

refined by least-square techniques by treating C, N, and O atoms anisotropically and fixing H atoms in calculated positions. Aromatic hydrogen atoms were refined with a common isotropic temperature factor, and methylene hydrogen atoms were treated similarly. Convergence was achieved with  $R = 0.055$ . Coordinates of nonhydrogen atoms, anisotropic thermal parameters, and hydrogen atoms parameters are given in the supplementary material.

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**Supplementary Material Available:** Coordinates for the nonhydrogen atoms in 9b (Table I), anisotropic thermal parameters (Table II), and hydrogen atom parameters (Table III) for the X-ray structure of 9b (3 pages). Ordering information is given on any current masthead page.

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## Acid-Mediated Rearrangement of Acylpyrroles<sup>1</sup>

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*N*-Alkyl-2-acylpyrroles are converted by strong anhydrous acid to 1-alkyl-3-acylpyrroles. An equilibrium mixture of 2- and 3-acylpyrrole is produced by treatment of a 2- or 3-acyl NH pyrrole with acid. Pyrrolecarboxaldehydes similarly afford isomeric mixtures. A cross-ring migration, 7 → 8, is observed when the adjacent position is blocked. The mechanism of acid-mediated rearrangement of acylpyrroles is discussed.

Reversibility of Friedel-Crafts acylation and acid-mediated rearrangement of aromatic ketones have been topics of recent attention.<sup>2</sup> While reversal of aromatic acylation is not common, examples have been found in which it is clearly involved.<sup>2-7</sup>

Several factors promote reversible acylation. For example, systems in which the carbonyl group is tilted out of the plane of the aromatic ring by a bulky neighboring substituent are prone to reversal of acylation.<sup>3,4</sup> Acyl derivatives of aromatic systems which are highly reactive toward electrophilic substitution are also susceptible to reversibility. Acyl derivatives of polycyclic aromatics undergo rearrangement under acidic conditions.<sup>5</sup> Acyl derivatives of  $\pi$  excessive nitrogen heterocycles have also been observed to undergo acid-mediated rearrangement. Palmer and co-workers studied the polyphosphoric acid (PPA) mediated cyclization of some 3-(2-pyrrolyl)propionic acids,<sup>6</sup> and they found products arising from both acyl and alkyl migration. Chastrette observed that 2-acetylindoles, on treatment with PPA, were converted to 3-acetylindoles.<sup>7</sup>

We report our findings on the acid-mediated rearrangement of acylpyrroles.

### Results and Discussion

**Synthetic Methods.** Treatment of 2-acyl-1-alkylpyrroles (1) with excess anhydrous strong acids at 70–120 °C afforded the corresponding 3-acyl-1-alkylpyrroles (2) as the sole monomeric neutral products. Reagents which have been successfully employed include PPA, trifluoroacetic acid (TFA), methanesulfonic acid (MsOH), toluenesulfonic acid (TsOH), trifluoromethanesulfonic acid (TfOH) and "metaphosphoric acid" [(HPO<sub>3</sub>)<sub>n</sub>]. Polymeric materials are the principal byproduct of the reaction. Highest yields are obtained by using TFA (Table I).

Ketones of type 1 where R is an electron-withdrawing group, e.g., trifluoromethyl or carboethoxy, did not rearrange under ordinary conditions and suffer decomposition under forcing conditions. 5-(4-Chlorobenzoyl)furan-2-acetonitrile did not undergo acyl rearrangement in PPA.<sup>8</sup> Reagents which have not proven effective include acetic acid, concentrated sulfuric acid (presumably because of oxidation of the substrate), and hydrogen chloride in organic solvents. Lewis acids including AlCl<sub>3</sub> and BF<sub>3</sub> did not bring about the rearrangement.

Structural assignments of the  $\beta$ -acylpyrroles (2) are based on the lack of a 3.8–4.0-Hz coupling constant in the <sup>1</sup>H NMR spectra which is characteristic of 3,4-proton substitution<sup>9</sup> and a 30–70-nm hypsochromic shift relative to the  $\alpha$  isomer (1) in the UV.<sup>10</sup>

(1) Presented in part at the 172nd National Meeting of the American Chemical Society, San Francisco, Sept 1976; J. R. Carson, U.S. Patent 4 002 643 (1977).

(2) I. Agranit, Y. Bentor, and Y.-S. Shih, *J. Am. Chem. Soc.*, **99**, 7068 (1977), and references cited therein.

(3) C. A. Buehler and D. E. Pearson, "Survey of Organic Synthesis", Wiley-Interscience, New York, 1970, p 653.

(4) A. D. Andreou, P. H. Gore, and D. F. C. Morris, *J. Chem. Soc., Chem. Commun.*, 271 (1978).

