(m, CH_2, 12 H), 2.3 (m, CH_2, 2 H), 2.33 (s, CH_3, 3 H), 2.7 (m, CH_2, 2 H); mass spectrum, m/e 181 (M^+). Anal. Calcd for $C_{11}H_{19}NO$: C, 72.88; H, 10.56; N, 7.73. Found: C, 72.84; H, 10.48; N, 7.60.

The analogous procedure was followed for the preparation of **8b**. To a suspension of 0.45 g (2.5 mmol) of potassium hydride (23% oil dispersion) in THF (5 mL) was added a solution of 0.26 g (1.0 mmol) of diester **7b** in THF (2 mL) at room temperature. The mixture was refluxed for 20 h and treated with 1.5 N HCl (3.5 mL). The aqueous solution was extracted with ether to eliminate the oil, 0.7 g (4.08 mmol) of baryum hydroxide was added to the aqueous solution, and the mixture was heated to reflux for 20 h, filtered, extracted with $CHCl_3$ (5 × 10 mL), dried over molecular sieves (4 Å), and evaporated to afford **8b**: yield 122 mg (73%); bp 110 °C (13 mmHg); IR (neat) 1710 cm^{-1}; NMR δ 1.6–2.2 (m, CH_2, 10 H), 2.4 (m, CH_2, 2 H), 2.45 (s, CH_3, 3 H), 3.0 (m, CH_2, 2 H); mass spectrum, m/e 167 (M^+).[2] Anal. Calcd for $C_{10}H_{17}NO$: C, 71.81; H, 10.25; N, 8.37. Found: C, 71.95; H, 10.10; N, 8.29. See the paragraph at the end of the paper about supplementary material.

Registry No. **4a**, 80754-31-0; **4b**, 3284-32-0; **5a**, 80754-32-1; **5b**, 80754-33-2; **7a**, 80754-34-3; **7b**, 80754-35-4; **8a**, 80754-36-5; **8b**, 71032-69-4; **9**, 80754-37-6; **10**, 80754-38-7; **11**, 80754-39-8; **12**, 80754-40-1; **15a**, 80754-41-2; **15b**, 80754-42-3; **16a**, 80754-43-4; **16b**, 80754-44-5; *N*-methyl caprolactam, 2556-73-2.

Supplementary Material Available: IR data for **4a**, **5**, **7–10**, **12**, **15**, and **16**, ^1H NMR data for **7**, **9**, **10**, **12**, **15**, and **16**, and ^{13}C NMR data for **5** and **8** (Table I) (5 pages). Ordering information is given on any current masthead page.

New Rearrangements of Arylhydrazones in Polyphosphoric Acid: Extension to the Thiophene and Indole Series. 5

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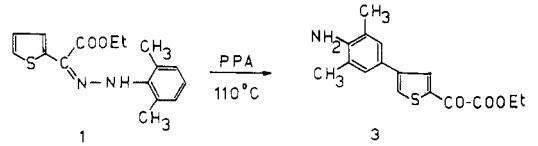
The behavior toward polyphosphoric acid of arylhydrazones of a few heterocyclic carbonyl compounds of the thiophene and indole series is described. The phenylhydrazone and 2,6-dimethylphenylhydrazone of ethyl α-thienylglyoxylate gave ethyl 4- and 5-(4-aminoaryl)-α-thienylglyoxylate, arising from two different sigmatropic rearrangements. The *N*,3,5-trimethylphenylhydrazone of 2-methylindole-3-carboxaldehyde afforded the 4-[4-(methylamino)-2,6-dimethylphenyl]-2-methylindole-3-carboxaldehyde resulting from a [5,5] sigmatropic rearrangement, while the 2,6-dimethylphenylhydrazone of the same carbonyl compound unexpectedly gave the 3-(4-amino-3,5-dimethylphenyl)-2-methylindole-3-carboxaldehyde generated through a [3,5] sigmatropic reaction. Chemical evidences are given for the assigned structures.

This report extends to some thiophene and indole substrates the previously studied polyphosphoric acid (PPA) induced rearrangements of arylhydrazones of aromatic carbonyl compounds.[1]

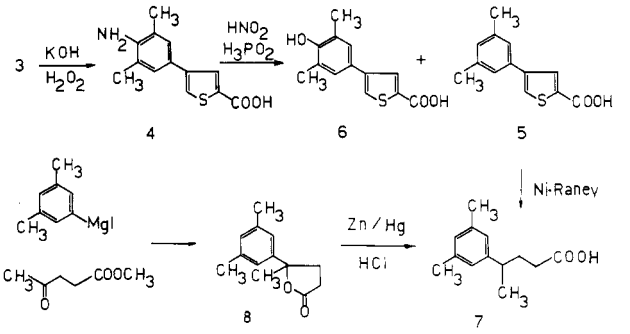
The thiophene derivatives, the 2,6-dimethylphenylhydrazone (**1**), and the phenylhydrazone (**2**) of ethyl α-thienylglyoxylate were treated with PPA under the experimental conditions usually employed for this type of reaction.

The workup of the reaction mixture for the former compound **1** gave an approximately 40% yield of a product assigned the structure of ethyl 4-(4-amino-3,5-dimethylphenyl)-2-thienylglyoxylate (**3**),[2] based on analytical and spectroscopic data. This structure assignment was confirmed chemically as shown in Scheme I.

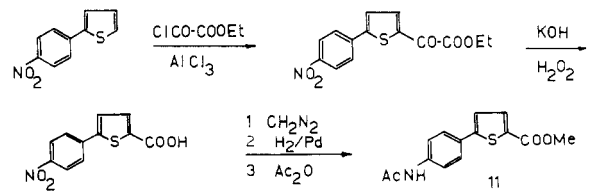


1 3

Scheme I



Scheme II



Treatment of the phenylhydrazone of α-thienylglyoxylic ester **2** with PPA gave an approximately 35% yield of a mixture of two isomeric rearrangement products, in an approximately 7:3 ratio. While these could not be separated by column chromatography, they were easily seen in HPLC and in the NMR spectrum.

(1) (a) Fusco, R.; Sannicolò, F. *Tetrahedron Lett.* **1977**, 3163. (b) *Ibid.* **1978**, 1233. (c) Fusco, R.; Sannicolò, F. *Tetrahedron Rep.* **1980**, *No. 72* 161. (d) Fusco, R.; Sannicolò, F. *J. Org. Chem.* **1981**, *46*, 83. (e) *Ibid.* **1981**, *46*, 90.

