Calcd for $C_8H_5N_5O_4Na_2 \cdot 3H_2O$: C, 28.66; H, 3.31; N, 20.89. Found: C, 28.67; H, 3.25; N, 20.86.

After drying at 100 °C under high vacuum, the crystals analyzed for a hemihydrate.

Acknowledgment. The authors thank Drs. G. H. Hitchings and H. J. Schaeffer for fruitful discussions and encouragement, Dr. B. S. Hurlbert and Mr. A. Ragouzeous for the NMR spectra, Dr. D. A. Brent and Ms. D. Rouse for mass spectral studies, and Mrs. P. Baker, Miss N. T. Rodgers, and Mrs. J. Miller for technical assistance.

Registry No.—**3**, 67873-54-5; **7a**, 67873-55-6; **7b**, 67873-56-7; **7c**, 67873-57-8; **7d**, 67873-58-9; **7e**, 67873-59-0; **8b**, 67873-60-3; **8c**, 67873-61-4; **8d**, 67873-62-5; **8e**, 67873-63-6; **9a**, 67873-64-7; **9b**, 67873-65-8; **9c**, 67873-66-9; **10**, 67873-67-0; **11a**, 67873-68-1; **12a**, 67873-69-2; **12b**, 67873-70-5; **13**, 67873-71-6; **14**, 67873-72-7; **15**, 67873-73-8; **16**, 67873-74-9; **16** disodium salt, 67873-75-0; **17** disodium salt, 67873-76-1; 6-chloroisocytosine, 1194-21-4; methylhydrazine, 60-34-4; ethylhydrazine, 624-80-6; 2-hydroxyethylhydrazine, 109-84-2; *n*-butylhydrazine, 3530-11-8; benzylhydrazine dihydrochloride, 20570-96-1; 6-chloro-2,4-diaminopyrimidine, 156-83-2; 2-amino-6-chloro-4-mercaptopyrimidine, 6310-02-7; 2-amino-4,6-dichloropyrimidine, 56-05-3; sodium methoxide, 124-41-4; 2-amino-4-chloropyrimidine, 3993-78-0; 6-hydrazinoisocytosine, 6298-85-7; diethyl ketomalonate, 609-09-6; dimethyl 2,2′[dithiobis[(2-amino-6,4-pyrimidinediyl)(2-methyl-2-hydrazinyl-1-ylidene)]]bis[propanoate], 67873-77-2.

Supplementary Material Available. Full data available include the following: microanalyses on compounds **3, 4u–x, 6, 7, 8c–e, 9b,c, 12b, 14** (by method B), and **16** (free acid); UV data on compounds **3, 4u–x, 6, 7, 8c–e, 9b,c, 10, 12b, 13, 14, and 16** (free acid); NMR data on compounds **3, 4u–x, 6, 7, 8c–e, 9b,c, 10, 12b,** and **16** (free acid); and mass spectral data on **6f, 6h, 6o, 6s, 9b,c 10, 13,** and **16** (free acid) (13 pages). Ordering information is given on any current masthead page.

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(17) Exchangeable with D_2O.
(18) A metastable ion for this fragmentation was detected by accelerating voltage scans, keeping the electric and magnetic sectors constant.
(19) When dissolved in 50 mL of methanol at room temperature for 20 days, 100 mg of **8b** provided 30 mg of the analytically pure disulfide as off-white crystals: mp 215–217 °C dec; NMR (Me_2SO-d_6) δ 2.21 (s, 3 H), 3.50 (s, 3 H), 3.69 (s, 3 H), 6.71 (br s, 2 H), 6.77 (s, 1 H); mass spectrum (field desorption), *m/e* 508 (M). Anal. Calcd for $C_{18}H_{24}N_{10}O_4S_2$: C, 42.51; H, 4.76; N, 27.54; S, 12.61. Found: C, 42.41; H, 4.82; N, 27.45; S, 12.58.
(20) It also proved convenient to utilize a 2:1 mixture as described (**7c**) for this synthesis since the hydrazone is easily separated from the reaction mixture by filtration.
(21) A metastable ion for this fragmentation was detected by the MIKES[8] technique.

2-(Trichloroacetyl)pyrroles as Intermediates in the Preparation of 2,4-Disubstituted Pyrroles

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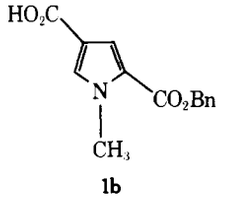
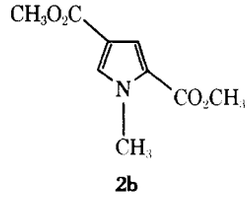
The preparation of several N–H and *N*-methyl-2,4-disubstituted pyrroles is described. Friedel–Crafts formylation using α,α-dichloromethyl methyl ether/$AlCl_3$ and a 2-substituted pyrrole as substrate introduced a 4-formyl group cleanly onto the pyrrole ring in high yield. The question of isomer production in this step was rigorously proven by preparing all isomers in contention and by comparison to known compounds. The use of 2-(trichloroacetyl)-pyrroles as substrates for the Friedel–Crafts formylation allows facile preparation of 4-formyl-2-carboxy-, -2-(alkoxycarbonyl)-, and -2-(aminocarbonyl)pyrroles and provides easy entry to 3-substituted pyrroles by removal of the 2-(trichloroacetyl) group via the carboxylic acid.