(5) I. Agranit and D. Avnir, *J. Chem. Soc., Chem. Commun.*, 362 (1973).

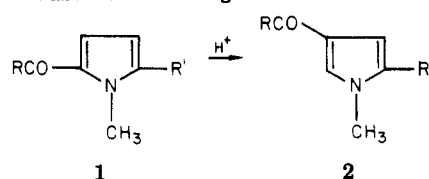
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(8) J. R. Carson, U.S. Patent 3 801 605 (1972).

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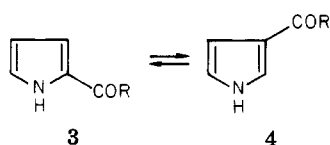
(10) U. Eisner and P. H. Gore, *J. Chem. Soc.*, 922 (1958).

Table I. Rearrangement of 1 to 2<sup>a</sup>

	substrate		reagent	time, h	temp, °C	% yield	for 2
	R	R'					mp [bp (pressure, torr)], °C
a	C <sub>6</sub> H <sub>5</sub>	H <sup>b</sup>	PPA	2	95	41 <sup>d</sup>	90-93
b	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	H	PPA	4	95	48 <sup>d</sup>	[153-157 (0.4)]
c	4-ClC <sub>6</sub> H <sub>4</sub>	H	TFA	8	72	78	48-49
			PPA	1	95	36	
d	3-CF <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	H	PPA	2.5	95	49 <sup>d</sup>	[136-142 (0.4)]
e	CH <sub>3</sub>	H <sup>c</sup>	PPA	0.5	95	58 <sup>e</sup>	[78-81 (0.1)]
			TFA	1.5	72	80	
f	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	PPA	1	95	64	119-120
			TsOH	1	104	53	
			(HPO <sub>3</sub> ) <sub>n</sub>	1	95	40	

<sup>a</sup> Satisfactory ( $\pm 0.4\%$ ) C and H analyses and spectra analogous to 2c were obtained for all of the above new compounds of type 2. <sup>b</sup> J. R. Pratt, F. H. Pinkerton, and S. F. Thames, *J. Organomet. Chem.*, **38**, 29 (1972). <sup>c</sup> H. J. Anderson, *Can. J. Chem.*, **35**, 21 (1957). <sup>d</sup> Rearrangement was carried out on crude 1 (containing about 25% of 2) from Vilsmeier arylation of 1-methylpyrrole. The yield is quoted as a percent of crude 1. <sup>e</sup> A. Ermili and A. J. Castro, *J. Org. Chem.*, **30**, 342 (1965).

Table II.



R	reagent <sup>a</sup>	time, h	% composition 4/3 (GLC)	% isolated yield of 4
a CH <sub>3</sub>	TFA	7	18.5/81.5	14
b 4-ClC <sub>6</sub> H <sub>4</sub>	TFA	36	27/73	44
	TfOH	24	54/46	

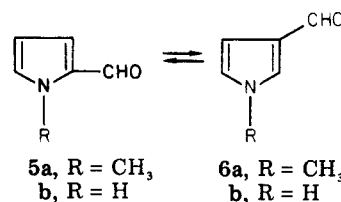
<sup>a</sup> The temperature was 72 °C in all cases.

Treatment of ketone 1f with acid brought about migration of the acyl group specifically to the 3-position of the pyrrole ring. This structure is consistent with the observed 1.5-Hz coupling between the pyrrole ring protons.

In contrast to the *N*-alkyl compounds 1 which were converted by acid completely to isomer 2, heating either a 2-acylpyrrole (3) or a 3-acylpyrrole (4) bearing hydrogen on nitrogen in strong anhydrous acid gave rise to an equilibrium mixture of both 3 and 4 (Table II). The composition of the mixture was dependent upon the nature of the medium employed. For example, the mixture obtained by treatment of 3b with TFA at 72 °C contained 73% 3b and 27% 4b, while treatment of the same compound with TfOH at 72 °C afforded a mixture containing 46% 3b and 54% 4b. Treatment of 4b with TFA or TfOH gave mixtures with the same composition as those from 3b. It is likely that the more acidic the medium, the greater the percentage of  $\beta$  isomer which is formed. The isomers can be readily separated by column chromatography. Thus the reaction is a viable synthetic method for preparing compounds of type 4 which are only otherwise accessible via multistep routes.<sup>9</sup>

