyethoxy)-1,4-butanediol (7a) was prepared in 91% yield by $LiAlH_4$ reduction of **6a** according to the procedure of Seebach et al.;[19] bp 108 °C (0.2 mmHg) [lit.[8] bp 99 °C (0.01 mmHg)].

Registry No. **1a**, 97-67-6; **2a**, 617-55-0; **3a**, 42890-76-6; **3b**, 70005-88-8; **4a**, 86087-23-2; **4a** (+)-α-methoxy-α-(trifluoromethyl)phenylacetate ester, 86014-40-6; **4b**, 86087-24-3; **5a**, 691-84-9; **6a**, 76494-95-6; **7a**, 72229-31-3; (+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride, 20445-33-4.

Preparation of Methyl 2,5-Dioxohexanoate: A Highly Convenient Reagent for the Introduction of the 2-Carboalkoxy-1,5-dialkylpyrrole Nucleus

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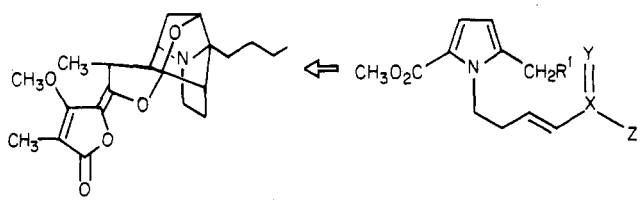
As part of an investigation directed at the synthesis of the potent natural insecticide stemofoline (**1**,[1] Scheme I) and structural variants, we required a general method for the rapid construction of 1,2,5-trisubstituted pyrroles (**2**) where either of the 2,5-substituents was an electron-withdrawing functionality. Our strategy was designed both to explore the intramolecular cycloaddition chemistry of pyrroles and to provide access to simpler structural analogues for biological evaluation.[2]

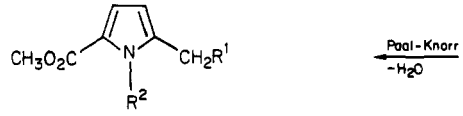
While a variety of useful methods for the synthesis of 1*H*-2-carboalkoxy-1,5-dialkylpyrroles have been developed, synthetic procedures for the 1-alkylated derivatives are scarce.[3-6] Since N-alkylation of 1,5-disubstituted pyrroles requires a sterically congested S_N2 transition state, low yields of products are obtained in the reaction of the 1-tetraalkylammonium or 1-metalated pyrroles with primary alkyl halides.[4]

While conceptually the carboalkoxy substituent could be introduced by metalation of a 1,2-dialkylated pyrrole,[3,4] this approach requires more synthetic manipulations when carbanion-sensitive functional groups are present in the target molecule. Construction of the pyrrole ring with the electron-withdrawing function affixed therefore increases the convergency of the synthesis as well as the inherent chemical stability of the products. Other methods which are amenable to the synthesis of 2-carboalkoxy-1,5-dialkylpyrroles such as the Hantzsch synthesis or the ring contraction of 1,2-oxazines suffer from the low chemical yields of pure products, lack of regioselectivity, or nongenerality.[5,6]

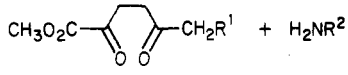
Scheme I



stemofoline, 1



2a, R^1 = H; R^2 = $CH_2CH_2CH_2OH$
b, R^1 = H; R^2 = $CH_2CH(OCH_3)_2$
c, R^1 = H; R^2 = CH_2Ph
d, R^1 = $CH_2CH_2CH_3$; R^2 = $CH_2CH_2CH_2OH$
e, R^1 = H; R^2 = (*R*)-$CH(CH_2OH)CH_2CH_3$
f, R^1 = H; R^2 = $CH_2CH_2CO_2H$



3

The most convergent approach for the preparation of these highly substituted pyrroles is the Paal–Knorr pyrrole synthesis[3] (Scheme I). The major obstacle to overcome in this approach is in the preparation of the 2,5-diketo esters **3**. Although the parent member of this potentially useful family of compounds, methyl 2,5-dioxohexanoate (**3a**), was first reported in 1973, we were unable to obtain synthetically useful quantities of pure material using the methodologies which the authors described.[7,8] While a lack of experimental details may have been a primary determinant in our difficulties, we elected to pursue an alternative, shorter route to the diketo ester **3a**, which obviates the necessity of handling offensive low-valent organosulfur intermediates.