In the course of our work on the synthesis of polypyrrole antibiotics, it became necessary to prepare, efficiently and on a large scale, *N*-methylpyrroles suitably substituted at C-2 and C-4. Specifically, we required 2-benzyloxycarbonyl-4-carboxy-*N*-methylpyrrole (**1b**). A recent report[1] of the synthesis of 2,4-bis(methoxycarbonyl)-*N*-methylpyrrole (**2b**) seemed to offer an excellent beginning. However, due to some shortcomings of that procedure, which will be discussed, we have developed an alternate process.

The key to the present method is the Friedel–Crafts formylation of a 2-substituted pyrrole by $AlCl_3/\alpha,\alpha$-dichloromethyl methyl ether. This combination was reported[2] to formylate 2-(methoxycarbonyl)pyrrole (**3a**) at −20 °C selectively in the 4 position. We have extended this process to now



1b



2b

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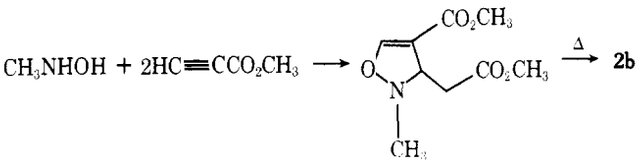
include not only the *N*-methylpyrrole ester **3b**, but also the very versatile 2-(trichloroacetyl)pyrroles, with ≤3% contamination by the corresponding 5-formylated products. The trichloroacetyl group can then be converted to the acid,[3] esters,[3] or amides[4,5] with facility. Also, this process can be used to synthesize not only many pyrroles having 2 and 4 substituents, but also 3-substituted pyrroles by simple removal of the trichloroacetyl group originally at C-2.

Specifically, the question of isomer distribution and identification resulting from formylation, confused in the earlier literature,[6] was rigorously established by careful examination of total crude reaction products and by unequivocal synthesis of all isomers in question. In general, the matter of isomer production is cause for concern in the substitution of any unsymmetrical substrate. Previous efforts to steer electrophilic substitution of 2-substituted pyrroles to the less favorable[7] 4 position by the use of an electron-withdrawing group in the 2 position have involved iminium salts,[8,9] thioesters,[10] or nitriles,[11] with varying degrees of success.

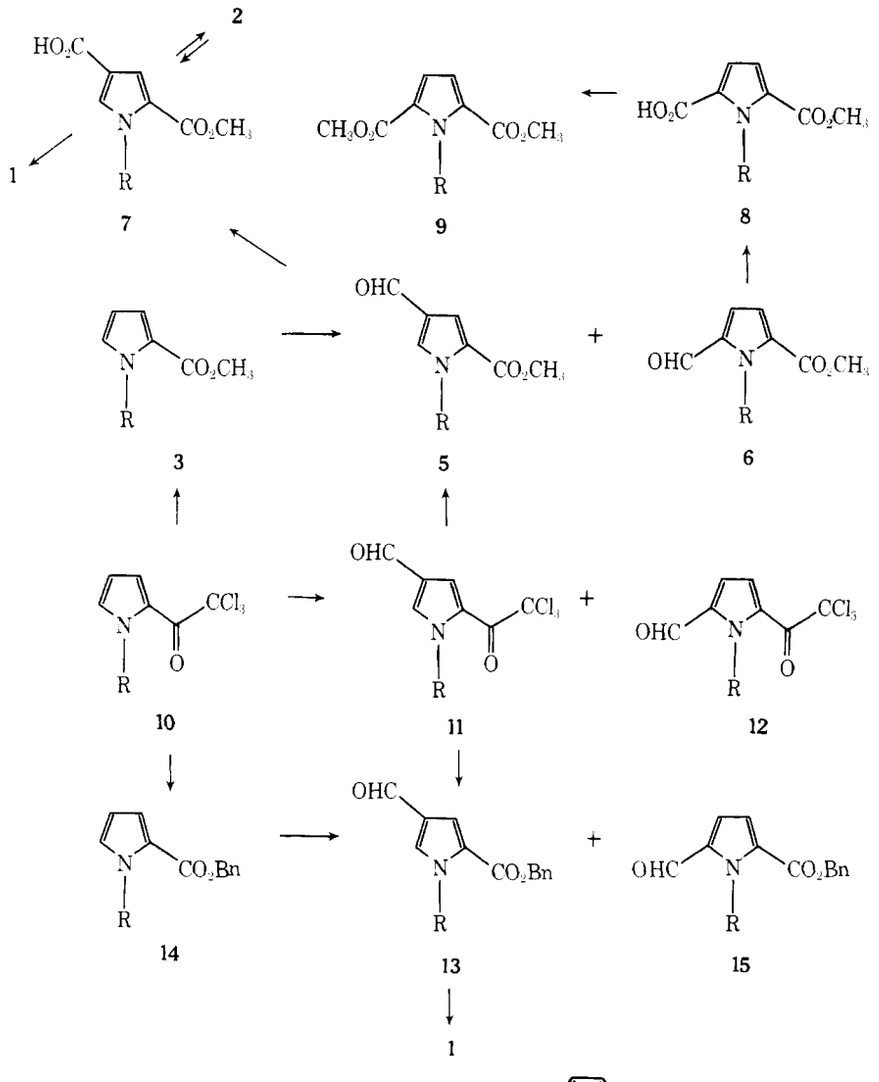
First, we examined the reported synthesis[1] of 2,4-bis(methoxycarbonyl)-*N*-methylpyrrole (**2b**) from methyl propiolate. The yield of isoxazoline **4** was good (85%) when one employed 200 mol % of *N*-methylhydroxylamine, obtained from the catalytic hydrogenation of nitromethane in THF using Pd/C as catalyst, and methyl propiolate.[12,13] The difficulty arose in that isoxazoline **4** must be purified by column chromatography if the subsequent rearrangement to pyrrole is to proceed with reproducibility. The pyrrolic product **2b** likewise must be chromatographed, and on the scale that was being employed (1–2 mol) this inconvenience overshadowed the attractive features that this route held. In addition, numerous attempts were made to duplicate the reported 88% yield of diester **2b**, but the best yield attainable in our hands was 58%.