Pyrrolecarboxaldehydes also underwent acid-mediated rearrangement. Isomeric mixtures were produced from both *N*-alkyl- and *N*-hydrogen-substituted substrates. However, the aldehydes are more prone to decomposition than the ketones so that the mixtures were not true equilibria. As in the equilibration of 3 and 4, the stronger the acid used, the greater the percentage of  $\beta$ -carbox-

aldehyde obtained in the mixture. A greater percentage of  $\beta$  isomer is produced from the *N*-methyl carboxaldehyde than from the *N*-H carboxaldehyde in a given acidic medium. Thus, in mixed TfOH-halocarbon medium, 1-methylpyrrole-2-carboxaldehyde (5a) was converted to a



mixture with an  $\alpha$ : $\beta$  ratio of 30:70 (GLC). The isolated yield of 6a was 41%. Similarly the *N*-H carboxaldehyde 5b gave a mixture with an  $\alpha$ : $\beta$  ratio of 63:37. A 60% isolated yield of 6b, corrected for recovered 5b, was obtained. To the best of our knowledge these are the first examples of acid-mediated rearrangements of aromatic aldehydes.

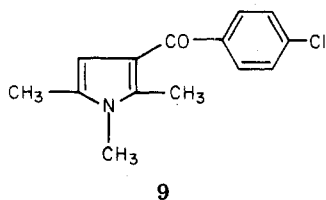
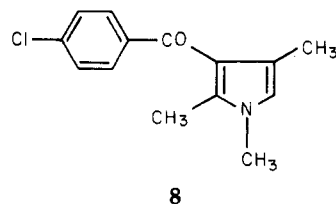
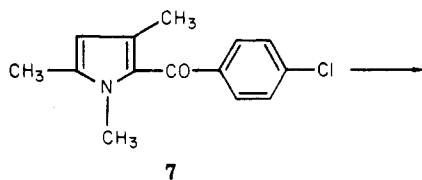
Ketone 7, upon being heated in PPA or on prolonged reflux in TfOH-TFA, gave the rearranged ketone 8 as the sole monomeric product. The isomeric selectivity in the previously discussed rearrangements, 1  $\rightarrow$  2, 3  $\rightleftharpoons$  4, and 5  $\rightleftharpoons$  6, might all be rationalized by assuming that the preferred isomer would have the least steric interaction between the acyl group and the adjacent substituents. Since the steric environment of the acyl group in 7 and 8 is identical, other factors must come into play to explain isomeric preference.

In order to rule out the possibility of methyl migration in the foregoing reaction, ketone 9 was synthesized by Vilsmeier arylation of 1,2,5-trimethylpyrrole and was not identical to 8.

**Mechanism.** In order to probe possible mechanisms of these rearrangements, we performed some experiments.

Fischer reported that treatment of 2,4-diethyl-3,5-dipropionylpyrrole with aqueous sulfuric acid gives 2,4-diethylpyrrole.<sup>11</sup> This suggested that rearrangement of

(11) H. Fischer, W. Siedel, and L. LeThierry D'Ennequin, *Justus Liebig's Ann. Chem.*, **500**, 178 (1933).



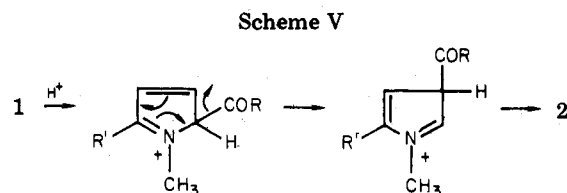
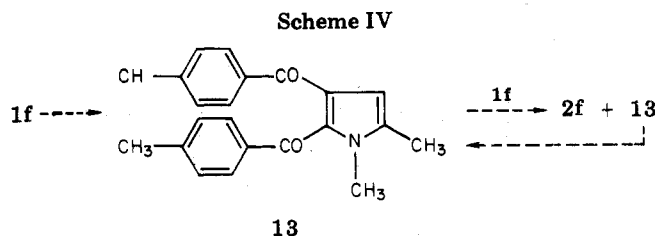
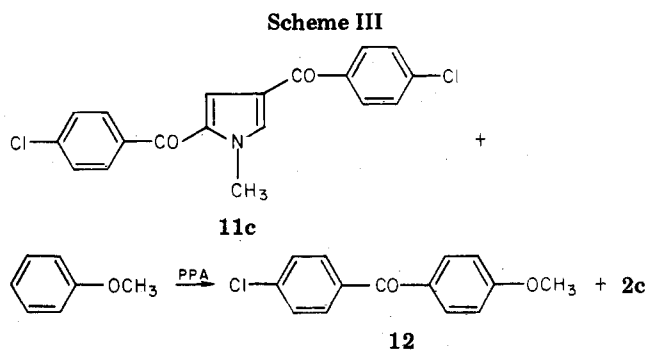
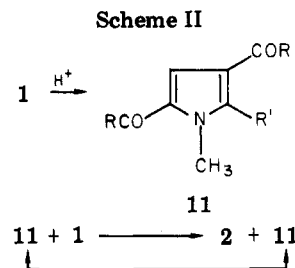
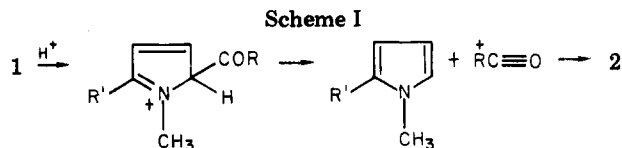
acylpyrroles might proceed by dissociation to acylium ion plus pyrrole, followed by recombination (Scheme I). We carried out TFA-mediated rearrangement of 1c to 2c in the presence of 1-*n*-butylpyrrole, anisole, and phenol, respectively. We observed no crossover acylation products (GLC/MS). If free acylium ions were present in TFA, they would be likely to be trapped by solvent to give a mixed anhydride. The acylation of pyrroles by mixed anhydrides in which one of the acyl groups is trifluoroacetyl has been shown to give rise preferentially to trifluoroacetylation.<sup>12</sup> No evidence for the presence of trifluoroacetylation products in the reaction mixture was found. Thus, while dissociation of acyl pyrrole to acylium ion plus pyrrole, followed by rapid recombination, cannot be ruled out as the mechanism for rearrangements in anhydrous acid, no evidence was uncovered, from experiments in anhydrous TFA, to support this mechanism.