(2) The NMR spectrum showed the presence of a small percentage of an isomeric compound, which, however, did not appear in thin-layer chromatography and which could not be separated by column chromatography. This isomer was lost in the successive chemical reactions. The compound was probably the 2,5-disubstituted thiophene derivative (see discussion for compound **2**).

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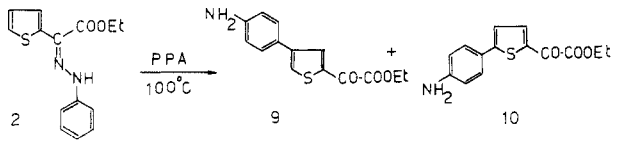
It was hypothesized that the major isomer in the mixture had structure **9** (analogous to **3**) and that the minor one had the isomeric structure of 2,5-disubstituted thiophene derivative **10**.



It was therefore decided to verify the assignment of structure **10** chemically. The mixture of **9** and **10** was thus converted to a mixture of the two methyl (acetylamino)-phenyl carboxylates by the following reactions: acetylation, hydrolysis of the ester function, oxidation with hydrogen peroxide, and reesterification with diazomethane.

The resulting 5-[4-(acetylamino)phenyl]-2-(methoxy-carbonyl)thiophene (**11**) was independently synthesized according to Scheme II.

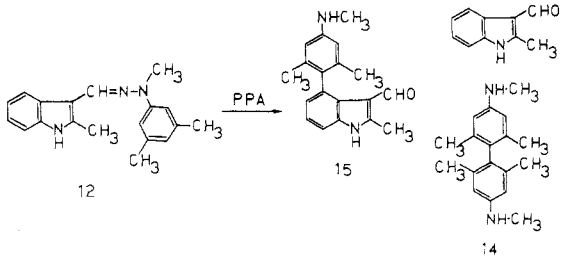
A detailed analysis of the NMR spectra of compound **11** and of the mixture of acetylamino esters which should contain it, as well as a comparison of the HPLC retention times of the two samples, verified the identity of the minor isomer as compound **10**.

As shown in Scheme III, the reaction pathways leading to the two isomeric thiophene derivatives could be classified as [5,5] sigmatropic rearrangements, analogous to our previous observations in the aromatic series. The greater electronic availability of the thiophene ring with respect to the benzene ring allows delocalization of the positive charge resulting from the protonation of the substrate on the sulfur atom, even in the absence of electron-donating groups. The latter were required for the rearrangement to occur in a benzene ring.

In mesomeric structure M, two formally dienic systems are numbered (2,3,4,5 and 2,3,4′,5′) which direct migration to positions 5 and 5′, respectively.

In the indole series, the behavior of polyphosphoric acid was examined with two substrates: *N*,3,5-trimethylphenylhydrazone (**12**) and 2,6-dimethylphenylhydrazone (**13**) of 2-methyl-3-indolecarboxaldehyde.

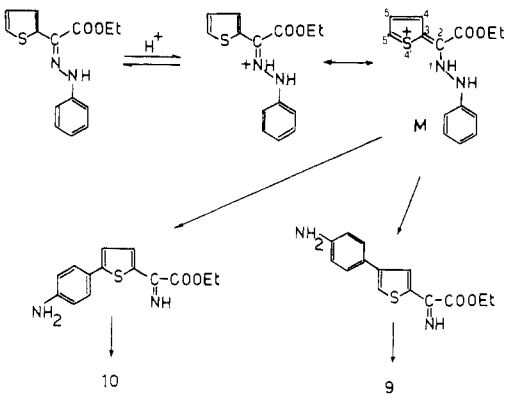
The first compound gave a mixture of reaction products from which the following were isolated: 2-methyl-3-indolecarboxaldehyde, 2,6,2′,6′-tetramethyl-4,4′-bis(methylamino)biphenyl (**14**), and the rearrangement product assigned the structure of 2-methyl-3-formyl-4-(2,6-dimethyl-4-[(methylamino)phenyl]indole (**15**).[3]



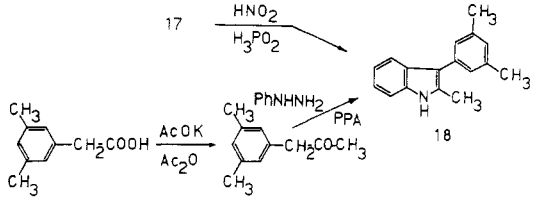
This assignment was confirmed by analytical, chemical, and spectroscopic (IR) data, but in particular by analysis of the NMR spectrum.

The formation of benzidine derivative **14** is not a new observation in arylhydrazone rearrangements; we have, in fact, demonstrated it in other cases, interpreting it as

Scheme III



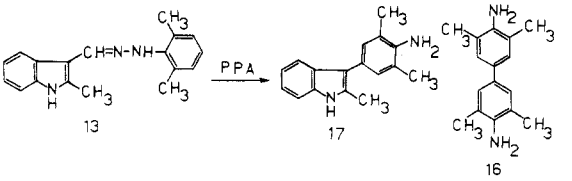
Scheme IV



dimerization of an arylamine radical formed by homolysis of the nitrogen–nitrogen bond in the hydrazone.[1c]

With regard to the mechanism of formation of indole derivative **15**, it could be seen as a [5,5] sigmatropic rearrangement occurring on the protonated substrate.[4]

However, the 2,6-dimethylphenylhydrazone of 2-methyl-3-indolecarboxaldehyde (**13**) behaves differently. In addition to the 3,5,3′,5′-tetramethylbenzidine (**16**) evidently formed in a mechanism similar to that suggested for the analogous **14**, an indole derivative with no aldehyde function was obtained and assigned the structure of 2-methyl-3-(3,5-dimethyl-4-aminophenyl)indole (**17**).



This assignment, based on analytical and spectroscopic data, was definitively confirmed by independent synthesis. Diazo deamination of the test compound gave 2-methyl-3-(3,5-dimethylphenyl)indole (**18**, Scheme IV), which was synthesized by indolization of the phenylhydrazone of (3,5-dimethylphenyl)acetone, obtained in turn from (3,5-dimethylphenyl)acetic acid.

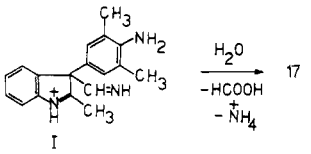
The formation of indole **17** represents a new type of arylhydrazone rearrangement to be added to the large number we have already observed. Our proposed mechanistic interpretation involves intermediate I formed first

(3) A fourth product was also found in the mixture, the structure of which seems to be bis[2,6-dimethyl-4-(methylamino)phenyl]methane on the basis of analytical and NMR data. This is formed in a side reaction which was not studied in depth.

