Some Novel Reactions of Pyrrolecarboxylic Acid Chlorides

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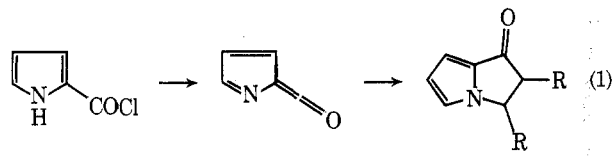
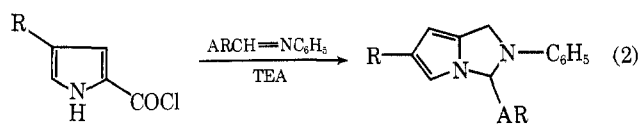
We have investigated the possibility of generating and trapping ketenes derived from pyrrole-2-carbonyl chloride and indole-2-carbonyl chloride as in eq 1. The reactivity of ketenes in cycloaddition reactions is well documented.[1-3]



(1)

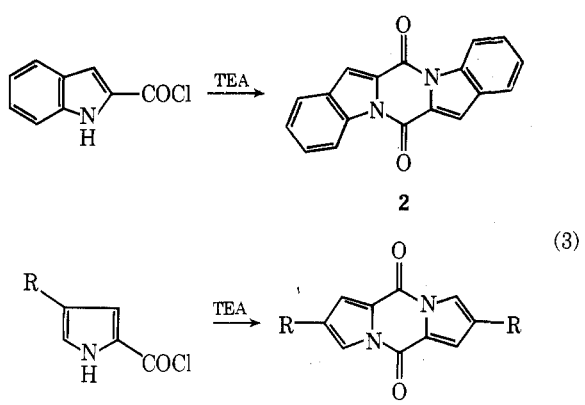
Pyrrole-2-carbonyl chloride[4] and 4-nitropyrrole-2-carbonyl chloride react with benzalaniline and *p*-methoxybenzalaniline in the presence of triethylamine (TEA) to afford the expected adducts (eq 2). In the case of indole-2-carbonyl chloride[5] no



(2)

1

similar adducts could be isolated; rather the novel ketene dimer (**2**) was isolated.[10] Similar dimers were obtained from pyrrole-2-carbonyl chloride (**3a**) and 4-nitropyrrole-2-carbonyl chloride (**3b**) when treated with TEA in the absence of a trapping agent (eq 3).

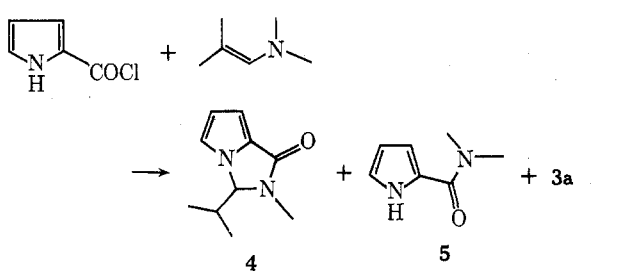


(3)

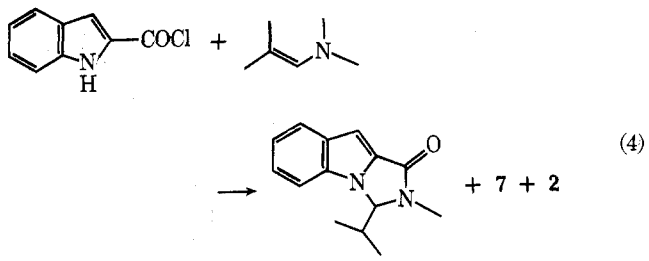
2

3a, R = H
b, R = NO_2

It was hoped that enamines could serve as traps of the presumably electrophilic ketenelike intermediates in this reaction. Reaction of pyrrole-2-carbonyl chloride with 2 equiv of isobutyraldehyde dimethyl enamine, however, gave **4** and **5** as major products[9] along with some dimer, **3a** (eq 4). Similar results were observed in the reaction of indole-2-carbonyl chloride with this enamine (eq 4). When these reactions were



