Rearrangement of Arylhydrazones of α,β-Unsaturated Carbonyl Compounds in Polyphosphoric Acid. 6

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The reactions of a series of *N*-methyl-*N*-arylhydrazones of α,β-unsaturated carbonyl compounds **1** with hot polyphosphoric acid are described. Three main courses were observed, depending on the structure of the carbonyl portion of the substrate. Unsaturated α-oxo ester hydrazones (**1a–c**) rearranged to give substituted 3-[2-(methylamino)aryl]-2-oxo-3-butenoic acid esters (**2a–c**); the reaction mechanism strictly resembles the initial steps of the Fischer indole synthesis. Unsaturated aldehyde hydrazones alternatively gave either the di-3-indolylmethane derivatives (**3a,b**) or the amino nitriles (**4a–c**). The first process develops through intermediates structurally similar to **2**; the latter was demonstrated to be exclusively intramolecular.

The rearrangement reactions of nonindolizable arylhydrazones in polyphosphoric acid have been the object of constant research in this laboratory for several years.[1] In some cases, these reactions are very similar to those of hydrazoarenes in acid medium, in particular to the benzidine[2] and *o*-semidine[3] rearrangements. The fact that the ene hydrazines, vinyl homologues of the hydrazoarenes, undergo a general [3,3] sigmatropic shift,[4] as intermediates in the Fischer indole synthesis, suggested a study of whether reactions of this type might also occur with the arylhydrazones of α,β-unsaturated carbonyl compounds. The results of this study are reported here.

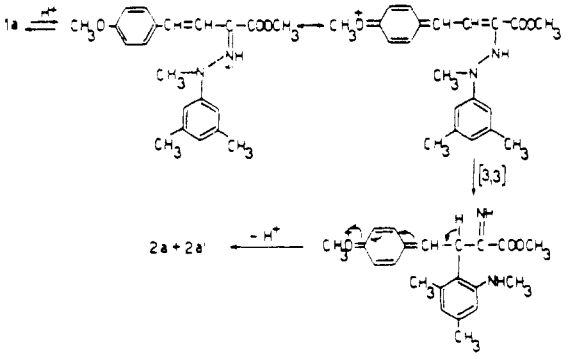
Results

The substrates studied were the arylhydrazones of the unsaturated α-keto esters and aldehydes of general formula **1** and were made to react with polyphosphoric acid (PPA) at 80–100 °C. Completely different results were obtained depending on the structure of the substrate; the three main reaction courses are shown in Scheme I. The reaction of **1a** with PPA preheated to 80 °C was exothermic and gave a fairly complex mixture of products; the two principal ones were isolated in the pure state by chromatography. They were assigned the structures of the *E* and *Z* isomers of methyl 4-(4-methoxyphenyl)-3-[2-(methylamino)-4,6-dimethylphenyl]-2-oxo-3-butenoate (**2a** and **2a′**).

Structure assignment was based on chemical tests, including catalytic hydrogenation in the presence of palladium on carbon in glacial acetic acid, which gave the same product from both compounds, that is, 2-(methoxycarbonyl)-3-(4-methoxybenzyl)-1,4,6-trimethylindole. This compound was not in the literature, and was synthesized independently by Fischer indolization of the *N*-methyl-*N*-(3,5-dimethylphenyl)hydrazone of methyl 4-(4-methoxyphenyl)-2-oxobutyrate. These results not only proved the structure but also demonstrated the stereoisomeric relationship between **2a** and **2a′**.

Another series of reactions significant in terms of proving the structure of **2a,a′** was alkaline saponification of the more abundant of the two isomers, followed by hydrogen peroxide oxidation in the same medium. The product was the 3-[(4-methoxyphenyl)methylene]-1,4,6-trimethyl-2-indolinone, deriving from lactamization of an intermediate amino acid not isolated. Structural assignment was based on analytical and spectroscopic data.

The formation of **2a** and **2a′** upon rearrangement of hydrazone **1a** may be interpreted on the basis of the following mechanism which involves the intervention of an ene hydrazine species undergoing the [3,3] sigmatropic shift typical of such systems, in accordance with the original hypothesis.