4

Thus, we needed to develop a new procedure, and our results are summarized in Scheme I. The Friedel–Crafts formylation proceeded selectively as reported[2] (**3a** → **5a**), giving comparable results at −20 °C; by purposely carrying out the reaction at 0 °C we obtained a 10:1 mixture of isomers **5a** and **6a**, respectively. A Vilsmeier reaction on the same substrate **3a** gave the same two isomers, now in a ratio of 1:2, and their identities were established as follows. The major isomer from the Friedel–Crafts reaction was converted to acid **7a** and diester **2a**, identical with the compounds that were obtained

Scheme I



from the rearrangement of isoxazoline **4**. Their physical properties differed substantially from those of the corresponding products (**8a** and **9a**) obtained from the minor isomer. Also, their NMR absorptions were as expected;[14] thus, the coupling constants of the 2,4 hydrogens on a pyrrole ring are about 2 Hz, while the $J_{3,4}$ value which one would observe for a 2,5 isomer is about 4 Hz.

The latter value was obtained from the minor isomer **6a** of the Friedel–Crafts reaction. This compound, being a symmetrically substituted pyrrole, was converted to the corresponding dimethyl ester **9a**, which then gave a singlet in the NMR for the ring protons, but only after treatment with D_2O to wash out coupling with the N–H. Both the 4-formyl (**5a**) and 5-formyl isomers (**6a**) were then converted to the corresponding *N*-methyl compounds (**5b, 6b**) by treatment with NaH and dimethyl sulfate. At this point, the Friedel–Crafts formylation at −20 °C was repeated using as substrate 2-methoxycarbonyl-*N*-methylpyrrole (**3b**). A single product was observed, which was identical with the 4-formyl isomer (**5b**) obtained by N-methylation of the known 4-formyl N–H compound **3a**. Thus, Friedel–Crafts formylation of an *N*-methylpyrrole 2-ester was shown to proceed with the same selectivity as with the N–H compound.

Additional structural proof for these isomers was obtained from their NMR spectra. Formylation of 2-benzyloxycarbonyl-*N*-methylpyrrole (**14b**) with the Vilsmeier reagent afforded a 2:1 mixture of **13b** and **15b**, respectively. Preparative GC of the crude reaction product enabled the isolation of a sufficient quantity of the 5 isomer **15b** to demonstrate differences from the 4 isomer **13b**. The ring protons of **15b** appear as an AB pattern (J = 4 Hz); this spectrum and that of **13b**, in which the ring protons appear as singlets, are quite distinct. In addition, **13b** was converted by oxidation to **1**, identical with that obtained from methyl ester **7b** via transesterification. Examination of 2-benzyloxycarbonyl-*N*-methylpyrrole (**14b**) reveals three multiplets for the pyrrole protons: δ 6.87 (dd, J = 2, 4 Hz), 6.65 (pseudo t, J = 2 Hz), 5.98 (dd, J = 2, 4 Hz). Irradiation of the highest field signal, that of the 4 proton, collapses the others to doublets (J = 2 Hz). The NMR spectrum of *N*-methyl-2-(trichloroacetyl)pyrrole (**10b**) shows similar behavior.

We then applied the formylation reaction to 2-(trichloroacetyl)pyrroles since the trichloroacetyl group would allow facile conversion to any ester, any amide, or a carboxylic acid, and the latter in turn could be removed to allow entry into the 3-substituted pyrrole series. Quite simply, the Friedel–Crafts formylation of N–H and *N*-methyl-2-(trichloroacetyl)pyrroles (**10a, b**) at −20 °C or below gave a 50:1 ratio of 4- (**11**)/5-formylated (**12**) compounds. Separation of isomers at this stage is difficult, but after conversion to the corresponding esters (methyl and benzyl) separation is easily effected. The identity of isomers from this reaction was again established by conversion to the same set of compounds obtained either by Friedel–Crafts formylation for the 2-(methoxycarbonyl)-pyrrole (**3a**) followed by N-methylation or by direct formylation of 2-methoxycarbonyl-*N*-methylpyrrole (**3b**). These results are summarized in Scheme I.