4 5



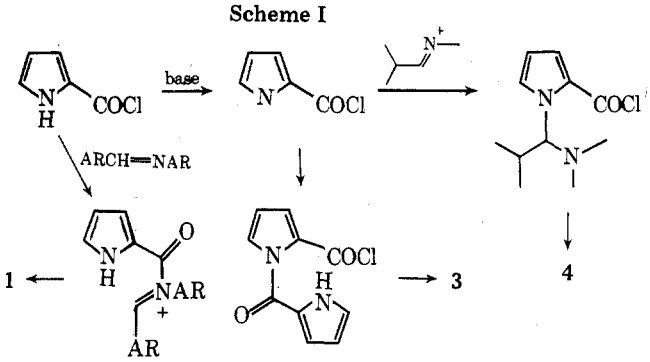
(4)

6

repeated in the presence of TEA neither **4** nor **6** were produced, the dimers **3a** and **2** and the *N,N*-dimethylamides (**5** and **7**) being isolated as the exclusive products. Attempted use of cyclohexanone pyrrolidine enamine, with or without added TEA, gave only dimers **3a** and **2** and the corresponding pyrrolidine amides.

While the above reactions could involve the intermediacy of the ketenes as in eq 1, these are not required by the data. An alternative simpler mechanism can be written as in Scheme I.[11]

Scheme I



Experimental Section[6]

Reagents. Acetone was dried over 4-Å molecular sieves and distilled fresh before use. Dimethoxyethane (DME) was distilled fresh from the sodium ketyl of benzophenone. Dichloromethane was dried over molecular sieves prior to use. Triethylamine (TEA) was distilled from molecular sieves.

Pyrrole-2-carbonyl Chloride. To a filtered solution of 3.0 g (27 mmol) of pyrrole-2-carboxylic acid in 100 ml of purified dimethoxyethane (DME) was added 5 ml of triethylamine. The solution was evaporated and dried at 0.5 mm for 4 h. The green, oily residue was then dissolved in 30 ml of DME and added dropwise, over a 10-min period, to a stirred, 0 °C solution of 30 ml of thionyl chloride in 50 ml of DME. The reaction mixture was then stirred at 0 °C for 30 min, filtered to remove a precipitate, and evaporated to afford 2.41 g of a light green solid: mp 74–83 °C; NMR (acetone-d_6) δ 6.43 (1 H, m), 7.22 (1 H, m), 7.41 (1 H, m), 11.5 (1.3 H, bs); ir ν_{KBr} 3373 and 1690 cm^{-1}; uv λ_{max} ($CHCl_3$) 288 nm (ϵ 17 000); mass spectrum *m/e* (peak match) 128.99806 (calcd for C_5H_4NOCl, 128.99814).

In a similar manner were prepared indole-2-carbonyl chloride,[5] mp 107–112 °C, *m/e* 179.01318 (calcd for C_9H_6NOCl, 179.01379), and 4-nitropyrrole-2-carbonyl chloride, mp 145–150 °C, δ 7.50 (1 H, d, J = 2.0 Hz) and 8.08 (1 H, d, J = 2.0 Hz).

Pyrrole-2-carbonyl Chloride and Benzalaniline. Adduct 1a. To a stirred solution of 0.27 g (2.1 mmol) of the above acid chloride and 0.61 g (3.4 mmol) of benzalaniline in 2 ml of dichloromethane was added at 0 °C 0.2 ml of triethylamine. After 5 min the reaction mixture was worked up to afford a gummy residue that was triturated with cold acetone. Sublimation (140 °C, 0.08 mm) afforded 0.35 g (62% yield) of adduct **1a** (Ar = C_6H_5): mp 207–208 °C; NMR (Me_2SO-d_6) δ 6.31 (1 H, dd, J = 3.7, 2.5 Hz), 6.53 (1 H, m), 6.81 (1 H, m), and 6.9–7.5 (1 H, m); ir ν_{KBr} 1695 cm^{-1}; uv λ_{max} (MeOH) 283 nm (ϵ 10 000) and 232 (7700); mass spectrum *m/e* 274.11069 (calcd for $C_{18}H_{14}N_2O$, 274.11061).

Anal. Calcd: C,78.80; H, 5.16; N, 10.22. Found: C, 78.84; H, 5.01; N, 10.33.