The presence of the methoxy group in **1a** should contribute to the stabilization of the ene hydrazine system, although in primciple the production of a simple benzylic carbonium ion should have been sufficient. The latter possibility was tested by treating the *N*-methyl-*N*-(3,5-dimethylphenyl)hydrazone of methyl 2-oxo-4-phenyl-3-butenoate (trans) (**1b**) with PPA. Although this reaction was not as clean as the previous one, an isomer of methyl 3-[2-(methylamino)-4,6-dimethylphenyl]-2-oxo-4-phenyl-3-butenoate (**2b**) could be isolated from the reaction products. The structure of **2b** was assigned on the basis of spectroscopic as well as hydrogenation reaction data. The latter gave 3-benzyl-2-(methoxycarbonyl)-1,4,6-trimethylindole, which was in turn synthesized independently by indolization in PPA of the *N*-methyl-*N*-(3,5-dimethylphenyl)hydrazone of methyl 2-oxo-4-phenylbutyrate.

This series of arylhydrazones deriving from unsaturated α-keto esters also included the *N*-methyl-*N*-phenylhydrazone of methyl 4-(4-methoxyphenyl)-2-oxo-3-butenoate (**1c**). Reaction of the latter with PPA led, as expected, to a mixture, unresolved in this case, of the *E* and *Z* isomers (one present in great excess) of methyl 4-(4-methoxyphenyl)-3-[2-(methylamino)phenyl]-2-oxo-3-butenoate (**2c**). However, completely different results were obtained in the case of the *N*-methyl-*N*-(3,5-dimethylphenyl)hydrazone and the *N*-methyl-*N*-phenylhydrazone of cinnamic aldehyde (**1d** and **1e**). Their reaction with PPA was slower than in the previous cases and led surprisingly to diindol-3-ylmethanes **3a** and **3b**, in good yield in the former case.

(1) Fusco, R.; Sannicolò, F. *Tetrahedron Lett.* **1977**, *36*, 3163; *J. Org. Chem.* **1981**, *46*, 83; *Ibid.* **1981**, *46*, 90. Sannicolò, F. *Gazz. Chim. Ital.* **1981**, *111*, 351.
(2) *Tetrahedron* **1980**, *36*, 166.
(3) Fusco, R.; Sannicolò, F. *Chim. Ind. (Milan)* **1978**, *60*, 909.
(4) Grandberg, I. I.; Sorokin, V. I. *Russ. Chem. Rev.* **1974**, *43*, 115.

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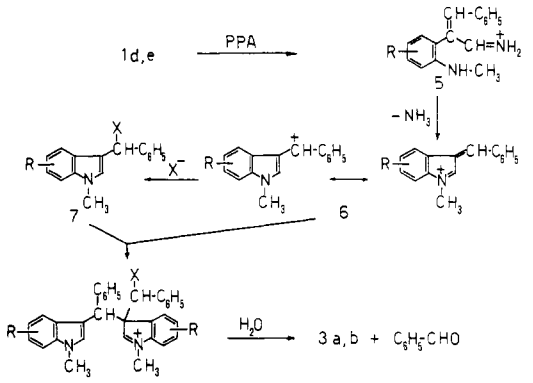
Structure assignment was based not only on analytical and spectroscopic data but also on the preparation of **3b**, already reported in the literature,[5] by independent synthesis starting from benzaldehyde and *N*-methylindole in acid medium.

The proposed mechanism for the formation of these products involves an initial transformation of the substrate completely analogous to that shown by the hydrazones of the keto esters **1a–c**. The 2-[2-(methylamino)aryl]-cinnamic aldehyde imine intermediate (**5**) which forms can



close the indole system intramolecularly, due to the particular reactivity of the imine group, and can capture a nucleophile from the medium (indicated with X^- but probably the phosphate ion). The new intermediate **7** can in turn react with the electrophilic species **6** to give the final diindolylmethane, expelling benzaldehyde.

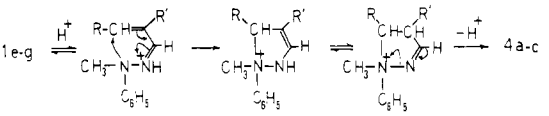
This hypothesis is in accord with the literature data,[6] which show that the 3 position of the indole nucleus is highly reactive to electrophiles even when substituted, as well as with the following experimental evidence. We have shown that the 3-(α-hydroxybenzyl)-1-methylindole, unknown in the literature and synthesized according to a traditional method (see Experimental Section), reacts very rapidly in dissociating solvents like aqueous acetic acid at 40–50 °C to form diindolylmethane **3b** and benzaldehyde.