(4) A rearrangement analogous to that described here is reported in a recent publication by Kornet et al.[5] Upon treatment of the *N*-methylphenylhydrazide of 1,2-dimethylindol-3-carboxylic acid with PPA, these authors obtained a naphthaindolic derivative possibly arising from a [5,5] sigmatropic rearrangement of the arylic portion in the 4-position of the indole, followed by intramolecular condensation of the carbon-amide group formed on the aromatic ring. Rearrangements of arylhydrazides, analogous to those of arylhydrazones were independently observed by us in aromatic series.[1c,6]

(5) Kornet, M. J.; Thio, A. P.; Tolbert, L. M. *J. Org. Chem.* **1980**, *45*, 30.

(6) Rosti, P. Thesis Dissertation, University of Milan, Milan, Italy, 1977.



I

via a [3,5] sigmatropic rearrangement, allowed by the Woodward–Hoffmann rules and occurring on protonated 17. Rearomatization is achieved by hydrolitic removal of the aldimine group.

The different behavior of the two arylhydrazones is not easily explained. However, it may be observed that in the first case the [3,5] sigmatropic rearrangement should be difavored by the steric hindrance of the two methyl groups ortho to the position of attack of the aryl residue on position 3 of the indole bearing the aldimine group.

Experimental Section

All melting points were determined on a Büchi apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 377 spectrophotometer. NMR spectra were recorded on a Varian EM-390 spectrometer with $CDCl_3$ as a solvent unless otherwise stated and with tetramethylsilane as an internal standard; chemical shifts are given in δ units and refer to the center of the signal: s, singlet; d, doublet; m, multiplet; dd, double doublet. All new products gave correct elemental analyses (±0.4%).

Hydrazines. 2,6-Dimethylphenylhydrazine is known in the literature.[7] *N*,3,5-Trimethylphenylhydrazine was prepared by $LiAlH_4$ reduction of *N*-nitroso-*N*,3,5-trimethylaniline, which was obtained by nitrosation of *N*,3,5-trimethylaniline; the latter was synthesized in turn from 3,5-dimethylaniline. Synthetic procedures for this reaction sequence are described below.

***N*,3,5-Trimethylaniline.** 3,5-Dimethylaniline (24 g) and tosyl chloride (40 g) immediately reacted in pyridine solution; the reaction was completed by short heating on a steam bath. The mixture was poured into a 5% HCl solution, and the separated product was extracted with CH_2Cl_2, washed with H_2O, and dried (K_2CO_3). Removal of the solvent left a solid which was dissolved in a 5% NaOH solution (200 mL). The resulting yellow solution was boiled to remove the residual pyridine and then treated with $(CH_3)_2SO_4$ (25 mL) at 40 °C. The mixture was warmed at 70 °C to complete the reaction and then cooled at room temperature. The *N*-methyl-*N*-(3,5-dimethylphenyl)-4-toluenesulfonamide separated as a sandy solid which was filtered, washed with H_2O, dried at 80 °C, and then treated with an 80% H_2SO_4 solution (80 mL). The mixture was heated at 160 °C for 20 min in an oil bath, cooled, and poured onto ice (200 g). The *N*,3,5-trimethylaniline separated by alkalinization with concentrated NH_4OH solution; it was extracted with Et_2O and, after the usual procedure, distilled in vacuo: bp 113 °C (16 mmHg); 12.2 g.

***N*-Nitroso-*N*,3,5-trimethylaniline.**[8] A solution of $NaNO_2$ (8.3 g) in H_2O (20 mL) was dropped into a solution of *N*,3,5-trimethylaniline (15.5 g) in a 25% H_2SO_4 solution at 10 °C. The separated oil was extracted with Et_2O, washed with H_2O and with a 5% $NaHCO_3$ solution, and dried (Na_2SO_4). The solvent was removed and the residue distilled in vacuo [bp 115 °C (0.2 mmHg)] to give the *N*-nitroso-*N*,3,5-trimethylaniline as a yellow oil, yield 93%.

***N*,3,5-Trimethylphenylhydrazine.** A solution of *N*-nitroso-*N*,3,5-trimethylaniline (16.8 g) in dry THF (30 mL) was dropped into a stirred slurry of $LiAlH_4$ (3.9 g) in dry THF (100 mL), the temperature being kept between 28 and 34 °C. The mixture was stirred for 15 min after the addition, cooled at 5 °C in an ice bath, and cautiously treated with H_2O (4 mL). A 35% NaOH solution (3 mL) was added and the inorganic precipitate filtered off. The clear filtrate, dried (K_2CO_3) and evaporated to dryness, afforded a residue which was distilled in vacuo [bp 125 °C (0.2 mmHg)] to give the *N*,3,5-trimethylphenylhydrazine (12.8 g) as a colorless oil which solidified in a refrigerator: ^1H NMR 6.44 (2 H, s, aromatic, positions 2 and 6), 6.33 (1 H, s, aromatic, position 4), 3.40 (2 H, s, exchangeable with D_2O, NH_2), 2.95 (2 H, s, NCH_3), 2.24 (6 H, s, $2CH_3$).

Carbonyl Compounds. Both the ethyl 2-thienylglyoxylate[9] and the 2-methylindole-3-carboxaldehyde[10] are known in literature.

Hydrazones. Hydrazones **1**, **12**, and **13** were prepared by reacting equimolar amounts of carbonyl compound and the suitable hydrazine without any solvent at 80 °C for a few minutes in the presence of AcOH traces. The synthesis of hydrazone **2** was carried out in refluxing MeOH solution. Substrates **1** and **2** were constituted by a mixture of two geometric isomers, easily detectable by chromatography and ^1H NMR spectroscopy and isolated in a pure state in the former case.