The 1,4 conjugate addition of methyl nitroacetate[10] with methyl vinyl ketone (MVK) proceeds smoothly on using a catalytic amount of base to give methyl 2-nitro-5-oxohexanoate (**5a**) in 65–74% yield after distillation (eq 1). This result sharply contrasts with our experience with the reaction of the anion derived from methyl 2,2-diethylthioacetate with MVK, which consistently afforded low yields (>30%) of monomeric conjugate addition product.[7] The efficacy of the nitroacetate conjugate addition presumably results from the rapid protonation of the intermediate ketone enolate anion ($pK_B \simeq 20$) by proton transfer from the α-nitroacetate function ($pK_A = 5.82$),[11] giving rise to a thermodynamically more stable nitronate

(1) Sakata, K.; Aoki, K.; Chang, C.-F.; Sakurai, A.; Tamura, S.; Murakoshi, S. *Agric. Biol. Chem.* **1978**, *42*, 457–63.

(2) We gratefully acknowledge the interest and cooperation of Willy D. Kollmyer of the Biological Chemistry Department of the Shell Development Co., Modesto, CA.

(3) For reviews on the synthesis of pyrroles: Jackson, A. H. In "Comprehensive Organic Chemistry"; Pergamon Press: New York, 1979; Vol. 4, Chapter 17.1, pp 275–320.

(4) Baltazzi, E.; Krimen, L. I. *Chem. Rev.* **1963**, *63*, 511–56.

(5) The Hantzsch pyrrole synthesis proceeds to give a maximum 50% yield of products, uses highly toxic α-halo ketones, and requires several steps for the 1,2,5-trisubstitution pattern: Roomi, M. W.; MacDonald, S. F. *Can. J. Chem.* **1970**, *48*, 1689–97.

(6) The ring contraction of 3-carboalkoxy-1,2-oxazines to 2-carboalkoxy-5-alkylpyrroles proceeds in excellent yields but is not useful for 1-alkyl derivatives which have protons on the carbon atom attached to the pyrrole nitrogen. The requisite starting material would be an alkyl nitroso compound bearing α-protons which are known to rapidly isomerize to the oximino tautomer. (a) Needleman, S. B.; Chang Kuo, M. C. *Chem. Rev.* **1962**, *62*, 405–31. (b) Belleau, B.; Au-Young, Y.-K. *J. Am. Chem. Soc.* **1963**, *85*, 64–71.

(7) The title compound, methyl 2,5-dioxohexanoate, was first reported to have been prepared "in excess of" 62% overall yield from dichloroacetic acid.[8] Conversion to methyl diethylmercaptoacetate is reported to proceed in 75% overall yield by using sodium ethyl mercaptide followed by methanolic hydrogen chloride. The best yield we were able to obtain overall for these conversions was ca. 30%. The key step in this methodology involves the 1,4-addition of the anion derived from methyl diethylmercaptoacetate to methyl vinyl ketone in a reported 93% yield.[8] We consistently obtained yields of less than 28% of pure distilled product. Finally, the hydrolysis of the diethyl thioketal using *N*-bromosuccinimide in aqueous acetonitrile[9] was reported to proceed "always in excess of 90%". While the procedure of Corey and Erickson was reproduced with no experimental difficulties, affording ethyl 3-phenylpyruvate from the corresponding acyl-1,3-dithiane in 78% yield, in the case of the 2,2-diethyl thioketal of methyl 2,4-dioxopentanoate, this procedure gave a 53% yield of product after evaporative distillation.

(8) Cregge, R. J.; Herrman, J. L.; Richman, J. E.; Romanet, R. F.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, 2595–8.

(9) Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1971**, *36*, 3553–60.

(10) Shipchandler, M. T. *Synthesis* **1979**, 666–86.

(11) Pearson, R. G.; Dillon, R. L. *J. Am. Chem. Soc.* **1953**, *75*, 2439–43.

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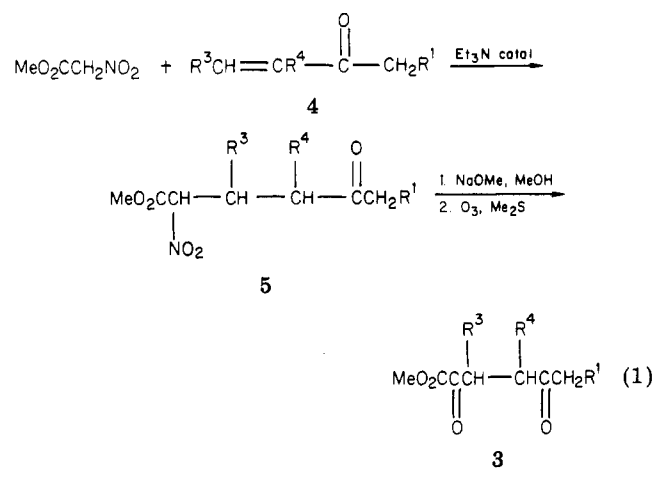

(1)

3a–5a, $R^1 = R^3 = R^4 = H$; **3b–5b**, $R^1 = CH_2CH_2CH_3$, $R^3 = R^4 = H$; **3c–5c**, $R^1 = R^4 = H$, $R^3 = CH_2CH_3$; **3d–5d**, $R^1 = R^3 = H$, $R^4 = CH_3$

anion, before polymerization can occur. Dialkylation is not a serious problem, since the unsubstituted nitronate is more reactive than the nitronate derived from product **5a**. Conversion to the nitronate mono anion by using a slight excess of sodium methoxide in methanol followed by ozonolysis and reductive workup[12] afforded decagram quantities of the desired 2,5-diketo ester **3a** in 92% yield after distillation. When obtained in this manner,[13] the diketo esters[14] **3a–5a** were colorless liquids which could be stored at room temperature for several weeks in sealed containers without noticeable decomposition.