Isomerization of substituents on a heterocyclic ring can, in certain circumstances, take place via the intermediacy of a disubstituted species serving as an electrophile transfer agent. For instance, the conversion of 1-alkyl-5-phenyltetrazoles to 2-alkyl-5-phenyltetrazoles takes place via 1,3-dialkyl-5-phenyltetrazolium salts.<sup>13</sup>

The operation of such a mechanism in the rearrangement of acylpyrroles is shown in Scheme II. Initiation, leading to 11, could take place by any process which would generate acylium ion from 1.

A compound of type 11 (11c; R = 4-ClC<sub>6</sub>H<sub>4</sub>, R' = H) was prepared by Friedel-Crafts acylation of 1c. Heating 11c in the presence of anisole gave rise to a mixture containing 4-chloro-4'-methoxybenzophenone (12) and 2c (Scheme III). Thus diacylpyrroles of type 11 are able to function as acyl-transfer agents either directly or by generation of acylium ion.

We feel, however, that acyl transfer is not likely to be the mechanism for the rearrangement of acylpyrroles. Rearrangement of 1c to 2c in TFA is not catalyzed by addition of 11c as would be expected if Scheme II were operative. The observed formation of 2f from 1f could not take place via an intermediate of type 11. Intermediate 13 would be required. Electron-withdrawing groups on the 2-position of a pyrrole are known to direct substitution to the 4-position.<sup>14</sup> Both formation and utilization of 13



would require electrophilic substitution to occur at the 3-position of a 2-acylpyrrole (Scheme IV).

A mechanism which deserves serious consideration for this reaction is the 1,2-acyl shift of C-protonated pyrroles (Scheme V).

The mechanism proposed by Chastrette for the isomerization of acetylindoles involved a 1,2-acyl shift of a C-protonated intermediate.<sup>7</sup> Scheme V illustrates this mechanism as applied to acylpyrroles. None of the experimental facts that we have uncovered seem to be inconsistent with this mechanism. Thus, at this time, we favor this reaction scheme or a minor variation of it over the other mechanisms we have considered.

### Experimental Section

Melting points were observed on a Thomas-Hoover Unimelt apparatus and are uncorrected. Spectra were obtained by using the following instruments: IR spectra, Perkin-Elmer 521 or

(12) S. Clementi and G. Marino, *Gazz. Chim. Ital.*, **100**, 556 (1970).

(13) T. Isida, S. Kozima, K. Nabika, and K. Sisido, *J. Org. Chem.*, **36**, 3807 (1971).

(14) A. Gossauer, "Die Chemie des Pyrrole", Springer-Verlag, West Berlin, 1974, p 119.

Perkin-Elmer 283 spectrophotometer; NMR spectra, Perkin-Elmer R-32 or Varian A60A spectrophotometer; UV spectra, Cary 14 spectrophotometer; mass spectra, Hitachi Perkin-Elmer RMU6 spectrometer. Microanalyses were performed by Scandinavian Laboratories.