Acylation of a 2-substituted pyrrole can, in theory, give several isomeric, disubstituted products of which we have so far considered only two, the 2,4 and 2,5 isomers. If the nitrogen is initially unsubstituted, it too might be acylated. We never observed N-acylation, although the known lability of amide bonds involving a pyrrole nitrogen[3] might preclude its isolation considering the hydrolytic isolation applied to Friedel–Crafts reaction mixtures. The other possibility is the 2,3 isomer; this product was likewise never observed in any of our reactions. Analysis of the crude product by GC showed at most only one minor impurity, which always turned out to be the 5 isomer. Previous work in this field also never observed the 2,3 isomer, and considering electronic and steric arguments[14] this is not surprising. The minor product we obtained clearly is not the 2,3 isomer by virtue of the identity of this minor product with the 2,5 isomer and its expected difference ($J_{4,5}$ = 3 Hz) from the 2,3 isomer.

Experimental Section

Melting points were taken on a Buchi melting point apparatus and are uncorrected. Gas chromatography conditions were the following: (A) Hewlett Packard 402 all glass system, 6 ft, 5% SE-30 on Chromosorb W, 80–100 mesh, He at 100 mL/min; (B) Aerograph Autoprep A-700, 5 ft, 3% OV-17 on Aeropack 30, 100–120 mesh.

^{1}H NMR spectra were taken on a Varian T-60 with internal Me_4Si. Combustion analyses were performed by the Analytical Laboratory, Department of Chemistry, University of California, Berkeley. ^{13}C NMR spectra were taken on a TT-23 (Brucker WH-90 console equipped with a Nicolet 80 computer and a Varian 25.14 MHz magnet). Computerized gas chromatographic/mass spectrometric analyses were done with a double-focusing DuPont 21-492B mass spectrometer interfaced with a Varian 204-1B gas chromatograph with a linear temperature programmer. The mass spectral data were acquired and processed with a DuPont 21-094 data system. Low- and high-resolution mass spectra were obtained with AEI-MS12 and CEC-110B spectrometers, respectively.

2-(Trichloroacetyl)pyrrole (10a),[3] 2-(methoxycarbonyl)-pyrrole (3a),[3] and 4-formyl-2-(methoxycarbonyl)pyrrole[2] (5a) [GC (conditions B, 180 °C), 238 s] were prepared according to literature procedures.

4-Carboxy-2-(methoxycarbonyl)pyrrole (7a) was made by the same procedure as the corresponding *N*-methyl compound **7b**, below: mp 249–252 °C dec; NMR ($CDCl_3$/Me_2SO-d_6) δ 10.3 (brd s, 1 H), 9.1 (brd s, 1 H), 7.4 (m, 1 H), 7.1 (m, 1 H), 2.8 (s, 3 H).

2,4-Bis(methoxycarbonyl)pyrrole (2a). Acid **7a** was dissolved in methanol saturated with HCl at 0 °C. After standing at 0 °C for several hours, the methanol was evaporated and the residue, dissolved in $CHCl_3$, was washed with aqueous $NaHCO_3$. Evaporation of the dried (Na_2SO_4) $CHCl_3$ phase left a residue which was sublimed (100 °C/200 μm): mp 122–123.5 °C (lit.[15] mp 125–126 °C); NMR ($CDCl_3$) δ 10.1 (brd s, 1 H), 7.5 (m, 1 H), 7.3 (m, 1 H), 3.9 (s, 3 H), 3.85 (s, 3 H).

5-Formyl-2-(methoxycarbonyl)pyrrole (6a). This compound was prepared as described:[16] mp 90–93 °C (lit.[15] mp 92–93 °C); NMR ($CDCl_3$) δ 11 (brd s, 1 H, NH), 9.8 (s, 1 H, CHO), 6.9 (d, J = 2 Hz, 2 H, ring H), 3.9 (s, 3 H, OCH_3); GC (conditions B, 180 °C), 84 s.

5-Carboxy-2-(methoxycarbonyl)pyrrole (8a) was prepared by the same procedure as **7b**: mp 241–242 °C (lit. mp 243[17] and 270 °C[18]); NMR (Me_2SO-d_6) δ 12.5 (brd s, 1 H, NH), 6.7 (d, J = 2 Hz, ring H), 3.75 (s, 3 H, OCH_3).

2,5-Bis(methoxycarbonyl)pyrrole (9a) was prepared by a Fischer esterification of **8a**, as described for **2a** above, and sublimed (80 °C/200 μm): mp 126–127.5 °C (lit.[6] mp 126–127 °C, which was incorrectly assigned to the 2,4-diester but subsequently reassigned correctly[16]); NMR ($CDCl_3$) δ 9.7 (brd s, 1 H, NH), 6.7 (2d, J = 2 Hz, ring H), 3.8 (s, 6 H, OCH_3).