The Paal–Knorr cyclization[15] of the diketo esters **3a** and **3b** proceeded cleanly and afforded the regiochemically pure 2-carbomethoxy-1,5-dialkylpyrroles **2a–f** in 65–94% yields after evaporative distillation or sublimation. The mildness of the method tolerates a variety of acid- and base-labile functional groups in the side-chain groups. Since nitroacetate undergoes efficient conjugate addition with α- or β-substituted enones, the method also becomes general for the preparation of 2-carboalkoxy trialkylated pyrroles.[16,18] The intramolecular cycloaddition chemistry of these pyrroles and their subsequent utility in the synthesis of stemofoline is currently under investigation in these laboratories.

Experimental Section

Melting points were determined on a Fisher-Johns melting point apparatus (uncorrected). ^1H NMR spectra (Me_4Si internal standard), were recorded on a Bruker WP-200 (200 MHz) spectrometer. Infrared (IR) spectra were recorded on a Perkin-Elmer 237 spectrophotometer. Analytical samples were prepared by subsequent evaporative distillation or sublimation of the final product. Elemental analyses were performed by MicAnal Organic Microanalysis of Tucson, AZ. Dry triethylamine (TEA) was obtained by distillation from P_2O_5. Since the nitro compounds were found to be light sensitive, they were stored in amber bottles in the refrigerator. When stored in this manner, no decomposition was evidenced by TLC or ^1H NMR after up to 3 months. Thin-layer chromatography (TLC) was performed by using E. Merck, 60F-254 (0.25 mm) TLC plates. The (*R*)-(−)-2-aminobutanol was purchased from Aldrich Chemical Co. and was used without further purification.

Methyl 2-Nitro-5-oxohexanoate (5a). To a stirred solution of 37.0 g (0.528 mol) of 1-buten-3-one and 65.6 g (0.551 mol) of methyl nitroacetate[19] in 549 mL of absolute ethanol was added 2.2 mL (4.81 mmol) of dry TEA. The solution was allowed to stand at room temperature under N_2 for 48 h. Removal of solvent under reduced pressure afforded a yellow oil. Evaporative distillation at 92 °C (0.02 mm) afforded 70.0 g (67%) of colorless oil: IR ($CHCl_3$) 1759 (vs, C=O), 1716 (vs, C=O), 1562 (vs), 1441 (s), 1371 (s), 1209 (vs), 1171 (m), 784 (vs) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.17 (s, 3 H, CH_3), 2.38–2.75 (complex m, 4 H, CH_2CH_2), 3.84 (s, 3 H, OCH_3), 5.28 (t, 1 H, J = 7.0 Hz, $CH-NO_2$). Anal. Calcd for $C_7H_{11}NO_5$: C, 44.44; H, 5.86; N, 7.40. Found: C, 44.62; H, 6.02; N, 7.40.

Methyl 2-Nitro-5-oxononanoate (5b). To a solution of 2.0 g (17.8 mmol) of 1-hepten-3-one[20] and 2.2 g (18.5 mmol) of methyl nitroacetate in absolute ethanol was added 0.08 mL of dry TEA. The solution was allowed to stand at room temperature under an N_2 atmosphere for 48 h. Removal of the solvent under reduced pressure afforded 4.0 g of crude product. Evaporative distillation at 150–160 °C (0.10 mm) afforded 3.5 g (85.4%) of colorless product: IR ($CHCl_3$) 1760 (s, C=O), 1718 (s, C=O), 1563 (vs), 1442 (m), 1209 (vs), 770 (vs), cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (t, 3 H, J = 7.1 Hz, CH_3), 1.31 (m, 2 H, CH_2CH_3), 1.56 (m, 2 H, $CH_3CH_2CH_2$), 2.35–2.65 (complex m, 6 H, $CH_2COCH_2CH_2$), 3.84 (s, 3 H, OCH_3). Anal. Calcd for $C_{10}H_{17}NO_5$: C, 51.94; H, 7.41; N, 6.06. Found: C, 51.69; H, 7.43; N, 6.24.