**2-(4-Chlorobenzoyl)-1-methylpyrrole (1c).** A mixture of 4-chloro-*N,N*-dimethylbenzamide (36.8 g, 0.2 mol) and phosphoryl chloride (20.2 mL, 0.22 mol) was warmed under nitrogen until an exothermic reaction occurred. The mixture was kept at 60 °C for 2 h. A solution of 16.2 g (0.20 mol) of 1-methylpyrrole in 200 mL of CH<sub>2</sub>Cl<sub>2</sub> was added and the solution heated under reflux for 16 h. A solution of 80 g (0.6 mol) of NaOAc·3H<sub>2</sub>O in 200 mL of water was added and the mixture heated under reflux for 30 min. The mixture was extracted with CHCl<sub>3</sub>. The organic solution was washed with NaHCO<sub>3</sub> solution and dried (MgSO<sub>4</sub>), and the solvent was evaporated in vacuo. The residue was recrystallized from MeOH to give 8.9 g (20% yield) of a white solid: mp 70–71 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.72 (2 H, d, *J* = 9 Hz), 7.32 (2 H, d, *J* = 9 Hz), 6.88 (1 H, t, *J* = 2.5 Hz), 6.68 (1 H, m), 6.12 (1 H, m), 4.03 (3 H, s); UV (MeOH) λ<sub>max</sub> 253 nm (ε 11 400), 308 (16 700).

Anal. Calcd for C<sub>12</sub>H<sub>10</sub>NO: C, 65.61; H, 4.58; N, 6.38. Found: C, 65.65; H, 4.59; N, 6.37.

**1,5-Dimethyl-2-(4-methylbenzoyl)pyrrole (1e).** A suspension of 31.5 g (0.1 mol) of sodium 1-methyl-5-(4-methylbenzoyl)pyrrole-2-acetate dihydrate<sup>15</sup> in 300 mL of propionic acid was heated under reflux for 18 h. The solution was poured into water and the solid collected by filtration. The solid was dissolved in ether, and the solution was washed with NaHCO<sub>3</sub> solution and saturated brine and dried (MgSO<sub>4</sub>). The solvent was evaporated in vacuo. The residue was recrystallized from hexane to give 19.2 g of white solid: mp 80–82 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.28 (2 H, d, *J* = 9 Hz), 7.83 (2 H, d, *J* = 9 Hz), 6.8 (1 H, d, *J* = 4 Hz), 5.9 (1 H, d, *J* = 4 Hz), 3.93 (3 H, s), 2.4 (3 H, s), 2.3 (3 H, s); UV (MeOH) λ<sub>max</sub> 254 nm (ε 9040), 315 (19 100).

Anal. Calcd for C<sub>14</sub>H<sub>15</sub>NO: C, 78.84; H, 7.09. Found: C, 78.80; H, 7.11.

**2-(4-Chlorobenzoyl)-1,3,5-trimethylpyrrole (7).** This compound was prepared from 5-(4-chlorobenzoyl)-1,4-dimethylpyrrole-2-acetic acid<sup>16</sup> by the procedure used for preparing 1e: yield, after recrystallization from MeOH, 80%; mp 99–100 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.60 (2 H, d, *J* = 9.0 Hz), 7.45 (2 H, d, *J* = 9.0 Hz), 5.76 (1 H, s), 3.70 (3 H, s), 2.22 (3 H, s), 1.70 (3 H, s); IR (CHCl<sub>3</sub>) ν<sub>max</sub> 3000, 1595 cm<sup>-1</sup>; UV (MeOH) λ<sub>max</sub> 253 nm (ε 12 100), 323 (13 100).

Anal. Calcd for C<sub>14</sub>H<sub>14</sub>ClNO: C, 67.88; H, 5.69. Found: C, 67.55; H, 5.67.

#### General Procedure for the Rearrangement of 1 to 2 Using TFA.

**3-(4-Chlorobenzoyl)-1-methylpyrrole (2c).** A solution of 0.5 g of 1c in 10 mL of TFA was heated under reflux under nitrogen for 7.5 h. It was cooled and poured into NaOH solution. The mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The CH<sub>2</sub>Cl<sub>2</sub> solution was washed with water, dried (MgSO<sub>4</sub>), and concentrated to dryness. The residue was recrystallized from hexane to give 0.39 g (78% yield) of 2c as a white solid: mp 48–49 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.80 (2 H, d, *J* = 8.5 Hz), 7.41 (2 H, d, *J* = 8.5 Hz), 7.18 (1 H, t, *J* = 2.2 Hz), 6.62 (2 H, d, *J* = 2.0 Hz), 3.71 (3 H, s); IR (CHCl<sub>3</sub>) ν<sub>max</sub> 3000, 1620 cm<sup>-1</sup>; UV (MeOH) λ<sub>max</sub> 254 (ε 14 400).

Anal. Calcd for C<sub>12</sub>H<sub>10</sub>ClNO: C, 65.60; H, 4.59. Found: C, 65.67; H, 4.62.