2,6-Dimethylphenylhydrazone of Ethyl 2-Thienylglyoxylate (1). The crude hydrazone (7.2 g), obtained from (2,6-dimethylphenyl)hydrazine (4.0 g) and ethyl 2-thienylglyoxylate (4.6 g), was chromatographed on a silica gel column with $CHCl_3$ as an eluent. Two isomeric hydrazones were isolated in a pure state. The first to be eluted, pale yellow crystals, showed the following: mp 85 °C (hexane); 2.0 g; ^1H NMR 12.45 (1 H, br s, NH), 7.45 (1 H, m, aromatic, position 3 of thiophene ring), 7.0 (5 H, m, aromatic), 4.43 (2 H, q, CH_2CH_3), 2.50 (5 H, s, $2CH_3$), 1.48 (3 H, t, CH_2CH_3). Second isomer: yellow crystals; mp 80 °C (diisopropyl ether); 1.0 g; ^1H NMR 8.49 (1 H, br s, NH), 7.56 (1 H, m, aromatic, position 3 of thiophene ring), 7.22 (2 H, m, aromatic, positions 4 and 5 of thiophene ring), 6.99 (3 H, s, aromatic), 4.32 (2 H, q, CH_2CH_3), 2.33 (6 H, s, $2CH_3$), 1.36 (3 H, t, CH_2CH_3). A third product was finally eluted, the *N*-(2,6-dimethylphenyl)-2-thienylglyoxylic acid hydrazide: mp 140 °C (diisopropyl ether–hexane); ^1H NMR 8.80 and 6.15 (each 1 H, 2 br s, 2NH), 8.42 (1 H, d, aromatic, position 3 of thiophene ring), 7.82 (1 H, d, aromatic, position 5 of thiophene ring), 7.15 (1 H, m, aromatic, position 4 of thiophene ring), 7.0 (5 H, m, aromatic), 2.48 (6 H, s, $2CH_3$). An isomeric mixture of **1** was subjected to the reaction with PPA.

Phenylhydrazone of ethyl 2-thienylglyoxylate (2): mp 103–107 °C (*i*-PrOH); yield 54%. ^1H NMR showed that the product was constituted by a 1:1 mixture of two geometrical isomers, which could not be separated through fractional crystallization: ^1H NMR 12.43 and 8.74 (2 br s, NH of two isomers), 7.2 (8 H, m, aromatic), 4.35 (2 H, 2 superimposed q, CH_2CH_3 of two isomers), 1.40 (3 H, 2 superimposed t, CH_2CH_3).

***N*,3,5-Trimethylphenylhydrazone of 2-methylindole-3-carboxaldehyde (12)**: mp 145 °C (*i*-PrOH); yield 65%; ^1H NMR 8.35 (1 H, m, aromatic, position 7), 7.70 (1 H, s, N=CH), 7.65 (1 H, br s, NH), 7.17 (3 H, m, aromatic of indole ring), 7.03 (2 H, s, aromatic, positions 2 and 6 of the xylidine ring), 6.65 (1 H, s, aromatic, position-4 of the xylidine ring), 3.36 (3 H, s, NCH_3), 2.43 (3 H, s, CH_3 in position 2), 2.36 (6 H, s, $2CH_3$).

2,6-Dimethylphenylhydrazone of 2-Methylindole-3-carboxaldehyde (13). The reaction was carried out at 140–150 °C for 45 min: yellow unstable solid; mp 123–125 °C (*i*-PrOH); yield 51%.

Reaction of Hydrazone 1 with PPA. Hydrazone **1** (6.5 g) was added portionwise to stirred PPA (70 g) preheated to 80 °C. The reaction was exothermic and the temperature rapidly rose to 110 °C; it was then increased to 120 °C and maintained there for 30 min. The resulting brown viscous mass was cooled, poured onto ice, and neutralized with 26% NH_4OH solution. The separated oil was extracted with $CHCl_3$, and the organic layer was washed with H_2O, dried (K_2CO_3), and evaported under reduced pressure. The residue (6.7 g) was chromatographed through a silica gel column (130 g) with C_6H_6 as an eluent. The first fractions eluted gave some starting carbonyl compound, followed by the ethyl 4-(4-amino-3,5-dimethylphenyl)-2-thienylglyoxylate (**3**), a red-brown solid which was triturated with diisopropyl ether: 2.2 g; mp 90–100 °C; ^1H NMR 8.30 (1 H, d, aromatic, position 3 of thiophene ring), 7.75 (1 H, d, aromatic, position 5 of thiophene ring), 7.20 (2 H, s, aromatic of xylidine ring), 4.47 (2 H, q, CH_2CH_3), 3.74 (2 H, br s, exchangeable with D_2O, NH_2), 2.25 (6 H, s, $2CH_3$), 1.45 (3 H, t, CH_2CH_3). In this spectrum the following

(7) Carlin, R. B.; Carlson, D. P. *J. Am. Chem. Soc.* **1959**, *81*, 4673.
(8) Biggs, I. D.; Lyn, D.; Williams, H. *J. Chem. Soc., Perkin Trans. 2* **1977**, *1*, 44.
(9) Blike, F. F.; Tsao, M. U. *J. Am. Chem. Soc.* **1944**, *66*, 1645.
(10) Leete, E. *J. Am. Chem. Soc.* **1959**, *81*, 6023.

signals of a phenylthiophene derivative isomeric to **3** (elemental analysis of **3** was unaffected) were detectable: δ 8.05 (d, aromatic, position 3 of thiophene ring), 7.32 (s, aromatic of xylidine ring), 7.28 (d, aromatic, position 4 of thiophene ring).

4-(4-Amino-3,5-dimethylphenyl)-2-thiophenecarboxylic Acid (4). A solution of **3** (2.0 g) and KOH pellets (1.3 g) in 90% EtOH (20 mL) was refluxed for 30 min. After removal of the solvent, the residue was dissolved in H_2O, an 33% H_2O_2 solution (1.5 mL) was added. The solution was refluxed for a few minutes and then made acidic with AcOH. Acid **4** separated as a green solid: 1.5 g; mp 219 °C; ^1H NMR 7.94 (1 H, d, aromatic, position 3 of thiophene ring), 7.50 (1 H, d, aromatic, position 5 of thiophene ring), 7.17 (2 H, s, aromatic), 6.18 (3 H, br s, NH_3^+), 2.23 (6 H, s, $2CH_3$). In this spectrum, the following signals of an isomeric phenylthiophenecarboxylic acid were detected: δ 7.60 (d, aromatic, positions 3 and 4 of thiophene ring), 7.21 (s, aromatic of xylidine ring).