In a similar manner there was prepared from 4-nitropyrrole-2-carbonyl chloride and benzalaniline a 67% yield of adduct **1b** (Ar = C_6H_5): mp 209–212 °C; NMR δ 7.1–7.8 (14 H, m) and 8.37 (1 H, s); ν_{max}

(KBr) 1690 cm^{-1}; λ_{max} (MeOH) 303 nm (ϵ 11 000) and 256 (16 000); *m/e* 319.09549 (calcd for $C_{18}H_{13}N_3O_3$, 319.09568).

Anal. Calcd: C, 67.30; H, 4.06; N, 13.08. Found: C, 67.68; H, 3.99; N, 12.91.

Methanolysis of **1b** ($NaOCH_3$, MeOH) afforded benzalaniline and methyl 4-nitropyrrole-2-carboxylate.

Repetition of the above experiment with *p*-methoxybenzalaniline afforded **1a** (Ar = $CH_3OC_6H_4$): mp 143–145 °C; NMR δ 3.72 (3 H, s), 6.41 (1 H, dd, J = 5, 3 Hz), 6.63 (1 H, d, J = 5 Hz), and 6.80–7.93 (10 H, m); ν_{max} ($CHCl_3$) 1705 cm^{-1}; λ_{max} (MeOH) 230 nm (ϵ 1300) and 282 (12 000).

Anal. Calcd: C, 74.97; H, 5.31; N, 9.21. Found: C, 75.02; H, 5.24; N, 9.15.

Dimer of Pyrrole-2-carbonyl Chloride (3a). To a stirred solution of 0.21 g (1.6 mmol) of the above acid chloride in 2.0 ml of chloroform was added, with stirring, 0.5 ml of triethylamine. The resulting dark green solution was stirred for 30 min, the solvent evaporated, and the residue triturated with 10 ml of water. Recrystallization from a mixture of Me_2SoMe_2SO and CCl_4 (1:1 v/v) afforded 11 mg (4.7%) of the dimer **3a** (sublimes without melting above 250 °C): NMR (Me_2SO-d_6) δ 6.63 (2 H, dd, J = 4.2, 4.0 Hz), 7.43 (2 H, dd, J = 4.2, 2.0 Hz), and 7.85 (2 H, dd, J = 4.0, 2.0 Hz); ir ν_{max} (KBr) 1700, 1555, and 1460 cm^{-1}; uv λ_{max} (MeOH) 315 nm (ϵ 13 000), 303 (12 500), 273 (14 000), and 235 (22 000); mass spectrum *m/e* (rel intensity) 186 (32) and 86 (100); found, *m/e* 186.04291 (calcd for $C_{10}H_6N_2O_2$, 186.04293.)

Anal. Calcd: C, 64.52; H, 3.26; N, 15.05. Found: C, 63.19; H, 3.02; N, 14.82.

In a similar manner was prepared the dimer of 4-nitropyrrole-2-carbonyl chloride (**3b**) in 85% yield as light pink needles (from Me_2SO): mp > 340 °C; NMR (Me_2SO-d_6) δ 8.03 (2 H, d, J = 2 Hz) and 8.89 (2 H, d, J = 2 Hz); ν_{max} (KBr) 1735, 1560, and 1510 cm^{-1}; λ_{max} ($CHCl_3$) 288 nm (ϵ 28 300) and 266 (34 500); *m/e* 276.01297 (calcd for $C_{10}H_4N_4O_6$, 276.01308).

Anal. Calcd: C, 43.48; H, 1.46; N, 20.29. Found: C, 42.91; H, 1.78; N, 18.97.

Repetition of the above with indole-2-carbonyl chloride yielded the dimer, **2**, as an extremely insoluble orange solid: mp > 340 °C; ν_{max} (KBr) 1695 and 1560 cm^{-1}; λ_{max} ($CHCl_3$) 380 nm (ϵ 20 000), 263 (22 000), 308 (18 000), and 276 (35 000); *m/e* 286.07531 (calcd for $C_{18}H_{10}N_2O_2$, 286.07422).