**PPA-Mediated Rearrangement of 1 to 2. 3-Benzoyl-1-methylpyrrole (2a).** Vilsmeier acylation of 1-methylpyrrole (27 g, 0.33 mol) was carried out by using 36 mL (0.33 mol) of phosphoryl chloride and 49.2 g (0.33 mol) of *N,N*-dimethylbenzamide as described for the preparation of 1e. From the hydrolysis of this reaction with 135 g (1.0 mol) of NaOAc·3H<sub>2</sub>O there was obtained 50.0 g (81% yield) of a dark oil containing primarily 2a and 1a in a ratio of about 3:1 by GLC. The oil was added to 500 g of PPA and the mixture stirred under nitrogen at 95° C for 2 h. It was poured into ice-water and extracted with ether. The ether solution was washed with NaHCO<sub>3</sub> solution and NaCl solution, dried (MgSO<sub>4</sub>), and concentrated to dryness to give 37 g of a dark yellow oil. This was distilled in vacuo; bp 134–145 °C

(0.2 torr). It was recrystallized from MeOH to give 21.9 g (41% yield) of 2a as a white solid: mp 90–93 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.96–7.47 (5 H, m), 7.20 (1 H, t, *J* = 2 Hz), 6.70 (2 H, m), 3.70 (3 H, s); IR (CHCl<sub>3</sub>) ν<sub>max</sub> 1620 cm<sup>-1</sup>; UV λ<sub>max</sub> (CH<sub>3</sub>OH) 248 nm (ε 10 400), 270 (10 600).

Anal. Calcd for C<sub>12</sub>H<sub>11</sub>NO: C, 77.81; H, 5.99. Found: C, 77.67; H, 5.94.

**3-(4-Chlorobenzoyl)pyrrole (4b).** A solution of 2.0 g (0.01 mol) of 3b<sup>17</sup> in 20 mL of TfOH was heated at 72 °C for 24 h under N<sub>2</sub>. It was cooled and poured into ice-NaOH solution, and the mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The CH<sub>2</sub>Cl<sub>2</sub> solution was dried (MgSO<sub>4</sub>) and concentrated to dryness. The residual oil (1.63 g) was chromatographed on silic-AR CC-4. The first fraction (eluted with cyclohexane-CH<sub>3</sub>CCl<sub>3</sub>, 1:1) on evaporation gave 0.91 g of a solid. It was recrystallized from *i*-PrOH to give 0.53 g of pink solid, mp 117–118 °C, undepressed by admixture with 3b. The second chromatographic fraction (eluted with cyclohexane-CH<sub>3</sub>CCl<sub>3</sub>, 1:3) upon evaporation gave 0.72 g of a solid, recrystallized successively from *i*-PrOH and ethyl acetate-methylcyclohexane to give 0.64 g (44% yield, 54% conversion) of 4b: mp 121–122 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.78 (2 H, d, *J* = 9 Hz), 7.41 (2 H, d, *J* = 9 Hz), 7.30 (1 H, m), 6.8 (2 H, m); UV (MeOH) λ<sub>max</sub> 254 nm (ε 15 000).

Anal. Calcd for C<sub>11</sub>H<sub>9</sub>ClNO: C, 64.26; H, 3.92. Found: C, 64.00; H, 3.90.

**1-Methylpyrrole-3-carboxaldehyde (6a).** A solution of 80 g (0.73 mol) of 5a in 600 mL of CHCl<sub>3</sub> and 500 mL of TfOH was heated under reflux for 30 h under N<sub>2</sub>. The mixture was cooled and poured into a solution of 1.5 kg of NaOAc·3H<sub>2</sub>O in 3 L of water. The mixture was stirred for 30 min. The CHCl<sub>3</sub> layer was separated, washed with Na<sub>2</sub>CO<sub>3</sub> solution, and dried (K<sub>2</sub>CO<sub>3</sub>). The solvent was evaporated in vacuo. The residue was taken up in ether, treated with charcoal, and concentrated to dryness to give 52 g of a reddish oil. The oil was distilled through a saddle-packed column to give 12.0 g of 5a [bp 25–27 °C (0.1 torr)] and 28.0 g of 6a, bp 70–72 °C (0.1 torr). The spectral characteristics of the higher boiling fraction were in accord with those previously reported for the substance.<sup>18</sup>

**Pyrrole-3-carboxaldehyde (6b).** A solution of 10.0 g of 5b in 100 mL of 1,2-dichloroethane and 100 mL of TfOH was heated under reflux for 21 h. The mixture was cooled and poured into a saturated solution of 350 g of NaOAc in H<sub>2</sub>O. The organic layer was separated. On evaporation, a small amount of a tough black gum was obtained. The aqueous layer was stored for 3 days and then continuously extracted with ether. The ether was dried (MgSO<sub>4</sub>) and concentrated to dryness. The residue was chromatographed on silica gel with ether as the eluant. The first fraction, upon evaporation, gave 5 g of 5b, mp 40–43 °C. The second fraction, upon evaporation and recrystallization from CCl<sub>4</sub>-hexane, gave 3.0 g of 6b as a brown solid, mp 63–65 °C (lit.<sup>18</sup> mp 63–63.5 °C). The spectral characteristics of 6b were in accord with previous reports.