Methyl 3-Ethyl-2-nitro-5-oxohexanoate (5c). To a solution of 1.0 g (10.2 mmol) of 3-hexen-2-one[24] (mixture of *E* and *Z*) and 1.2 g (10.1 mmol) methyl nitroacetate in 10.8 mL of absolute EtOH was added 0.046 mL of dry TEA. The solution was allowed to stand at room temperature under a nitrogen atmosphere for 48 h. Removal of the solvent on a rotary evaportor followed by slow evaporative distillation at 100–140 °C (0.14 mm) afforded 0.5 g (22.7%) of light yellow product as a mixture of diastereomers. An analytical sample was prepared by preparative thin-layer chromatography on silica gel by utilizing 50% petroleum ether (low boiling) in diethyl ether, followed by evaporative distilation: IR ($CHCl_3$) 1753 (vs, C=O), 1715 (vs, C=O), 1563 (vs), 1458 (m), 1430 (s), 1412 (m), 1365 (vs), 1205 (vs), 1073 (s), 1015 (m), 725 (vs) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90–1.02 (m, 3 H, CH_2CH_3), 1.39–1.62 (m, 2 H, CH_2CH_3), 2.17 (s, 3 H, CH_3CO), 2.45–2.95 (complex m, 3 H, $COCH_2CH$), 3.82 (s, 3 H, OCH_3), 5.30–5.45 (m, 1 H, $CHNO_2$). Anal. Calcd for $C_9H_{15}NO_5$: C, 49.76; H, 6.96; N, 6.45. Found: C, 49.47; H, 6.90; N, 6.76.

(12) McMurry, J. E.; Melton, J.; Padgett, H. *J. Org. Chem.* **1974**, *39*, 259–60.

(13) An alternative procedure utilizing (methylthio)methyl sulfoxide as a formyl carbanion equivalent was employed for diketo ester **3a**, using a protected 3-keto nitrile as the electrophile. While this methodology did prove useful for the preparation of small quantities of material, we found this methodology to be less convenient on a large scale: Ogura, K.; Katoh, N.; Yoshimura, I.; Tsuchihaski, G.-L. *Tetrahedron Lett.* **1978**, 375–8.

(14) For a leading reference to the synthesis of 2-keto esters and their usefulness and potent enzyme inhibitors see: Hangauer, D. G., Jr. *Tetrahedron Lett.* **1981**, *22*, 2439–42.

(15) Nedenskov, P.; Elming, N.; Nielson, J. T.; Clauson-Kaas, N. *Acta Chem. Scand.* **1955**, *9*, 17–22.

(16) Certain pyrroles having this substitution pattern have been found to exhibit a high level of biological activity. As an example, the analgesic drug Zomax (Zompirac), is a 2-acyl-1,3,5-trialkylpyrrole which is currently prescribed for the treatment of pain. This substance is free from CNS depressant effects commonly associated with opiate-like drugs but is more effective than aspirin or codeine for relief of arthritic or postsurgical pain.[17]

(17) (a) Baird, W. M.; Turek, D. *J. Clin. Pharmacol.* **1980**, *20*, 243–9. (b) Wallenstein, S. L.; Rogers, A.; Kaiko, R. F.; Heidrich, G., III; Houde, R. W. *Ibid.* **1980**, *20*, 250–8. (c) Forrest, W. H. *Ibid* **1980**, *20*, 259–60. (d) Pruss, T. P.; Gardocki, J. F.; Taylor, R. J.; Muschek, L. D. *Ibid.* **1980**, *20*, 216–22. (e) Mehlisch, D. R.; Joy, E. D.; Moore, T. E.; Porter, K.; Stumpf, A. J.; Wolfe, S. H. *Ibid.* **1980**, *20*, 271–8.

(18) While methyl nitroacetate underwent conjugate addition with either α- or β-monosubstituted enones (examples **5c** and **5d**), α,β-disubstituted enones such as 1-acetylcyclohexene did not react with methyl nitroacetate under the conditions described herein.

(19) Zen, S.; Koyama, M.; Koto, S. *Org. Synth.* **1976**, *55*, 77–80.

(20) 1-Hepten-3-ol was prepared in 72% yield [bp 60–67 °C (17 mm); lit.[21] bp 55–56 °C (12 mm)] by the addition of vinylmagnesium bromide in tetrahydrofuran to pentanal using the general procedure described by Normant; Normant, H. *Bull. Soc. Chim. Fr.* **1957**, *24*, 728–33. Oxidation to 1-hepten-3-one was effected in 34% yield [bp 60–67 °C (17 mm); lit.[22] bp 36 °C (12 mm)] by using the procedure of Corey and Suggs[23] (buffered pyridinium chlorochromate).

(21) Murahashi, S. *Chem. Zentralbl.* **1938II**, 1249.

(22) Stetter, H.; Landscheidt, A. *Chem. Ber.* **1979**, *112*, 1410–9.

(23) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647–50.

(24) The 3-hexen-2-one was prepared as a mixture of *E* and *Z* isomers by using the method described by: Tischenko, I. G.; Stanishevskii, L. S. *Zh. Obshch. Khim.* **1963**, *33*, 141–5.