Literature data[7] suggest that the formation of **3** does not require the preliminary partial scission of **7** into benzaldehyde and *N*-methylindole. Compounds structurally related to **5** have been shown to be precursors to the diindolylmethanes by the fact that heating **2c** in aqueous acetic acid solution gives diindolylmethane **3c**. The latter was identified clearly on the basis of analysis and spectroscopic data.[8]

The secondary products of the reaction between substrate **1e** and PPA include, in addition to diindolylmethane **3b**, a base which was isolated and identified as 3-(*N*-methylanilino)-3-phenylpropionitrile (**4a**).

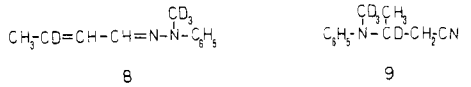
When the reaction with PPA was extended to the *N*-methyl-*N*-phenylhydrazones of other α,β-unaturated aldehydes **1f** and **1g**, formation of the amino nitriles **4b** and **4c** only was observed. Yields are variable and depend on the facility with which PPA transforms the amino nitriles into the corresponding amides and this makes product isolation more difficult.

This kind of transformation recalls two reports of the literature: the reaction of acrolein and unsymmetrical dialkylhydrazines in a buffered medium followed by alkaline treatment to give 3-(dialkylamino)propionitriles[9] and the production of the 3-(dimethylamino)isobutyronitrile as a byproduct of the hydrolysis, effected by hot aqueous mineral acids, of the dimethylhydrazone of 2-methylacrolein. The mechanism of amino nitrile **4** formation is described below and involves the intermediate formation of a pyrazolinium salt; a tautometer of the latter affords the final amino nitrile by expelling a proton.



However, it proved impossible to reject a priori a mechanism involving the preliminary scission of the N–N bond of the substrate followed by recombination of the resulting fragments, an α,β-unsaturated nitrile and an aromatic amine. Even though the intramolecular mechanism seemed by far the more probable on the basis of experimental (*N*-methylaniline does not add to cinnamonitrile in PPA to give **4a**) and literature data (some pyrazolinium salts are known to undergo ring opening in the presence of strong bases,[11] while some pyrazolines do so photochemically[12]), we felt the need for some irrefutable proof that the reaction is intramolecular.

The mass spectrum of the rearrangement product of an equimolar mixture of hydrazones **1g** and **8** with the latter



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labeled with deuterium in both the carbonyl and hydrazine moiety (for its synthesis see Experimental Section) showed two molecular peaks only, at 174 and 178, corresponding to **4c** and **9**. There were no peaks at all for intermediate molecular weight products (177 and 175), which could have been formed only by an intermolecular pathway.

Conclusions

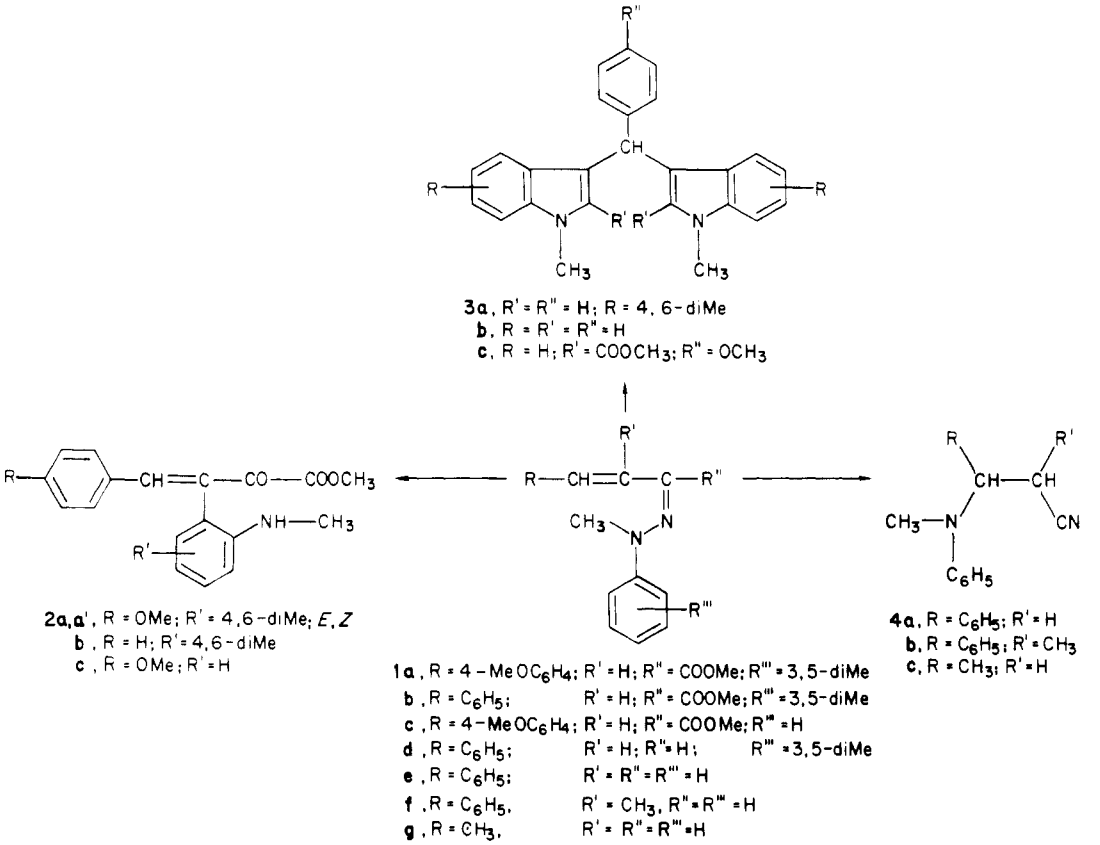
Our study of the rearrangement reactions of the arylhydrazones of α,β-unsaturated carbonyl compounds revealed three reaction courses occurring alternatively or in competition depending on the nature of the substrate. The formation of diindolylmethanes **3** and of α,β-unsaturated carbonyl compounds with a (*N*-methylamino)aryl group in the position 2 are intimately connected; the former result from further reaction of the latter, fairly facile in some cases but more difficult in others. In these cases, the observed behavior may be compared to that of the ene hydrazines. We have called such reaction *pseudo-Fischer*. The third reaction pathway leading to amino nitrile **4** involves the intermediate formation of a pyrazolinium salt. It has been shown to be strictly intramolecular.