**3-(4-Chlorobenzoyl)-1,2,4-trimethylpyrrole (8).** A solution of 2.0 g of 7 in 2 mL of TfOH and 7 mL of TFA under argon was heated under reflux for 6 days. It was poured into NaOH solution and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The CH<sub>2</sub>Cl<sub>2</sub> solution was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to dryness. The solid residue (1.5 g) was concentrated to dryness and recrystallized successively from MeOH and ether-cyclohexane to give 0.89 g (44% yield) of white solid: mp 103–105 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.64 (2 H, d, *J* = 9 Hz), 7.35 (2 H, d, *J* = 9 Hz), 6.28 (1 H, s), 3.45 (3 H, s), 2.14 (3 H, s), 1.88 (3 H, s); UV (CH<sub>3</sub>OH) λ<sub>max</sub> 249 nm (ε 13 600), 275 (sh, 8790).

Anal. Calcd for C<sub>14</sub>H<sub>14</sub>ClNO: C, 67.83; H, 5.69; N, 5.65. Found: C, 67.85; H, 5.74; N, 5.65.

**3-(4-Chlorobenzoyl)-1,2,5-trimethylpyrrole (9).** The preparation was carried out from 4-chloro-*N,N*-dimethylbenzamide and 1,2,5-trimethylpyrrole: yield, after recrystallization from MeOH, 15%; mp 86–87 °C; mp (upon admixture with 8) 68–72 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.69 (2 H, d, *J* = 9 Hz), 7.36 (2 H, d, *J* = 9 Hz), 6.0 (1 H, s), 3.51 (3 H, s), 2.52 (3 H, s), 2.18 (3 H, s); IR (CHCl<sub>3</sub>) 3005, 1620 cm<sup>-1</sup>; UV (CH<sub>3</sub>OH) λ<sub>max</sub> 249 nm (ε 14 900), 323 (5390).

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Anal. Calcd for  $C_{14}H_{14}ClNO$ : C, 67.88; H, 5.69; N, 5.65. Found: C, 67.93; H, 5.75; N, 5.66.

**2,4-Bis(4-chlorobenzoyl)-1-methylpyrrole (11c).** A solution of 10.0 g (0.045 mol) of **1c**, 5.8 mL (0.045 mol) of 4-chlorobenzoyl chloride, and 6.05 g (0.045 mol) of  $AlCl_3$  in 1,2-dichloroethane was stirred for 4 h at 25 °C and then heated under reflux for 16 h. Additional portions of 4-chlorobenzoyl chloride (5.8 mL) and  $AlCl_3$  (6.05 g) were added. The mixture was heated under reflux for 5 h. The mixture was poured into dilute HCl and extracted with  $CHCl_3$ . The  $CHCl_3$  solution was decanted to separate the insoluble solid. The  $CHCl_3$  solution was washed successively with *N,N*-(dimethylamino)propylamine solution, dilute HCl, and  $NaHCO_3$  solution and dried ( $MgSO_4$ ). The solvent was evaporated in vacuo. The residue (16 g) was dissolved in a smaller quantity of  $CHCl_3$ , the insoluble solid removed by filtration, and the solvent evaporated. The residue was recrystallized from EtOAc to give 2.0 g (12% yield) of white solid:  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.80-7.46 (9 H, m), 7.10 (1 H, d,  $J = 1.5$  Hz), 4.05 (3 H, s); UV (MeOH)  $\delta$  254 nm ( $\epsilon$  29 600), 307 (21 300).

Anal. Calcd for  $C_{19}H_{13}Cl_2NO_2$ : C, 63.70; H, 3.65; N, 3.90. Found: C, 63.29; H, 3.76; N, 3.90.

**4-Chloro-4'-methoxybenzophenone (12).** A mixture of 0.5 g (1.4 mmol) of **11c** and 0.3 mL (2.8 mmol) of anisole was heated at 95 °C in 10 g of PPA. After 1 h, 0.15 mL of anisole was added. The mixture was heated for 5 h. It was poured into water and extracted with  $CH_2Cl_2$ . The  $CH_2Cl_2$  solution was washed with  $NaHCO_3$  solution, dried ( $MgSO_4$ ), and concentrated to dryness.