4-(3,5-Dimethylphenyl)-2-(ethoxycarbonyl)thiophene (5) and 4-(3,5-Dimethyl-4-hydroxyphenyl)-2-(ethoxycarbonyl)thiophene (6). A solution of $NaNO_2$ (0.45 g) in H_2O (3 mL) was carfully dropped into a well-stirred ice-cooled mixture of amino acid **4** (2 g) and 10% H_2SO_4 solution (15 mL): a dark yellow diazocompound separated. A 40% H_3PO_2 solution (7 mL) was added, the resulting slurry was stirred at 25 °C for 3 h, and *i*-PrOH (15 mL) was added. Nitrogen was rapidly evolved, and the reaction was shown to be complete after 30 min. After distillation of *i*-PrOH, a solid separated which was chromatographed on a silica gel column (20 g) with AcOEt as an eluent. The first fractions eluted gave a pink solid (1.0 g) which was refluxed with 8 N HCl solution in EtOH (20 mL) for 1 h. Solvent was distilled off, and the residue was dissolved in $CHCl_3$, washed with a 5% $NaHCO_3$ solution, and dried (Na_2SO_4). Removal of the solvent left an oil (1.0 g) which was chromatographed in turn with $CHCl_3$ as an eluent. The first fractions eluted gave 4-(3,5-dimethylphenyl)-2-(ethoxycarbonyl)thiophene (**5**) as a colorless solid: mp 67 °C (pentane); 0.40 g; ^1H NMR 8.09 (1 H, d, aromatic, position 3 of thiophene ring), 7.64 (1 H, d, aromatic, position 5 of thiophene ring), 7.25 (2 H, s, aromatic, positions 3 and 5 of phenyl group), 7.00 (1 H, s, aromatic, position 4 of phenyl group), 4.40 (2 H, q, CH_2CH_3), 2.39 (6 H, s, $2CH_3$), 1.40 (3 H, t, CH_2CH_3). Final fractions gave 4-(3,5-dimethyl-4-hydroxyphenyl)-2-(ethoxycarbonyl)thiophene (**6**): orange solid; mp 102 °C (heptane); 0.55 g; ^1H NMR 8.07 (1 H, d, aromatic, position 3 of thiophene ring), 7.55 (1 H, d, aromatic, position 5 of thiophene ring), 7.24 (2 H, s, aromatic), 5.08 (1 H, br s exchangeable with D_2O, OH), 4.40 (2 H, q, CH_2CH_3), 2.31 (6 H, s, $2CH_3$), 1.40 (3 H, t, CH_2CH_3).

4-(3,5-Dimethylphenyl)pentanoic Acid (7). (A) Desulfurization of 5. Ester **5** described above (0.39 g) was refluxed with an equimolar amount of KOH in EtOH solution (10 mL) for 30 min, the solvent was removed under reduced pressure, and the residue was diluted with a 5% $NaHCO_3$ solution (8 mL). A slurry of Raney Ni W-6[11] (0.4 g) and H_2O (30 mL) was then added, and the resulting mixture was stirred on a steam bath for 2 h. The catalyst was filtered off and washed with a 5% $NaHCO_3$ solution, and the clear filtrate was dropped into a 15% HCl solution (10 mL). The oily acid that separated was extracted with Et_2O and, after the usual procedure, distilled in vacuo to give 4-(3,5-dimethylphenyl)pentanoic acid (**7**): ^1H NMR 11.06 (1 H, br s, exchangeable with D_2O, COOH), 6.60 (3 H, s, aromatic), 2.6–1.4 (11 H, m with an s emerging at 2.20, $2CH_3$'s on the phenyl group and $CHCH_2CH_2$), 1.19 (3 H, d, $CHCH_3$). Acid **7** gave the corresponding methyl ester when treated with CH_2N_2 in Et_2O solution: bp 130 °C (0.5 mmHg); ^1H NMR 6.80 (3 H, s, aromatic), 3.65 (3 H, s, OCH_3), 2.60 (1 H, m, CH_3CHCH_2), 2.29 (6 H, s, $2CH_3$'s on the phenyl group), 2 (4 H, m, CH_2CH_2), 1.23 (3 H, d, $CHCH_3$).

(B) Reduction of 8. A mixture of lactone **8** (1.0 g) described below, amalgamated zinc dust (2.5 g), AcOH (10 mL), and 35% HCl solution (2.5 mL) was refluxed under stirring for 2 h. AcOH was removed under reduced pressure, and the residue was diluted with H_2O and extracted with Et_2O. The organic layer was exhaustively extracted with a 8% NH_4OH solution, and the combined aqueous extracts were made acidic with concentrated HCl solution. Acid **7** was extracted with Et_2O and, after the usual treatment of the solution, distilled in vacuo; its physical and spectral data were idential with those obtained from the acid resulting from reaction A. The methyl esters were identical as well.

4-(3,5-Dimethylphenyl)-γ-valerolactone (8). 3,5-Dimethyliodobenzene[12] (13.5 g) was added to a stirred suspension of Mg turnings (1.37 g) in dry THF (50 mL). When the Mg was completely consumed, the solvent was distilled off and replaced with dry benzene (50 mL). The resulting gray solution was dropped into a stirred solution of methyl levulinate (12 g) in dry benzene (70 mL), keeping the temperature at 10 °C. The temperature was then increased to 40 °C and maintained there for 10 min. A 5% HCl solution was cautiously added, the organic layer washed with H_2O, and the solvent removed under reduced pressure. The residue was refluxed in a 4 M alcoholic KOH solution (50 mL), the solvent was distilled off, and the residue was dissolved in H_2O. Some neutral material was extracted with ether, and the aqueous layer was made acidic with concentrated HCl solution. The oily acid that separated was extracted with Et_2O and, after the usual procedure, distilled in vacuo [bp 140 °C (0.5 mmHg)] to give 4-(3,5-dimethylphenyl)-γ-valerolactone (**8**) as an oil which became solid on standing: mp 50 °C; ^1H NMR 6.92 (2 H, s, aromatic, positions 2 and 6 of the phenyl group), 6.82 (1 H, s, aromatic), 2.4 (10 H, m with an s emerging at 2.32, $2CH_3$'s on the phenyl group and CH_2CH_2), 1.64 (3 H, s, CH_3 on saturated carbon).