Experimental Section

Melting points are uncorrected. NMR spectra were recorded on a Varian EM-390 spectrometer with $CDCl_3$ as a solvent unless otherwise stated and with Me_4Si as an internal standard.

(5) Fischer, E. *Chem. Ber.* **1886**, *19*, 2988; *Liebigs Ann. Chem.* *242*, 377.
(6) Treibs, W.; Bhranaramba, A. *Tetrahedron Suppl.* **1966**, *8* (*1*), 165. Teramura, K.; Itagaki, H.; Oda, R. *J. Chem. Soc. Jpn. Ind. Chem. Sect.* **1954**, *57*, 407. Kamal, A.; Qureshi, A. A. *Tetrahedron* **1963**, *19*, 513. Jackson, A. M.; Naidoo, B.; Smith, A. E.; Bailey, A. S.; Vandrevala, M. H. *Chem. Commun.* **1978**, 779.
(7) Biswas, K. M.; Jackson, A. H. *Tetrahedron* **1969**, *25*, 227.
(8) On exposure to air and light **2c** is transformed into an intensely colored pink compound, according to a known behavior of diindolylmethane derivatives. Mingoia, Q. *Gazz. Chim. Ital.* **1926**, *56*, 772. Oddo, B.; Toffoli, C. *ibid.* **1934**, *64*, 359. Fischer, E.; Wagner, P. *Chem. Ber.* **1887**, *20*, 815. Scholz, M. *Chem. Ber.* **1913**, *46*, 1082, 2138.
(9) Ioffe, B. V.; Zelenin, K. N. *Dokl. Akad. Nauk. SSSR* **1960**, *134*, 1094.
(10) Ioffe, B. V.; Zelenin, K. N. *Dokl. Akad. Nauk. SSSR* **1962**, *144*, 1303.
(11) Zelenin, K. N.; Ioffe, B. V. *Vestn. Leningr. Univ., Fiz. Khim.* **1968**, *23*, 159; *Zh. Obshch. Khim.* **1963**, *33*, 3231.
(12) Hoffmann, R. W.; Eicken, K. R. *Tetrahedron Lett.* **1968**, 1759.

Scheme I



Chemical shifts are given in δ units and refer to the center of the signal: s, singlet; d, doublet; t, triplet; sx, sextet; m, multiplet; dd, double doublet; dq, double quartet. Coupling constants are given in Hz.

Carbonyl Compounds. All carbonyl compounds mentioned are in the literature and references are given to those not commercially available.