The residue was chromatographed on silic-AR CC-4 with a hexane- $CH_2Cl_2$  step gradient as eluant. The first compound-bearing fraction, upon evaporation and recrystallization of the residue from MeOH, gave 0.091 g of **12** as a white solid: mp 125-126 °C (lit.<sup>19</sup> mp 125 °C); IR ( $CHCl_3$ )  $\nu_{max}$  3005, 1650, 1600  $cm^{-1}$ ; mass spectrum,  $m/e$  246, 245, 218, 210, 138, 134.

The second chromatographic fraction on TLC ( $SiO_2$ ; EtOAc-cyclohexane, 1:2) corresponded to a mixture of **2c** and **11c**.

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**Registry No.** **1a**, 37496-06-3; **1b**, 62128-31-8; **1c**, 62128-32-9; **1d**, 62128-33-0; **1e**, 932-16-1; **1f**, 62128-36-3; **2a**, 62128-30-7; **2b**, 62128-43-2; **2c**, 62128-44-3; **2d**, 62128-45-4; **2e**, 932-62-7; **2f**, 62128-39-6; **3a**, 1072-83-9; **3b**, 13169-71-6; **4a**, 1072-82-8; **4b**, 62128-38-5; **5a**, 1192-58-1; **5b**, 1003-29-8; **6a**, 36929-60-9; **6b**, 7126-39-8; **7**, 62128-28-3; **8**, 62128-48-7; **9**, 76010-94-1; **11c**, 76024-67-4; **12**, 10547-60-1; 4-chloro-*N,N*-dimethylbenzamide, 14062-80-7; 1-methylpyrrole, 96-54-8; 1-methyl-5-(4-methylbenzoyl)pyrrole-2-acetate Na, 35711-34-3; 5-(4-chlorobenzoyl)-1,4-dimethylpyrrole-2-acetic acid, 33369-31-2; 1,2,5-trimethylpyrrole, 930-87-0; 4-chlorobenzoyl chloride, 122-01-0; anisole, 100-66-3; *N,N*-dimethylbenzamide, 611-74-5.

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## Linearly Fused Isoquinolines. 3.<sup>1</sup> Positional Effect of Substitution on Equilibrium of Tetrazole-Azide Systems. Anomalous Behavior in Trifluoroacetic Acid

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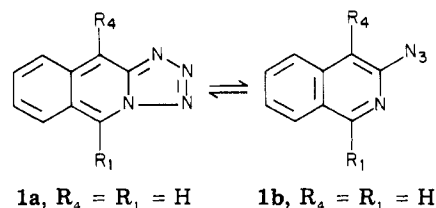
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A new method for synthesis of heteroaromatic azides has been elaborated, and a series of substituted tetrazolo[1,5-*b*]isoquinoline derivatives has been synthesized. The effect of  $R_1$  and  $R_4$  substituents on the equilibrium between 3-azidoisoquinoline (**1b**) and tetrazolo[1,5-*b*]isoquinoline (**1a**) was investigated. Only a slight difference in influence of substituents in the opposite positions  $R_1$  and  $R_4$  was found. In contrast to earlier examples, the equilibria discussed here are shifted to the tetrazole form in TFA!

Recently we have reported<sup>1,2</sup> that tetrazolo[1,5-*b*]isoquinoline (**1a**), in contrast to its two angular isomers, tetrazolo[5,1-*a*]isoquinoline and tetrazolo[1,5-*a*]quinoline, forms an equilibrium with its isomeric azido compound, 2-azidoisoquinoline (**1b**) (Scheme I). The equilibrium constants, 0.2 and 1.3 in chloroform and dimethyl sulfoxide, respectively, seemed highly suitable values for investigation of slight shifts of the equilibrium caused by different substituents or solvents. Both carbon atoms neighboring the "fusion site" of the title system can be substituted. This system is ideal for study of substituent effects exerted by  $R_1$  or  $R_4$  on opposite sides of the tetrazole ring fusion.

For this purpose, suitable model compounds bearing the same substituents  $R_1$  and  $R_4$  have been synthesized. The method reported by us<sup>1</sup> for the parent ring system allowed

Scheme I



the preparation of 5-methyltetrazolo[1,5-*b*]isoquinoline (**6a**).

Oxidation of 3-chloro-1-methylisoquinoline<sup>3</sup> with *m*-chloroperbenzoic acid led to *N*-oxide **3** which under relatively forced conditions afforded the hydrazino *N*-oxide compound **4**. The surprisingly stable 3-hydrazino-1-methylisoquinoline (**5**) was prepared by titanium tri-

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