Pyrrole-2-carbonyl Chloride and *N,N*-Dimethylisobutenylamine. Adduct 4. To a stirred solution of 0.43 g (3.2 mmol) of the above acid chloride in 2 ml of dry acetone was added a solution of 0.66 g (6.6 mmol) of the above enamine in 2 ml of acetone. The resulting solution was stirred for 30 min and solvent was evaporated, and the oily residue was subjected to thick layer chromatography (silica gel PF-254, 1.5 mm thick, 6% methanol in chloroform) to afford three fractions. (a) Pyrrole dimer **3a:** 11 mg. (b) Adduct **4:** 330 mg (58%), mp 79–81 °C (carbon tetrachloride); NMR (CCl_4) δ 0.62 (3 H, d, J = 7 Hz), 1.08 (3 H, d, J = 7 Hz), 2.25 (1 H, m), 2.95 (3 H, s), 5.08 (1 H, d, J = 1.5 Hz), 6.27 (1 H, m), 6.39 (1 H, m), and 6.76 (1 H, m); ν_{max} ($CHCl_3$) 1690 cm^{-1}; λ_{max} (MeOH) 278 nm (ϵ 8900), 242 (5500), and 235 (5800); *m/e* 178.11061 (calcd for $C_{10}H_{14}N_2O$, 178.11061).

Anal. Calcd for $C_{10}H_{14}N_2O_4$: C, 71.01; H, 8.36; N, 16.57. Found: C, 70.92; H, 8.21; N, 16.51.

(c) *N,N*-Dimethylpyrrole-2-carboxamide (**5**): 32 mg (8%) (sublimed at 55 °C 0.08 mm); mp 96–98 °C (lit.[7] 100–101 °C); NMR δ 3.18 (6 H, s), 6.13 (1 H, m), 6.58 (1 H, m), 6.93 (1 H, m), and 10.7 (1 H, bs); ν_{max} ($CHCl_3$)3450 and 1685 cm^{-1}; λ_{max} (MeOH) 263 nm (ϵ 12 000); *m/e* 138.07919 (calcd for $C_7H_{10}N_2$, 138.07931).

Repetition of the above experiment using 1 equiv each of the enamine and triethylamine afforded a 55% yield of the dimer (**3a**) and 18% yield of the dimethylamide (**5**).

If this experiment is repeated using the pyrrolidine enamine of cyclohexanone one obtains a 32% yield of the dimer and 24% yield of pyrrolidinopyrrole-2-carboxamide: mp 109–112 °C; δ NMR 1.97 (4 H, bs), 3.72 (4 H, bs), 6.28 (1 H, m), 6.62 (1 H, m), 6.97 (1 H, m), 6.97 (1 H, m), and 10.25 (1 H, bs); ν_{max} ($CHCl_3$) 3450 and 1590 cm^{-1}; λ_{max} (MeOH) 266 nm (ϵ 15 500) and 227 (7000).

Indole-2-carbonyl Chloride and *N,N*-Dimethylisobutenylamine. Adduct 6. To a stirred solution of 0.427 g (2.39 mmol) of the acid chloride in 2 ml of dry acetone was added a solution of 0.506 g (5.06 mmol) of *N,N*-dimethylisobutenylamine in 2 ml of acetone. The resulting solution was stirred for 4 h and evaporated, and the residue triturated with 25 ml of chloroform to afford 64 mg of the indole dimer (**2**) as an insoluble orange solid. The soluble material was subjected to thick layer chromatography (silica gel G, 6% MeOH in chloroform) to afford two components. (a) Adduct **6:** 399 mg, mp 139–131.5 °C (after sublimation); NMR ($CDCl_3$) δ 0.80 (3 H, d, J = 8 Hz), 0.70 (3 H, d, J = 8 Hz), 2.6 (1 H, m), 3.14 (3 H, s), 3.38 (1 H, d, J = 1.5 Hz), and 6.8–7.8 (5 H, m); ν_{max} ($CHCl_3$) 1695 cm^{-1}; λ_{max} (MeOH) 312 nm (ϵ 9700), 298 (13 000), 290 (11 500), and 236 (11 700); *m/e* 228.1262 (calcd for $C_{14}H_{16}N_2O$, 228.1262).