Hydrazines. *N*-Methyl-*N*-phenylhydrazine and *N*-methyl-*N*-(3,5-dimethyl)phenylhydrazine[13] are in the literature. *N*-(Trideuteriomethyl)-*N*-phenylhydrazine was prepared, starting from 4-toluenesulfonanilide, according to the synthetic procedure described below.

***N*-(Trideuteriomethyl)aniline.** A solution of 4-toluenesulfonanilide (42.6 g) in dry DMF (150 mL) was cautiously added to a stirred slurry of NaH (55% dispersion in mineral oil, 8.3 g) in dry DMF (500 mL), keeping the temperature below 50 °C. The mixture was warmed to 60 °C then cooled to 40 °C and trideuteriomethyl iodide (25 g) slowly added to it. This temperature was maintained for a further 12 h after the addition. The reaction mixture was poured into H_2O and the precipitated *N*-(trideuteriomethyl)-4-toluenesulfonanilide filtered and then, still wet (56.4 g, mp 91 °C), suspended in 70% H_2SO_4 (320 mL). As the temperature was raised to 130 °C on an oil bath, sulfonamide gradually came into solution. The clear solution was poured onto ice and the pH adjusted to 7 with 35% NaOH solution; the separated oil was extracted with Et_2O, dried (Na_2SO_4), and evaporated to dryness to give the *N*-(trideuteriomethyl)aniline as a residue: bp 88 °C (25 mmHg) (12.3 g); ^1H NMR δ 7.2 (2 H, m, aromatic in meta positions), 6.65 (3 H, m, aromatic), 3.55 (1 H, broad s, exchangeable with D_2O NH).

***N*-Nitroso-*N*-(trideuteriomethyl)aniline.** The method reported in the literature for the synthesis of the parent unlabeled compound[13] was followed.

***N*-(Trideuteriomethyl)-*N*-phenylhydrazine.** A solution of *N*-nitroso-*N*-(trideuteriomethyl)aniline (13.7 g) in dry THF (27 mL) was dropped into a stirred slurry of $LiAlH_4$ (3.8 g) in dry THF (80 mL), the temperature being kept between 35 and 40 °C. The mixture was stirred for 15 min after the addition, cooled to 5 °C in an ice bath, and cautiously treated with H_2O (6 mL); a 35% NaOH solution (5 mL) was added and the inorganic precipitate was filtered off. The filtrate was evaporated to dryness and the residue, purified through an acid–base treatment, carefully rectified under reduced pressure. The main fraction (5.9 g) (bp 115–120 °C (20 mmHg)) contained only traces of *N*-(trideuteriomethyl)aniline: ^1H NMR δ 6.5–7.3 (5 H, m, aromatic), 3.7 (2 H, broad s exchangeable with D_2O, NH_2).

Hydrazones. The syntheses of **1a**, **1d**, and **1e** were carried out by reacting equimolar amounts of the carbonyl compound and the suitable hydrazine in refluxing 50% AcOH solution; hydrazones separated from the reaction mixture on cooling and were purified by crystallization. Hydrazones **1b** and **1c** were similarly prepared, but MeOH was employed as solvent and AcOH traces were added; solvent was evaporated under reduced pressure, the unreacted hydrazine removed through an acid treatment, and the product purified by chromatography on a silica gel column. In the cases of substrates **1f** and **1g** reagents were warmed at 80 °C without any solvent for 20 min. The presence of two isomeric hydrazones could be detected by TLC or ^1H NMR spectroscopy; this observation is not unexpected.[14] In a few cases they could be separated by chromatography or fractional crystallization.

***N*-Methyl-*N*-(3,5-dimethylphenyl)hydrazone of Methyl 4-(4-Methoxyphenyl)-2-oxo-3-butenoate (1a).** Crude oily hydrazone was chromatographed on a silica gel column (eluent $CHCl_3$) to give **1a** (yield 50%): mp 90–91 °C (*i*-PrOH). Anal. Calcd for $C_{21}H_{24}N_2O_3$: C, 71.60; H, 6.86; N, 7.95. Found: C, 72.25; H, 6.83; N, 8.05. ^1H NMR δ 7.35 (2 H, d of an AA'BB' system, aromatic in position meta to the OCH_3 group), 7.25 (1 H, d of an AB system, CH=C*H*—C=N, J = 15), 6.8 [6 H, m resulting from the superimposition of a d (6.87, AA'BB', aromatic in position ortho to the OCH_3 group), a s (6.85, aromatic in position 2 and 6 of xylidine ring), a s (6.66 aromatic in position 4 of xylidine ring) and a d (6.67, Ar—C*H*=CH)], 3.96 and 3.85 (2 × 3 H, 2 s, 2 OCH_3), 3.47 (3 H, s, NCH_3), 2.35 (6 H, s, 2 CH_3).