Reaction of Hydrazone 2 with PPA: 4-[4-(Acetylamino)phenyl]-2-(methoxycarbonyl)thiophene and 5-[4-Acetylamino)phenyl]-2-(methoxycarbonyl)thiophene (11). Hydrazone **2** (13.3 g) was added portionwise under stirring to PPA (140 g) preheated to 80 °C; an exothermic reaction occurred. When it subsided, the temperature was maintained at 110 °C for 20 min, and then the reaction mixture was cooled and poured into H_2O (500 mL). The solution was neutralized with NH_4OH solution (ice was simultaneously added), and the separated organic products were extracted with $CHCl_3$. The organic layer was washed with a 5% $NaHCO_3$ solution, dried (Na_2SO_4), and evaporated to dryness. The residue was triturated with Et_2O to remove some insoluble tarry material and then chromatographed (7.2 g) on a silica gel column by using a $CHCl_3$/AcOEt (97:3) mixture. The main fraction eluted (4.4 g) was further purified by precipitating its hydrochloride from an Et_2O solution. The filtered salt was then reconverted into the free base (3.2 g). ^1H NMR analysis showed that this product was a 2:1 mixture of two components (**9** and **10**) easily detected by HPLC chromatography: ^1H NMR 8.28 (d, aromatic, position 3 of thiophene ring of **9**), 8.00 (d, aromatic, position 3 of thiophene ring of **10**), 7.68 (d, aromatic, position 5 of thiophene ring of **9**), 6.65 (2 H, 2 superimposed d, aromatic, position ortho to the NH_2 group of **9** and **10**), 7.3 (m, aromatic), 4.43 (2 H, q, CH_2CH_3), 3.60 (2 H, br s, exchangeable with D_2O, NH_2), 1.43 (3 H, t, CH_2CH_3). Part of this mixture (2.5 g) was easily converted into a mixture of the corresponding *N*-acetyl derivatives (2.6 g) by short refluxing with an equimolar amount of Ac_2O in AcOH solution. A sample of this mixture was refluxed with an equimolar amount of KOH in EtOH solution for a few minutes. The solvent was removed, the residue diluted with H_2O, and the resulting clear solution treated with an excess of a 33% H_2O_2 solution at 80 °C for 10 min. Acidification gave a mixture of two acetylamino acids which were converted into the corresponding methyl esters with CH_2N_2 in AcOEt solution; purification was achieved by column chromatography (eluent AcOEt). The overall yield was 46%. HPLC and NMR techniques confirmed the presence of two isomeric acetylamino esters in a 2:1 ratio: ^1H NMR 8.02 and 7.73 (2 d, aromatic, position 3 of thiophene ring of two isomers), 7.4 (6 H, m, aromatic and NH), 3.94 (3 H, s, OCH_3), 2.20 (3 H, s, $COCH_3$).

2-(Methoxycarbonyl)-5-(4-nitrophenyl)thiophene. Oxalic acid ethyl ester chloride (1.4 g) was dropped into a mixture of 2-(4-nitrophenyl)thiophene[13] (1.7 g), $AlCl_3$ (2.5 g) and dry $CHCl_3$ (50 mL) under stirring. The mixture was left to stand at room temperature for 24 h and then decomposed with a 10% HCl solution; unsoluble tars were removed by filtration on a cell cake.

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The organic layer, after the usual treatment, gave a residue which was refluxed with a 5% KOH alcoholic solution (20 mL) for 1 h. Solvent was distilled off, the residue was diluted with boiling H_2O, and then a 33% H_2O_2 solution (2 mL) was added. After the mixture was heated for 1 h, the pH was adjusted to 4 with AcOH to precipitate 5-(4-nitrophenyl)-thiophene-2-carboxylic acid (0.53 g). An ice-cooled suspension of the crude acid in AcOEt was treated with an excess of CH_2N_2 (ethereal solution); the acid went rapidly in solution. Evaporation of the solvent left 2-(methoxycarbonyl)-5-(4-nitrophenyl)thiophene: 0.51 g; mp 182 °C (*i*-PrOH); ^1H NMR 8.29 and 7.80 (each 2 H, AA'BB' system, aromatic of the phenyl group), 7.72 (1 H, d, aromatic, position 3 of thiophene ring), 7.25 (1 H, d, aromatic, position 4 of thiophene ring), 3.95 (3 H, s, OCH_3).

5-[4-(Acetylamino)phenyl]-2-(methoxycarbonyl)thiophene (11). A solution of 2-(methoxycarbonyl)-5-(4-nitrophenyl)-thiophene described above (0.5 g) in MeOH (20 mL) was hydrogenated at room temperature under 40 atm of hydrogen in the presence of 5% palladized charcoal (0.1 g). When the theoretical amount of hydrogen had been consumed, the catalyst was filtered off and the solvent removed under reduced pressure. Crude amino ester (0.4 g) was very difficult to crystallize and was used for the reaction with Ac_2O without further purification: mp 136 °C; ^1H NMR (Me_2SO) 7.72 (1 H, d, aromatic, position 3 of thiophene ring), 7.45 and 6.75 (each 2 H, AA'BB' system, aromatic of the phenyl group), 7.15 (1 H, d, aromatic, position 4 of thiophene ring), 4.47 (2 H, br s, exchangeable with D_2O, NH_2), 3.90 (3 H, s, OCH_3). Crude amino ester was refluxed with a stoichiometric amount of Ac_2O in AcOH to give the title compound which was purified by trituration with diisopropyl ether. Its retention time in HPLC analysis and its spectral data were identical with those shown by the product obtained from transformation of **9**: ^1H NMR 7.73 (1 H, d, aromatic, position 3 of thiophene ring), 7.50 (5 H, aromatic of the phenyl group and NH), 7.25 (1 H, d, aromatic, position 4 of thiophene ring), 3.94 (3 H, s, OCH_3), 2.20 (2 H, s, $COCH_3$).

Reaction of Hydrazone 12 with PPA. Hydrazone **12** (8.5 g) was added portionwise under stirring to PPA (100 g) preheated to 60 °C. The mixture was heated at 140–150 °C for 1 h and then poured into ice-cold H_2O (500 mL). The resulting solution was made alkaline with concentrated NH_4OH solution and exhaustively extracted with $CHCl_3$. The combined organic extracts were washed with H_2O, dried (K_2CO_3), and evaporated to dryness. The oily residue was treated with Et_2O, and the sandy solid that separated gave the 2-methylindole-3-carboxaldehyde (0.97 g) which was purified by column chromatography. The ethereal solution left a residue (4.6 g) which was chromatographed in turn on a silica gel column (50 g; eluent $CHCl_3$/AcOEt, 4:1). Two main groups of fractions were collected. The first fractions eluted (1.15 g) were subjected to an acid–base treatment. The basic solid obtained was crystallized from diisopropyl ether, but a satisfactory purity was not achieved (0.35 g). On the basis of ^1H NMR data, the structure of bis[2,6-dimethyl-4-(methylamino)phenyl]methane was assigned: ^1H NMR 6.28 (4 H, s, aromatic), 3.90 (2 H, s, CH_2), 3.30 (2 H, br s, exchangeable with D_2O, 2NH), 2.80 (6 H, s, $2NHCH_3$), 2.08 (12 H, s, 4 CH_3). Mother liquors left a residue (0.5 g) which was chromatographed in turn on a silica gel column (15 g) using $CHCl_3$ as eluent to give crude 4,4'-bis(methylamino)-2,2',6,6'-tetramethylbiphenyl (**14**): ^1H NMR 6.41 (4 H, s, aromatic), 3.50 (2 H, s, exchangeable with D_2O, 2NH), 2.82 (6 H, s, $2NCH_3$), 1.85 (12 H, s, $4CH_3$). **14** could be isolated in a pure state as the *N*-acetyl derivative: mp >230 °C (*i*-PrOH); ^1H NMR 7.00 (4 H, s, aromatic), 3.33 (6 H, s, $2NCH_3$), 1.94 (18 H, s, $2COCH_3$ and 2 Ar CH_3's). The second group of chromatographic fractions gave the 2-methyl-4-[2,6-dimethyl-4-(methylamino)phenyl]-indole-3-carboxaldehyde (**15**, 1.6 g); a further acid–base treatment to remove some 2-methylindole-3-carboxaldehyde could be required: mp 230 °C (C_6H_6); ^1H NMR (Me_2SO) 9.11 (1 H, s, CHO), 7.34 (2 H, m, aromatic, position 7 and indolic NH), 7.20 (1 H, t, aromatic, position 6), 6.88 (1 H, d, aromatic, position 5), 6.41 (2 H, s, aromatic of xylidine ring), 4.66 (1 H, br s, exchangeable with D_2O, $NHCH_3$), $NHCH_3$), 2.80 (3 H, s, $NHCH_3$), 2.69 (3 H, s, CH_3 in position 2), 1.88 (6 H, s, $2CH_3$).