Anal. Calcd for $C_{14}H_{16}N_2O_4$: C, 73.65; H, 7.08; N, 12.28. Found: C, 73.64; H, 7.04; N, 12.21.

(b) *N,N*-Dimethylindole-2-carboxamide (**7**): 12 mg (3% yield); mp 183–185 °C (lit.[8] 180–182 °C); NMR (acetone-d_6) δ 3.32 (6 H, s), 6.80–7.70 (5 H, m), and 10.5 (1 H, bs); ν_{max} ($CHCl_3$) 3450 and 1610 cm^{-1}; λ_{max} (MeOH) 293 nm (ϵ 17 500); *m/e* 188.09480 (calcd for $C_{11}H_{12}N_2O$, 188.09496).

Repetition of the above experiment using 1 equiv each of the enamine and triethylamine afforded a 5% yield of the dimer (**2**) and a 9% yield of the amide (**7**).

If this experiment is repeated using the pyrrolidine enamine of cyclohexanone one obtains a 13% yield of the dimer (**2**) and a 15% yield of pyrrolidinopyrrole-2-carboxamide: mp 193–197 °C; NMR (Me_2SO-d_6) δ 1.98 (4 H, m), 3.67 (2 H, m), 3.87 (2 H, m), 7.0–7.8 (5 H, m), and 11.6 (1 H, bs); ν_{max} (KBr) 3240 and 1590 cm^{-1}; λ_{max} (MeOH) 293 nm (ϵ 17 000) and 225 (16 500).

Registry No.—**1a** (Ar = C_6H_5), 58881-38-2; **1a** (Ar = $CH_3OC_6H_4$), 58881-39-3; **1b** (Ar = C_6H_5), 58881-40-6; **2**, 58881-41-7; **3a**, 484-73-1; **3b**, 58881-42-8; **4**, 58881-43-9; **5**, 7126-47-8; **6**, 58881-44-0; **7**, 7511-14-0; pyrrole-2-carbonyl chloride, 5427-82-7; pyrrole-2-carboxylic acid, 634-97-9; indole-2-carbonyl chloride, 58881-45-1; 4-nitropyrrole-2-carbonyl chloride, 28494-49-7; benzalaniline, 538-51-2; *p*-methoxybenzalaniline, 836-41-9; *N,N*-dimethylisobutenylamine, 692-31-9; pyrrolidine enamine of cyclohexanone, 1125-99-1; pyrrolidinopyrrole-2-carboxamide, 58904-52-2.

References and Notes

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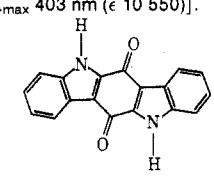
(6) Where not quoted, the spectral properties of compounds were those expected for the structures given.
(7) C. W. N. Cumper and J. W. M. Wood, *J. Chem. Soc. B*, 1811 (1971).
(8) W. Chindler, *Helv. Chim. Acta*, **40**, 2156 (1957).
(9) This type of tertiary amine cleavage reaction has been documented: J. D. Hobson and J. G. McCluskey, *J. Chem. Soc. C*, 2015 (1967).
(10) A somewhat similar indole dimer has been prepared: J. Szmuskovicz, *J. Org. Chem.*, **28**, 2930 (1963). This structure for **2** was ruled out by comparison of uv data [**8**, λ_{max} 403 nm (ϵ 10 550)].



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^{15}N–^{13}C Coupling for Determination of the Site of N-Alkylation of Nitrogen Heterocycles. *linear*-Benzopurines

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Observation of spin–spin coupling between ^{15}N and ^{13}C nuclei in ^{13}C NMR spectroscopy can be of considerable assistance in solving structural problems. For example, this technique has been used to advantage in the structure elucidation of the metabolites tenellin and bassianin,[1] and ^{13}C assignments have been determined from the magnitude of ^{15}N–^{13}C coupling constants.[2] In this paper we report the use of such coupling for determining the site of alkylation in a nitrogen heterocycle.

The benzylation products of 8-methylthioimidazo[4,5-*g*]quinazoline (1) have recently been assigned as 3-benzyl-