***N*-Methyl-2-(trichloroacetyl)pyrrole (10b).**[19] To CH_2Cl_2 (60 mL, distilled from P_2O_5) and trichloroacetyl chloride (18.2 g, 0.1 mol) was added *N*-methylpyrrole (8.11 g, 0.1 mol) in 40 mL of CH_2Cl_2 over a period of 3 h; vigorous stirring and a nitrogen sweep during this time aided the removal of HCl as it was formed. The magenta solution was stirred overnight and then was evaporated, dried, and sublimed (75 °C/0.1 mm) to give 21.3 g (94%) of **10b**: NMR ($CDCl_3$) δ 7.50 (dd, J = 2, 4 Hz, 1 H), 6.96 (pseudo t, J = 2 Hz, 1 H), 6.20 (dd, J = 3, 4 Hz, 1 H), 3.98 (s, 3 H); GC (conditions A, 150 °C), 144 s.

2-Methoxycarbonyl-*N*-methylpyrrole (3b)[20] was prepared from 2-trichloroacetyl-*N*-methylpyrrole (**10b**) by the same procedure as for **3a** and Kugelrohr distilled (80 °C/200 μm): NMR ($CDCl_3$) δ 6.95 (m, 1 H), 6.75 (m, 1 H), 6.1 (m, 1 H), 3.95 (s, 3 H), 3.85 (s, 3 H).

4-Formyl-2-methoxycarbonyl-*N*-methylpyrrole (5b). To 2.47 g (17.8 mmol) of *N*-methyl ester **3b** and 5.7 g (42.6 mmol) of $AlCl_3$ in 75 mL of a 1:1mixture of 1,2-dichloroethane/nitromethane, kept at −20 °C, was rapidly added 2.45 g (21.3 mmol) of dichloromethyl methyl ether in 10 mL of dichloroethane, and the reaction mixture was maintained at −20 °C overnight. It was poured over 50 g of ice, the layers were separated, the water layer was washed with ether, and the combined organic fractions were dried over Na_2SO_4. After filtration and evaporation, a residue was obtained which was recrystallized from ether/hexane to yield 2.66 g of crystals in two crops, 89% yield: mp 97–99 °C; GC (conditions B, 180 °C), 198 s; NMR ($CDCl_3$)

δ 9.8 (s, 1 H), 7.4 (m, 2 H), 4.0 (s, 3 H), 3.9 (s, 3 H). Anal. Calcd for $C_8H_9NO_3$: C, 57.5; H, 5.4; N, 8.4. Found: C, 57.4; H, 5.4; N, 8.4.

4-Carboxy-2-methoxycarbonyl-*N*-methylpyrrole (7b). To a solution of 1.0 g (6 mmol) of formyl ester **5b** in 150 mL of reagent acetone was added over 2 h a solution of $KMnO_4$ (1.8 g, 12 mmol) in 200 mL of acetone/water (1:1). After 3 h, the purple solution was poured into 250 mL of a solution of 10% $NaHSO_3$ in 1 N HCl and the solution was extracted with $CHCl_3$ (3 × 200 mL). The combined chloroform extracts were washed with H_2O (1 × 200 mL) and then with 5% $NaHCO_3$ (3 × 200 mL). The bicarbonate washes were carefully acidified to pH 3 and extracted with $CHCl_3$ (3 × 200 mL), and the chloroform was washed with saturated aqueous NaCl, dried over Na_2SO_4, filtered, and evaporated, leaving 966 mg (5.3 mmol, 88% yield) of acid **7b**: mp 183–184 °C; NMR ($CDCl_3$) δ 8.2 (s, 1 H), 7.4 (m, 2 H), 4.0 (s, 3 H), 3.9 (s, 3 H). Anal. Calcd for $C_8H_9NO_4$: C, 52.5; H, 5.0; N, 7.7. Found: C, 52.4; H, 5.0; N, 7.7.

2,4-Bis(methoxycarbonyl)-*N*-methylpyrrole (2b) was prepared by a Fischer esterification of **7b**, as described for **2a** above. It was identical with the compound prepared from isoxazoline **4**[1] in melting point (98–101 °C), NMR, and GC (conditions B, 180 °C; 147 s).

5-Formyl-2-methoxycarbonyl-*N*-methylpyrrole (6b). *N,N*-dimethylformamide (2.3 mL, 58 mmol) was added over 15 min to phosphorus oxychloride (4.9 mL, 58 mmol) followed by 10 mL of 1,2-dichloroethane, and the solution was cooled to 5 °C while adding, over an hour, 3.62 g (26 mmol) of 2-methoxycarbonyl-*N*-methylpyrrole (**3b**) in 10 mL of dichloroethane. The solution was refluxed for 15 min, allowed to cool to room temperature, and treated with aqueous NaOAc (13.1 g in 30 mL of H_2O). The organic phase was removed, the aqueous layer was extracted with ether, the combined organic layers were washed with aqueous bicarbonate and dried, and the solvent was evaporated to leave 3.76 g (23 mmol) of a 1:2 mixture of 4- and 5-formylated products, **5b** and **6b**. The 5 isomer, **6b**, was fractionally distilled from the mix (110 °C/300 μm) and recrystallized from ethanol/water: mp 104–106 °C (lit.[16] mp 100–102 °C); NMR ($CDCl_3$) δ 6.9 (s, 2 H, ring H), 4.3 (s, 3 H, NCH_3), 3.9 (s, 3 H, OCH_3); GC (conditions B), 98 s.