Reaction of Hydrazone 13 with PPA. Hydrazone **13** (13.0 g) was added portionwise under stirring to PPA (130 g) preheated to 60 °C; the reaction was exothermic, and the temperature spontaneously increased to 80 °C. The mixture was heated to 100 °C, maintained there for an additional 30 min, and then poured onto ice. The resulting solution was neutralized with concentrated NH_4OH solution. The aqueous layer was decanted from the precipitated viscous mass; the latter was treated with boiling EtOH, removing undissolved tars by filtration. The alcoholic solution was cooled, filtered, and evaporated to dryness. The residue was treated with $CHCl_3$, and some undissolved material was filtered off. The solvent was removed to leave a residue (8.2 g) which was chromatographed on a silica gel column (160 g) with $CHCl_3$ as an eluent with increasing percentages of AcOEt. The fractions first eluted afforded 2,6-dimethylaniline (0.77 g). Intermediate fractions gave 3-(4-amino-3,5-dimethylphenyl)-2-methylindole (**17**): 2.53 g; mp 167–168 °C (C_6H_6–hexane); ^1H NMR 7.67 (2 H, m, NH and aromatic H in position 7), 7.12 (5 H, m, aromatic), 3.51 (2 H, br s, exchangeable with D_2O, NH_2), 2.38 (3 H, s, CH_3 in position 2), 2.24 (6 H, s, $2CH_3$). The final fractions gave 4,4'-diamino-3,3',5,5'-tetramethylbiphenyl (**16**): 1.85 g; mp 156–157 °C (*i*-PrOH); ^1H NMR 6.82 (4 H, s, aromatic), 3.52 (4 H, br s, exchangeable with D_2O, $2NH_2$), 2.22 (12 H, s, $4CH_3$).

3-(3,5-Dimethylphenyl)-2-methylindole (18). (A) Deamination of 17. A solution of $NaNO_2$ (0.030 g) in H_2O (2 mL) was dropped into a mixture of amine **17** (0.107 g) and a 10% H_2SO_4 solution (10 mL) under stirring at 0–5 °C. Finally, a 50% H_3PO_2 solution (2 mL) was added. The mixture was left to stand at room temperature for 10 h and then, after addition of *i*-PrOH (1 mL), warmed at 50 °C for 4 h. The product separated was extracted with $CHCl_3$. The organic layer was washed with a 5% NaOH solution, dried (Na_2SO_4), and then evaporated to dryness. The residue was chromatographed on a silica gel column with $CHCl_3$ as an eluent. The first-eluted fractions contained 3-(3,5-dimethylphenyl)-2-methylindole (**18**), a light yellow oil which was purified by distillation in vacuo [bp 185 °C (0.5 mmHg)]. The distillate became solid on being allowed to stand in a refrigerator: mp 95 °C; ^1H NMR 7.82 (1 H, br s, NH), 7.64 (1 H, m, aromatic, position 7), 6.93 (1 H, s, aromatic, position 4 of the xylene ring), 7.1 (5 H, m, aromatic), 2.46 (3 H, s, CH_3 in position 2), 2.47 (6 H, s, $2CH_3$).

(B) Fischer Reaction of the Phenylhydrazone of 1-(3,5-Dimethylphenyl)propan-2-one. 1-(3,5-Dimethylphenyl)-propan-2-one (0.9 g) and phenylhydrazine (0.6 g) were heated at 70–80 °C in an oil bath for a few minutes. PPA (15 g) was added to the hydrazone, and the resulting mixture was heated to 110 °C, kept at this temperature for 20 min, poured into H_2O (80 mL), and extracted with Et_2O. The usual treatment of the organic layer afforded a residue (0.7 g) which was chromatographed on a silica gel column (40 g) with CCl_4 as an eluent. The combined final fractions gave 3-(3,5-dimethylphenyl)-2-methylindole (**18**) which was purified by distillation in vacuo followed by crystallization from pentane; mp 97 °C. Spectral and chromatographic data were identical with those shown by the product resulting from path A.

1-(3,5-Dimethylphenyl)propan-2-one. A mixture of (3,5-dimethylphenyl)acetic acid[14] (2 g), Ac_2O (1.2 g), and AcOK (1.72 g) was refluxed for 12 h, diluted with H_2O, and neutralized with a concentrated NaOH solution. The separated oil was extracted with Et_2O and, after the usual treatment, distilled in vacuo [bp 125 °C (1 mmHg)]. The product obtained was rather impure, but it was used for the synthesis of **18** without further purification: ^1H NMR 6.9 (m, aromatic), 3.62 (s, CH_2), 2.40 (s, $COCH_3$), 2.30 (s, $2CH_3$).