Methyl 4-Methyl-2-nitro-5-oxohexanoate (5d). To a solution of 310 mg (3.69 mmol) of 3-methyl-3-buten-2-one[25] and 894 mg (7.51 mmol, 2 equiv) of methyl nitroacetate in 3.9 mL of MeOH was added 3 drops of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN). The solution was allowed to stand at room temperature under a nitrogen atmosphere for 48 h. Removal of the solvent on a rotary evaporator followed by slow evaporative distillation at 80–110 °C (0.05 mm), afforded 420 mg (56.0%) of product as a mixture of diastereomers: IR ($CHCl_3$) 1760 (vs, C=O), 1715 (s, C=O), 1560 (vs), 1460 (m), 1362 (m), 1270 (s), 1205 (s), 725 (vs) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90–1.30 (m, 3 H, $CHCH_3$), 2.00–2.75 [complex m, 6 H, $CH(CH_3)CH_2$ and CH_3CO (δ 2.19, s)], 3.83 (s, 3 H, OCH_3), 5.15–5.32 (m, 1 H, $CHNO_2$). Anal. Calcd for $C_8H_{13}NO_5$: C, 47.29; H, 6.45; N, 6.89. Found: C, 47.22; H, 6.52; N, 6.85.

Methyl 2,5-Dioxohexanoate (3a). To a stirred solution of 10.0 g (52.9 mmol) of methyl 2-nitro-5-oxohexanoate in 150 mL of anhydrous methanol (MeOH) under an N_2 atmosphere was added 3.2 g (59.2 mmol, 1.1 equiv) of sodium methoxide (NaOMe). After being stirred for 10 min at room temperature, the solution was cooled (dry ice–acetone bath) and allowed to stir for an additional 10 min. Ozone from a Welsbach ozone generator was then introduced into the solution until a white solid precipitated.[26] The mixture was allowed to stir in the cold for 0.5 h and was then purged with N_2, using a gel dispersion tube, for 30 min. After addition of 27.7 mL (360 mmol) of dimethyl sulfide (Me_2S) the mixture was allowed to warm to room temperature over 16 h. An additional 27.7 mL of Me_2SO was added, and after the mixture was allowed to stir for 1 h, it was poured into 150 mL of CH_2Cl_2. After filtation and removal of the solvent under reduced pressure (rotary evaporator in the hood!), the crude residue was taken up in CH_2Cl_2 and extracted three times with saturated brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to an oil (7.8 g, 92.8%). evaporative distillation at 120–130 °C (0.04 mm) afforded 6.1 g (72.6%) of colorless product: IR ($CHCl_3$) 1760–1700 (br, vs, C=O's), 1285 (s), 1210 (vs), 1165 (m), 1090 (vs), 1050 (s), 735 (vs) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2,21 (s, 3 H, CH_3), 2.83 (AA', 2 H, line spacing = 6 Hz, CH_3COCH_2), 3.09 (BB', 2 H, line spacing = 6 Hz, CH_2COCO_2Me), 3.88 (s, 3 H, OCH_3). Anal. Calcd for $C_7H_{10}O_4$: C, 53.16; H, 6.37. Found: C, 52.87; H, 6.06.

Methyl 2,5-Dioxononanoate (3b). To a stirred solution of 3.0 g (13.0 mmol) of methyl 2-nitro-5-oxononanoate (**5b**) in 33 mL of anhydrous MeOH under N_2 was added 0.8 g (14.8 mmol, 1.1 equiv) of NaOMe. Ozonolysis and a workup as described above for **3a** afforded 2.6 g of crude product. Evaporative distillation from 130 to 160 °C (0.15 mm) afforded 2.2 g (84.6%) of colorless product: IR ($CHCl_3$) 1765–1690 (br, vs, C=O's), 1285 (s), 1210 (vs), 1100 (m), 1065 (vs), 730 (vs) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (t, 3 H, J = 7.2 Hz, CH_3), 1.32 (m, 2 H, CH_3CH_2), 1.58 (m, 2 H, $CH_3CH_2CH_2$), 2.47 (t, 2 H, J = 7.3 Hz, n-C_3H_7–CH_2), 2.81 (AA', 2 H, line spacing = 6 Hz, $CH_2CH_2COCO_2Me$), 3.08 (BB', 2 H, line spacing = 6 Hz, CH_2COCO_2Me). Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 59.73; H, 8.30.