This material was identical with a sample derived from N-methylation of 5-formyl-2-(methoxycarbonyl)pyrrole (**6a**).

5-Carboxy-2-methoxycarbonyl-*N*-methylpyrrole (8b) was prepared by permanganate oxidation of **6b** in the same manner as the isomeric 4-carboxylic acid **7b**: mp 186 °C; NMR ($CDCl_3$) δ 9.8 (brd s, 1 H, CO_2H), 7.1 (d, J = 4 Hz, 1 H, ring H), 6.95 (d, J = 4 Hz, 1 H, ring H), 4.3 (s, 3 H, NCH_3), 3.9 (s, 3 H, OCH_3).

2,5-Bis(methoxycarbonyl)-*N*-methylpyrrole (9b) was prepared by a Fischer esterification of the 5-carboxylic acid **8b** as described for **2a** above and sublimed (80 °C/200 μm): mp 76–78 °C (from ethanol/H_2O) (lit.[18] mp 78–80 °C); NMR ($CDCl_3$) δ 6.7 (s, 2 H), 4.2 (s, 3 H), 3.75 (s, 6 H); GC (conditions B), 105 s.

4-Formyl-*N*-methyl-2-(trichloroacetyl)pyrrole (11b). A solution of $AlCl_3$ (19.2 g, 0.144 mol), nitromethane (120 mL), *N*-methyl-2-(trichloracetyl)pyrrole (**10b**) (13.6 g, 0.06 mol), 1,2-dichloroethane (120 mL), and CH_2Cl_2 (120 mL) was cooled to −55 °C, and dichloromethyl methyl ether (8.27 g, 0.072 mol) in 18 mL of dichloroethane was added over 15 min. After 40 min, the reaction was complete and the orange solution was warmed to −20 °C, poured onto 2 L of ice/H_2O, and allowed to stand overnight. The mixture was extracted with $CHCl_3$ (twice), dried (Na_2SO_4), and evaporated to give 15.07 g (98.5%) of crude product. Sublimation at 100 °C (10 μm) gave 13.8 g (91%) of pure product: mp 118–123 °C; NMR δ 9.79 (s, 1 H), 7.85 (d, J = 1.5 Hz, 1 H), 7.51 (d, J = 1.5 Hz, 1 H), 4.05 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 184.7, 173.8, 136.0, 124.8, 123.8, 123.0, 95.4, 39.3; GC (conditions A, 160 °C), 6 min 4 s (5 isomer) and 7 min 8 s (4 isomer), 1.2% of the 5 isomer is present in the crude product. GC/MS (150 ft × 0.030 in. 10% OV-10 support coated open tubular column; temperature programmed at 130 to 250 °C at 4 °C/min; source 270 °C; injector 250 °C; He at 2 mL/min at 70 eV) revealed that the two peaks are isomers: *m/e* 257 (0.1), 255 (0.1), 253 (0.2), 223 (0.8), 221 (4.5), 219 (6.4), 187 (2.4), 185 (7.1), 158 (2.9), 157 (9), 151 (1), 136 (100), 120 (3), 108 (6), 92 (4), 79 (14), 53 (21), 42 (13). Separation of the isomers could not be effected at this stage. Anal. Calcd for $C_8H_6Cl_3NO_2$: C, 37.8; H, 2.4; N, 5.5. Found: C, 37.8; H, 2.5; N, 5.4.

4-Formyl-2-(trichloroacetyl)pyrrole (11a) was prepared by formylation using the same procedure as used for 4-formyl-*N*-methyl-2-(trichloroacetyl)pyrrole (**11b**). The crude product (97% yield) was converted to the 2-methyl ester (**5a**) and shown by GC (conditions B) to contain 3% of the 5-formyl isomer (**6a**).

2-Benzyloxycarbonyl-4-formyl-*N*-methylpyrrole (13b). A solution of 4-formyl-*N*-methyl-2-(trichloroacetyl)pyrrole (**11b**) (7.65 g, 0.030 mol), benzyl alcohol (32.44 g, 0.30 mol), and triethylamine (3.8 g, 0.038 mol) was stirred at room temperature overnight, and the solvent was evaporated, concluding with Kugelrohr distillation to remove excess benzyl alcohol to give a quantitative yield of crude product: GC (conditions A, 220 °C), 5 (5 isomer) and 7 min (4 isomer). The 5 isomer is 2% of the mixture, and it can be preferentially removed by maintaining the Kugelrohr at 95–100 °C (70 μm) for several hours. For pure **13b**: mp 80 °C; NMR ($CDCl_3$) δ 9.65 (s, 1 H), 7.29 and 7.22 (s, s, 7 H total), 5.17 (s, 2 H), 3.89 (s, 3 H). Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.1; H, 5.4; N, 5.8. Found: C, 69.1; H, 5.5; N, 5.8.