Registry No. (*E*)-**1**, 80387-50-4; (*Z*)-**1**, 80387-51-5; (*E*)-**2**, 80387-52-6; (*Z*)-**2**, 80387-53-7; **3**, 80387-54-8; **4**, 80387-55-9; **5**, 80387-56-0; **6**, 80387-57-1; **7**, 80387-58-2; **7** methyl ester, 80387-59-3; **8**, 80387-60-6; **9**, 80387-61-7; **9** *N*-acetyl, 80387-62-8; **10**, 80387-63-9; **10** *N*-acetyl, 80387-64-0; **11**, 80387-65-1; **11** deacetyl, 80387-66-2; **12**, 80387-67-3; **13**, 80387-68-4; **14**, 80387-69-5; **14** *N,N'*-diacetyl, 80387-70-8; **15**, 80387-71-9; **16**, 54827-17-7; **17**, 80387-72-0; **18**, 80387-73-1; 3,5-dimethylaniline, 108-69-0; *N*-methyl-*N*-(3,5-dimethylphenyl)-4-toluenesulfonamide, 80387-74-2; *N*,3,5-trimethylaniline, 13342-20-6; *N*-nitroso-*N*,3,5-trimethylaniline, 62959-13-1; *N*,3,5-trimethylhydrazine, 80398-80-7; 2-methylindole-3-carboxaldehyde, 5416-80-8;

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(2,6-dimethylphenyl)hydrazine, 603-77-0; ethyl 2-thienylglyoxylate, 4075-58-5; *N*-(2,6-dimethylphenyl)-2-thienylglyoxylic acid hydrazide, 80387-75-3; ethyl 5-(4-amino-3,5-dimethylphenyl)-2-thienylglyoxylate, 80387-76-4; 5-(4-amino-3,5-dimethylphenyl)-2-thiophenecarboxylic acid, 80387-77-5; 3,5-dimethyliodobenzene, 22445-41-6; methyl levulinate, 624-45-3; 4-(4-acetamidophenyl)-2-(methoxycarbonyl)thiophene, 80387-78-6; oxalic acid ethyl ester chloride, 4755-77-5; 2-(4-nitrophenyl)thiophene, 59156-21-7; 5-(4-nitrophenyl)thiophene-2-carboxylic acid, 80387-79-7; 2-(methoxycarbonyl)-5-(4-nitrophenyl)thiophene, 61100-12-7; bis[2,6-dimethyl-4-(methylamino)phenyl]methane, 80387-80-0; 2,6-dimethylaniline, 87-62-7.

Azabutadiene Derivatives in the Synthesis of Five-Membered Heterocycles. Unequivocal Synthesis of 1*H*-Pyrrole-2-carboxylates

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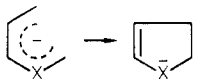
1,3-Diimines **1** react with glycine ethyl ester hydrochloride **2** as well as ethyl chloroacetate **9** in pyridine, giving rise to 1*H*-pyrrole-2-carboxylates **8** in both cases. The formation of heterocycles **8** can be explained in terms of an electrocyclic closure of the azapentadiene anion intermediate **6**.

The formation of aromatic and heteroaromatic compounds by electrocyclic ring closure with elimination is of high interest in organic synthesis.[1] This type of process is applied to form not only six-membered rings but also five-membered heterocycles.[2] In this last case, the electrocyclic reaction of the pentadienyl anion ⇌ cyclopentadienyl anion type is relatively unimportant. However, the presence of a heteroatom in the 2- or 4-position of the pentadiene favors the electrocyclic closure since the negative charge is supported by a heteroatom (N, O).



Azabutadiene derivatives **1** are easily obtained by reaction of Schiff bases with saturated nitriles in the presence of $AlCl_3$[3] and are useful precursors for the synthesis of six-membered heterocyclic rings. Usually the cyclization steps consist of a double condensation reaction[4] or an addition followed by the electrocyclic ring closure of the resulting intermediate.[5]

The azabutadienes **1** appeared to be potential precursors for the synthesis of five-membered heterocycles. With this in mind we have investigated the reaction of **1** with glycine ethyl ester hydrochloride and with ethyl chloroacetate. We report in this paper a new and unequivocal synthesis of 1*H*-pyrrole-2-carboxylates involving an azabutadiene anion (X = N).

Results and Discussion

Azabutadiene derivatives **1** react with glycine ester hydrochloride **2** at 80 °C in pyridine as solvent, giving, in high yields products whose structures from their elemental analyses and spectroscopic data are consistent with **7** or **8**.

The heterocyclization can be explained in terms of an exchange reaction between the amino group of the glycine and the imino group present in one of the tautomer forms of the azabutadiene.[6] Deprotonation of intermediates **3** and/or **4** leads to azapentadienyl anions **5** and/or **6**, which can undergo an electrocyclic closure, giving 1*H*-pyrrole-2-carboxylates (see Scheme I).

Table I. Pyrroles 8 from Diimines 1 and Glycine Ethyl Ester Hydrochloride 2

8	R^2	R^3	R^4	% yield	mp, °C
a	C_6H_5	CH_3	C_6H_5	88	135-137
b	C_6H_5	CH_3	p-$CH_3C_6H_4$	90	138-140
c	C_6H_5	CH_3	C_3H_7	80	111-113
d	C_6H_5	CH_3	c-C_6H_{11}	85	118-120
e	C_6H_5	CH_3	p-ClC_6H_4	85	178-180
f	C_6H_5	H	C_6H_5	81	137-139
g	C_6H_5	H	p-$CH_3C_6H_4$	87	168-170
h	p-ClC_6H_4	CH_3	C_6H_5	83	172-174
i	p-ClC_6H_4	CH_3	p-$CH_3C_6H_4$	85	173-175

In a previous paper on the reaction of **1** with heterocumulenes[5] we showed (by isolating the intermediate resulting from the addition of the imine NH to the heterocumulene) that the unsubstituted imine group is the main reactive center in the azabutadiene. Taking this into account, one can propose, that the reaction of **1** with **2** takes place through path b leading to pyrroles **8** (Scheme II). In addition, the same products are obtained from the reaction of **1** with either ethyl chloroacetate (**9**) or glycine ethyl ester hydrochloride (**2**).

Additional evidence to confirm this reaction mechanism lies in the isolation of the intermediate **4**. In this way diimine **1** (R^1 = c-C_6H_{11}, R^2 = C_6H_5, R^3 = CH_3, R^4 = p-$CH_3C_6H_4$) reacts with **2** at room temperature to afford **4b** (see Experimental Section). Moreover, ammonium chloride is identified. When **4b** is dissolved in pyridine and heated at 80 °C, the heterocycle **8b** is formed and isolated in quantitative yield.

Whereas the synthesis of alkylpyrroles has been widely developed,[7] this cannot be said of aryl pyrroles. By use of classical synthetic methods such as modified Knorr[8] and Hantzsch[9] procedures in order to prepare asymmetric

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