General Procedure for the Preparation of the Pyrroles. Methyl 1-(3-Hydroxypropyl)-5-methyl-2-pyrrolecarboxylate (2a). To a stirred solution of 2.0 g (12.6 mmol) of diketo ester **3a** in 19.4 mL of glacial acetic acid, warmed to 50–60 °C under N_2, was added a solution of 1.9 g (25.3 mmol) of 3-aminopropanol in 6.7 mL of MeOH over 5 min. After 1.5 h, the reaction mixture was poured into 50 mL of water and extracted with four 30-mL portions of ethyl acetate (EtOAc). The organic extracts were dried over $MgSO_4$, filtered, and then concentrated under reduced pressure. Toluene was added to the crude concentrate to assist (azeotropically) in the removal of acetic acid. After the mixture was dried under reduced pressure, evaporative distillation of the residue at 140 °C (0.05 mm) afforded 2.4 g (96%) of the pure pyrrole: IR ($CHCl_3$) 3580 (vw, nonbonded OH), 3550–3250 (br, m, OH), 1675 (vs, C=O), 1475 (vs), 1460 (s), 1430 (s), 1385 (s), 1325 (s), 1285 (s), 1237 (vs), 1200 (vs), 1135 (vs), 1070 (m), 1030 (m), 1010 (s), 725 (vs) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.92 (m, 2 H, CH_2CH_2OH), 2.28 (s, 3 H, CH_3), 3.58 (t, 2 H, J = 5.5 Hz, CH_2OH), 3.72 (br s, 1 H, OH), 3.78 (s, 3 H, OCH_3), 4.41 (t, 2 H, J = 6.7 Hz, CH_2), 5.92 (d, 1 H, J = 3.8 Hz, C_4 pyrrole H), 6.92 (d, 1 H, J = 3.9 Hz, C_3 pyrrole H). Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.66; N, 7.10. Found: C, 60.80; H, 7.91; N, 7.02.

Methyl 1-(2,2-Dimethoxyethyl)-5-methyl-2-pyrrolecarboxylate (2b). From 1.5 g (9.48 mmol) of diketo ester **3a** and 2.0 g (19.0 mmol) of dimethoxyethylamine, using the general procedure described above for the preparation of pyrrole **2a**, there was obtained 1.9 g (86%) of the pure pyrrole, after evaporative distillation [125–135 °C (0.05 mm)], as a colorless oil which rapidly darkened on standing:[27] IR ($CHCl_3$) 1689 (vs, C=O), 1482 (vs), 1434 (s), 1389 (m), 1332 (m), 1272 (vs), 1205 (vs), 1147 (vs), 1095 (s), 750 (vs) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.29 (s, 3 H, CH_3), 3.36 (s, 6 H, OCH_3), 3.79 (s, 3 H, CO_2CH_3), 4.32 (d, 2 H, J = 5.3 Hz, CH_2), 4.56 (t, 1 H, J = 5.3 Hz, $CH(OMe)_2$), 5.90 (d, 1 H, J = 3.8 Hz, C_4 pyrrole H), 6.91 (d, 1 H, J = 3.9 Hz, C_3 pyrrole H). Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54; N, 6.16. Found: C, 57.91; H, 7.51; N, 6.06.

Methyl 5-Methyl-1-(phenylmethyl)-2-pyrrolecarboxylate (2c). From 1.5 g (9.48 mmol) of diketo ester **3a** and 2.0 g (18.7 mmol) of benzylamine, using the general procedure described above for the preparation of pyrrole **2a**, there was obtained a dark gummy solid. Sublimation at 50–57 °C (0.03 mm) afforded 1.6 g (72%) of a light yellow solid. A second sublimation afforded analytically pure, colorless crystals: mp 63.5–65 °C; IR ($CHCl_3$) 1690 (vs, C=O), 1480 (vs), 1465 (m), 1449 (s), 1430 (s), 1415 (m), 1390 (m), 1355 (m), 1325 (m), 1260 (vs), 1190 (s), 1140 (vs), 1075 (w), 1040 (s), 956 (m), 923 (m), 725 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.18 (s, 3 H, CH_3), 3.74 (s, 3 H, OCH_3), 5.61 (s, 2 H, CH_2), 5.99 (d, 1 H, J = 3.9 Hz, C_4 pyrrole H), 6.85–7.02 [complex multiplet consisting of the C_3 pyrrole H at 6.98 (d, J = 3.9 Hz) and two aromatic H's], 7.15–7.35 (m, 3 H, aromatic H's). Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.34; H, 6.57; N, 6.13.

Methyl 5-Butyl-1-(3-hydroxypropyl)-2-pyrrolecarboxylate (2d). From 1.5 g (7.49 mmol) of diketo ester **3b** and 1.1 g (14.6 mmol) of 3-aminopropanol, using the general procedure described above, there was obtained, after evaporative distillation at 124–135 °C (0.04 mm), 1.5 g (83.3%) of the pyrrole as a light yellow oil: IR ($CHCl_3$) 3575 (vw, nonbonded OH), 3545–3250 (br, w, OH), 1680 (vs, C=O), 1478 (vs), 1433 (s), 1390 (s), 1315 (m), 1283 (m), 1203 (vs), 1140 (vs), 1100 (m), 1075 (m), 1000 (m), 750 (vs) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (t, 3 H, J = 7.2 Hz, CH_3), 1.42 (m, 2 H, CH_3CH_2), 1.65 (m, 2 H, CH_3CH_2), 1.93 (m, 2 H, CH_2CH_2OH), 2.5–2.8 (br s, 1 H, OH), 2.59 (t, 2 H, J = 7.6 Hz, n-C_3H_7–CH_2), 3.59 (t, 2 H, J = 5.6 Hz, CH_2OH), 3.79 (s, 3 H, OCH_3), 4.42 (t, 2 H, J= 6.8 Hz, NCH_2), 5.95 (d, 1 H, J = 4.0 Hz, C_4 pyrrole H), 6.95 (d, 1 H, J = 4.0 Hz, C_3 pyrrole H). Anal. Calcd for $C_{13}H_{21}NO_3$: C, 65.25; H, 8.84; N, 5.85. Found: C, 65.17; H, 8.91; N, 5.80.