2-Benzyloxycarbonyl-4-carboxy-*N*-methylpyrrole (1b). A solution of $KMnO_4$ (11.85 g, 75 mmol) in 1.35 L of 1:1 acetone/H_2O was added with stirring over 3 h to 2-benzyloxycarbonyl-4-formyl-*N*-methylpyrrole (**13b**) (6.08 g, 25 mmol) in 750 mL of acetone. The resulting mixture was treated with 400 mL of 10% $NaHSO_3$ in 1 M HCl (w/w), and the clear solution was extracted with $CHCl_3$ (three times). The chloroform was dried (Na_2SO_4) and evaporated to give 6.28 g (97%) of **1b**: mp 160–161.5 °C (after crystallization from ethanol), identical with material prepared from **7** by transesterification; NMR ($CDCl_3$) δ 9.52 (s, 1 H), 7.40 and 7.35 (s, s, 7 H total), 5.25 (s, 2 H), 3.95 (s, 3 H); IR (KBr) 3436, 1698, 1553 cm^{-1}. Anal. Calcd for $C_{14}H_{13}NO_4$: C, 64.9; H, 5.0; N, 5.4. Found: C, 64.7; H, 5.1; N, 5.3.

2-Benzyloxycarbonyl-*N*-methylpyrrole (14b). A solution of *N*-methyl-2-(trichloroacetyl)pyrrole (453 mg, 2 mmol), benzyl alcohol (2.2 g, 20 mmol), and triethylamine (252 mg, 2.5 mmol) was stirred in a 60 °C oil bath for 12 h, after which it was evaporated, concluding with Kugelrohr distillation (60 °C/0.1 min) to remove excess benzyl alcohol. The residue was a quantitative yield of **14b**: NMR ($CDCl_3$) δ 7.32 (s, 5 H), 6.87 (dd, J = 2, 4 Hz, 1 H), 6.65 (pseudo t, J = 2 Hz, 1 H), 5.98 (dd, J = 2, 4 Hz, 1 H), 5.22 (s, 2 H), 3.95 (s, 3 H); irradiation at δ 5.98 gave δ 6.87 (d, J = 2 Hz) and 6.65 (d, J = 2 Hz); GC (conditions B, 245 °C), 72 s. MS Calcd for $C_{13}H_{13}NO_2$: *m/e* 215.0946. Found: *m/e* 215.0945.

2-Benzyloxycarbonyl-5-formyl-*N*-methylpyrrole (15b). A solution of 1,2-dichloroethane (0.5 mL), DMF (80 mg, 1.1 mmol), and $POCl_3$ (70 mg, 1.1 mmol) was warmed to room temperature and then cooled in an ice bath as a solution of 2-benzyloxycarbonyl-*N*-methylpyrrole (**14b**) (211 g, 1.0 mmol; crude product from previous reaction) in 0.5 mL of dichloroethane was added in 5-μL portions over 0.5 h. After 10 additional min, the solution was refluxed in an oil bath for 30 min and then poured onto 10 mL of 15% aqueous $Na_3PO_4 \cdot 12H_2O$, refluxed for 15 min, and partitioned between $CHCl_3$ and H_2O. The organic layer was dried (Na_2SO_4) and evaporated to give 238 g (98%) of a mixture of **15b** and **13b**. GC (conditions A, 250 °C): 2.4 [5 isomer (**15b**)] and 4.2 min [4 isomer (**13b**)]; ratio 2:1. Preparative GC (conditions B, 250 °C) gave 11.8 mg of the 5 isomer (**15b**): NMR ($CDCl_3$) δ 9.75 (s, 1 H), 7.42 (s, 5 H), 6.94 (q, J = 4 Hz, 2 H), 5.35 (s, 2 H), 4.15 (s, 3 H). MS Calcd for $C_{14}H_{13}NO_3$: *m/e* 243.0895. Found: *m/e* 243.0901.

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Registry No.—**1b,** 67858-46-2; **2a,** 2818-07-7; **2b,** 29182-34-1; **3a,** 1193-62-0; **3b,** 37619-24-2; **5a,** 40611-79-8; **5b,** 67858-47-3; **6a,** 1197-13-3; **6b,** 1198-75-0; **7a,** 67858-48-4; **7b,** 67858-49-5; **8a,** 1199-64-0; **8b,** 67858-50-8; **9a,** 1757-29-5; **9b,** 1757-30-8; **10a,** 35302-72-8; **10b,** 21898-65-7; **11a,** 67858-51-9; **11b,** 67858-52-0; **13b,** 67858-53-1; **14b,** 67858-54-2; **15b,** 67858-55-3; trichloroacetyl chloride, 76-02-8; *N*-methylpyrrole, 96-54-8; dichloromethyl methyl ether, 4885-02-3; 5-formyl-*N*-methyl-2-(trichloroacetyl)pyrrole, 67858-56-4.