Methyl 1-[1(*R*)-Ethyl-2-hydroxyethyl]-5-methyl-2-pyrrolecarboxylate (2e). Condensation of 1.5 g (9.48 mmol) of diketo ester **3a** with 1.7 g (19.0 mmol) of (*R*)-(−)-2-aminobutanol, in the manner described above for the preparation of the pyrrole **2a**, gave a crude oil. Evaporative distillation at 130–140 °C (0.035 mm) afforded 1.3 g (65%) of a light yellow oil. An analytical sample was prepared by flash chromatography on silica gel by using 40% EtOAc in cyclohexane, followed by evaporative distillation at 130–140 °C (0.035 mm): $[\alpha]^{25}_D$ +12.8° (*c* 0.18, $CHCl_3$); IR ($CHCl_3$) 3537 (vw, nonbonded OH), 3512–3250 (br, vw, OH), 1690 (vs, C=O), 1480 (vs), 1460 (m), 1437 (s), 1405 (m), 1345 (s), 1265 (m), 1212 (vs), 1150 (s), 1120 (m), 1045 (m), 1035 (m), 730 (vs) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.76 (br t, 3 H, CH_3CH_2), 1.84 (br m, 2 H, CH_3CH_2), 2.30 (br s, 3 H, pyrrole CH_3), 2.70 (br s, 1 H, OH), 3.74 (s, 3 H, OCH_3), 3.75–3.92 (complex m, 2 H, CH_2OH), 3.95–4.5 (complex m, 1 H, NCH), 5.89 (d, 1 H, J = 3.9 Hz, C_4 pyrrole H), 6.96 (br s, 1 H; C_3 pyrrole H). Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.27; H, 8.29; N, 6.60.

3-[2-(Methoxycarbonyl)-5-methyl-1-pyrrolyl]propanoic Acid (2f). Condensation of 1.5 g (9.48 mmol) of the diketo ester **3a** with 1.7 g (19.1 mmol) of β-alanine,[28] in the manner described above for the preparation of pyrrole **2a**, gave a crude solid.

(25) Colonge, J.; Cumet, L. *Bull. Soc. Chim. Fr.* **1947**, *14*, 838–41.
(26) While the precipitate (sodium nitrate) is not explosive, care should always be exercised in any ozonolysis.
(27) The discolored sample produced satisfactory spectral and analytical results.
(28) The solid amino acid was added in one portion without solvent.

Sublimation at 100 °C (0.065 mm) afforded 1.5 g (75%) of a light yellow solid. A second sublimation afforded analytically pure, colorless crystals: mp 135–137 °C; IR ($CHCl_3$) 3505–2755 (br, w, OH), 1713 (s, C=O), 1687 (s, C=O), 1485 (s), 1435 (m), 1412 (m), 1390 (m), 1330 (m), 1280 (m), 1250 (s), 1200 (s), 1140 (s), 1062 (m), 925 (w), 725 (vs) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.29 (s, 3 H, CH_3), 2.82 (AA′, t, 2 H, apparent J = 7.5 Hz, CH_2CO_2H), 3.80 (s, 3 H, OCH_3), 4.53 (BB′, t, 2 H, apparent J = 7.5 Hz, NCH_2), 5.91 (d, 1 H, J = 3.9 Hz, C_4 pyrrole H), 6.91 (d, 1 H, J = 3.9 Hz, C_3 pyrrole H), 10.85–11.15 (br s, 1 H, OH). Anal. Calcd for $C_{10}H_{13}NO_4$: C, 56.87; H, 6.20; N, 6.63. Found: C, 56.97; H, 5.88; N, 6.57.

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Registry No. **2a**, 86129-38-6; **2b**, 86129-39-7; **2c**, 86129-40-0; **2d**, 86129-41-1; **2e**, 86129-42-2; **2f**, 86129-43-3; **3a**, 43227-83-4; **3b**, 86129-44-4; **4** ($R^1 = R^3 = R^4$ = H), 78-94-4; **4** ($R^1 = CH_2CH_2CH_3$; $R^3 = R^4$ = H), 2918-13-0; **4** ($R^1 = R^3$ = H; $R^4 = CH_3$), 814-78-8; **5a**, 83483-17-4; **5b**, 86129-45-5; **5c** (isomer 1), 86129-46-6; **5c** (isomer 2), 86129-47-7; **5d** (isomer 1), 86129-48-8; **5d** (isomer 2), 86129-49-9; (*E*)-3-hexen-2-one, 4376-23-2; (*Z*)-3-hexen-2-one, 86129-50-2; dimethoxyethylamine, 22483-09-6; (*R*)-(−)-2-aminobutanol, 5856-63-3; methyl nitroacetate, 2483-57-0; 3-aminopropanol, 156-87-6; benzylamine, 100-46-9; β-alanine, 107-95-9.

Indoles as Dipolarophiles toward 3,5-Dichloro-2,4,6-trimethylbenzonitrile Oxide

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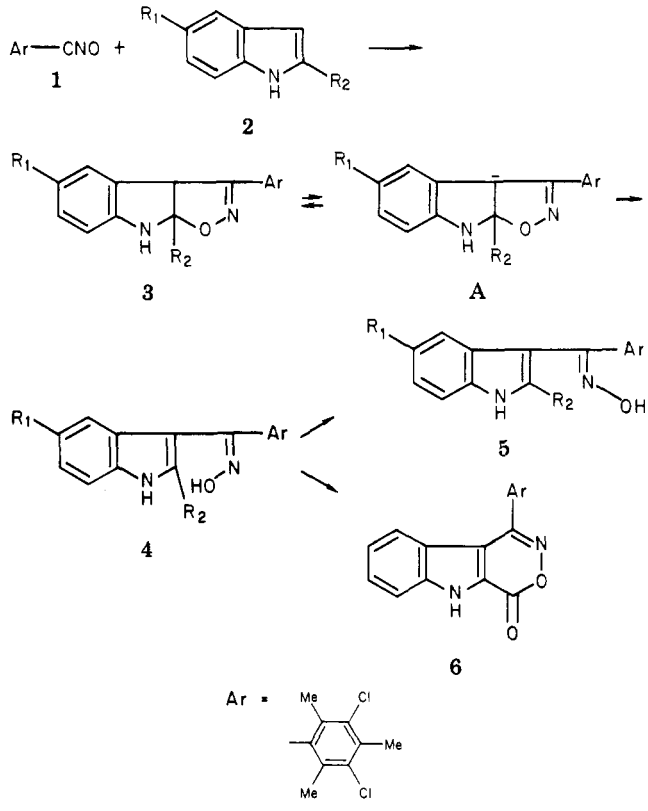
In spite of the well-known propensity of aromatic heterocycles to undergo substitution rather than addition reactions, 1,3-dipolar cycloadditions to five-membered, electron-rich heteroaromatics are documented in the chemical literature.[1-10] Our previous contribution in this area was concerned with the behavior of 3,5-dichloro-2,4,6-trimethylbenzonitrile oxide (1) toward furan, thiophene, and their benzoderivatives.[9] Recently, a report appeared dealing with the reaction of benzonitrile and mesitonitrile oxides with indole and N-substituted indoles.[11] This paper prompted us to report the results obtained in our laboratory upon treatment of 1 with the indole derivatives **2a–e**.

Scheme I



[a] a, $R_1 = R_2$ = H; b, R_1 = OMe, R_2 = H; c, $R_1 = NO_2$, R_2 = H; d, R_1 = H, R_2 = Me; e, R_1 = H, R_2 = COOEt;

The reaction between 1 and 2 was carried out in boiling benzene by using a large excess of the potential dipolarophile to minimize side reactions of 1. Heating was continued until the disappearance of the starting nitrile oxide; reaction times, products, and yields are collected in Table I.

Although both oximes **4a** and **5a** could be isolated in pure form by column chromatography, the *Z* isomer **4a** was found to rearrange completely to the stable *E* form **5a** (Scheme I) on heating for a few hours or by standing at room temperature for several days. It was ascertained that the tricyclic compounds **3c** and **3e** are not stable in boiling benzene but change slowly to give **5c** and **6**, respectively. In harmony with this trend, the TLC analyses of the reaction mixtures showed that **5c** and **6** were practically absent at short times, thus suggesting that these compounds are secondary products. On the other hand, when the reaction of **2a** was monitored by periodic TLC analyses, an intermediate product became evident, the isolation of which through chromatographic procedures was precluded by its lability. This goal, however, was reached upon treatment of 1 with a modest excess of **2a** followed by removal in vacuo of the volatile components and fractional recrystallization of the resulting mixture. The new product, which was formulated as **3a**, was shown to originate on heating a mixture of **4a** and **5a**; the same oximes were obtained when passing **3a** through a silica gel column. Interestingly, the rearrangement of the cycloadducts **3a,c** to ring-opened oximes was greatly accelerated by the presence of triethylamine, being complete within 1 h at

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