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Thermal Decomposition of 1-(Dialkylphosphoryl)imidazoles[1,2]

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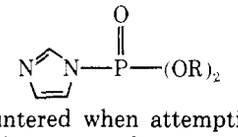
A number of 1-(dialkylphosphoryl)imidazoles, $(RO)_2PONC_3H_3N$, were synthesized in order to gain information requisite to a systematic search for compounds of this type in biological systems. Compounds containing short straight alkyl chains (R = methyl, ethyl, *n*-butyl, allyl) decompose at temperatures below 80 °C, giving 1-alkylimidazole, trialkyl phosphate, and 1,3-dialkylimidazolium polyphosphate. The di-*tert*-butyl ester decomposes to isobutylene and imidazolium polyphosphate, while the diisopropyl ester is thermally stable. The decomposition appears to result from an initial nucleophilic attack by the 3-nitrogen of one 1-(dialkylphosphoryl)imidazole on the α-alkyl carbon of another 1-(dialkylphosphoryl)imidazole.

Although a number of 1-phosphorylimidazole protein derivatives have been reported,[3-9] naturally occurring 1-(dialkylphosphoryl)imidazoles[1] have not been found. Interest in these compounds arises from the expectation that they would have a high phosphate group transfer potential and therefore might function as biological "high energy" intermediates. As a first step toward developing techniques whereby a search for compounds of this type in biological systems could be systematically undertaken, a number of 1-(dialkylphosphoryl)imidazoles were synthesized. An unanticipated property of these compounds is the ease with which lower members of the series spontaneously decompose at temperatures only slightly above room temperature. This communication concerns the products and mechanism of the decomposition.

Although thermal decomposition of a variety of phosphate esters has been known for many years, most take place at reasonably high temperatures.[10] Instability of 1-(dialkylphosphoryl)imidazoles of the general structure



was initially encountered when attempting to purify the compounds by high vacuum distillation. Nikolenko and Degterev[11] reported that the diethyl ester could be distilled at 79–80 °C (0.3 torr) with accompanying decomposition, but in our hands this compound decomposed completely within minutes at 40–45 °C (0.3 torr) and no 1-(diethylphosphoryl)-imidazole was ever detected in the distillate. The diisopropyl ester can be distilled at approximately 110 °C (0.3 torr) without significant decomposition as previously reported.[12,13] However, this compound appears to be unique among the short alkyl chain diesters in regard to thermal stability.

All of the straight chain dialkyl esters decompose at temperatures increasing with increasing chain length. 1-(Dimethylphosphoryl)imidazole decomposes explosively at temperatures only slightly above room temperature, whereas the dibutyl ester decomposes rapidly at 50–55 °C. With the exception of the diisopropyl and dilauryl esters, all of the compounds undergo extensive decomposition within a matter of hours at room temperature. However, the rate of decomposition is much slower in dilute anhydrous CCl_4 or $CHCl_3$ solution.

The products of the decompositions were separated and characterized and are listed in Table I. Two products, the corresponding 1-alkylimidazole and the trialkyl phosphate, were obtained by high vacuum distillation of the straight chain esters. After distillation, a highly viscous residue remained which dissolved completely in water to give an acidic solution showing a faintly positive reaction with ammonium molybdate. The phosphorus-containing product could be converted completely to orthophosphate by heating at 100 °C for 10 min in 2 N sulfuric acid, suggesting that the residue is mainly a polyphosphate. Thin-layer chromatography of the residue on cellulose powder eluting with either an acidic[14] or basic[15] solvent system showed essentially no material with chromatographic mobility. This behavior is characteristic of polyphosphates with a degree of polymerization greater than 4. The cationic component of the residues was identified as a 1,3-dialkylimidazolium ion from their characteristic NMR spectra; the C-4 and C-5 protons are equivalent, and in D_2O at pH approximately 9 the C-2 proton exchanged completely with deuterium within 10 min, consistent with the previous report of Olofson et al.[16] for the 1,3-dimethylimidazolium ion.

It should be noted that since the products are easily isolated in a pure form, the synthesis of 1-(dialkylphosphoryl)imidazoles followed by thermal decomposition provides a convenient single-step preparative method for both 1-alkylimidazoles and 1,3-dialkylimidazolium salts. The corresponding reaction was not observed with 1-(diphenylphosphoryl)imidazole, and therefore the method is not applicable to diaryl esters.

The formation of 1-phosphorylimidazole from orthophosphate in the autoxidation of diimidazole ferroheme[17] appears to occur by a free-radical mechanism,[18,19] and therefore it was considered possible that the thermal decomposition of 1-(dialkylphosphoryl)imidazoles might also be a free-radical reaction. However, the observation that the diallyl ester decomposes without formation of any polymeric carbon compounds would appear to exclude a free-radical mechanism for the decomposition. Supporting this conclusion, free radicals were not detected by ESR in neat samples of the dibutyl ester heated to 60 °C for 1 min and then plunged into liquid nitro-