***N*-Methyl-*N*-(3,5-dimethylphenyl)hydrazone of Methyl 4-Phenyl-2-oxo-3-butenoate (1b).** Crude hydrazone was chro-

(13) Fusco, R.; Sannicolò, F. *J. Org. Chem.* **1982**, *47*, 1691.

(14) Idoux, J. P.; Sikorski, J. A. *J. Chem. Soc., Perkin Trans. 2* **1972**, 921. Hegarty, A. F.; Scott, F. L. *Chem. Commun.* **1967**, 521.

matographed on a silica gel column (eluent CCl_4); a red viscous oil was obtained (1:1 mixture of two isomeric hydrazones) which was submitted to the reaction with PPA without any further purification.

***N*-Methyl-*N*-phenylhydrazone of Methyl 4-(4-Methoxyphenyl)-2-oxo-3-butenoate (1c).** The crude oily hydrazone was chromatographed on a silica gel column (eluent $CHCl_3$). The *N*-methyl-*N*-phenylhydrazone of anisaldehyde (mp 112 °C)[15] was first eluted and then a mixture of two isomeric hydrazones (yield 76%); final fractions gave one in a pure state: ^1H NMR δ 7.0 (11 H, m, aromatic and vinylic), 3.95 and 3.83 (2 × 3 H, 2 s, 2 OCH_3), 3.48 (3 H, s, NCH_3). This oily hydrazone was reconverted on standing into the initial mixture of two isomers.

***N*-Methyl-*N*-(3,5-dimethylphenyl)hydrazone of Cinnamic Aldehyde (1d).** Yellow solid with mp 96 °C (hexane) (yield 62%). Anal. Calcd for $C_{18}H_{20}N_2$: C, 81.81, H, 7.57; N, 10.61. Found: C, 81.54; H, 7.50; N, 10.59.

***N*-Methyl-*N*-phenylhydrazone of Cinnamic Aldehyde (1e).** Yellow solid with mp 110 °C (hexane) (yield 65%). Anal. Calcd for $C_{16}H_{16}N_2$: C, 81.36; H, 6.78; N, 11.86. Found: C, 80.90; H, 6.83; N, 11.20. ^1H NMR δ 7.5–6.6 (13 H on unsaturated carbons, m), 3.37 (3 H, s, CH_3).

***N*-Methyl-*N*-phenylhydrazone of 2-Methylcinnamic Aldehyde (1f).** Orange-yellow solid with mp 107 °C (hexane) (yield 56%). Anal. Calcd for $C_{17}H_{18}N_2$: C, 81.60; H, 7.20; N, 11.20. Found: C, 81.25; H, 7.43; N, 11.24. ^1H NMR δ 7.33 (10 H, m, 2 C_6H_5), 6.88 (1 H, m, CHC_6H_5), 6.65 (1 H, s, CH=N), 3.40 (3 H, s, NCH_3), 2.30 (3 H, s, CH_3).

***N*-Methyl-*N*-phenylhydrazone of Crotonic Aldehyde (1g).** Oil with bp 110 °C (0.2 mmHg). Anal. Calcd for $C_{13}H_{14}N_2$: C, 75.86; H, 8.04; N, 16.09. Found: C, 75.40; H, 8.14; N, 15.97. ^1H NMR δ 7.30 (5 H, m, C_6H_5), 6.9 (1 H, dq, CH=N), 6.36 (1 H, dd, CH=C*H*CHN), 5.85 (1 H, dq, CH_3CH), 3.30 (3 H, s, NCH_3), 1.89 (3 H, s, CH_3CH); $J_{H_1H_2}$ = 8.5, $J_{H_2H_3}$ = 16.5, $J_{H_3CH_3}$ = 7, $J_{H_2CH_3}$ = 1.5, $J_{H_1CH_3}$ = 1.

***N*-(Trideuteriomethyl)-*N*-phenylhydrazone of Crotonic-*3-d* Aldehyde (8).** Anal. Calcd for $C_{11}H_{10}D_4N_2$: C, 74.16; H/D, 7.87; N, 15.73. Found: C, 74.34; H/D, 8.28; N, 15.66. ^1H NMR δ 7.3 (5 H, m, aromatic), 6.9 (1 H, dq, CH=N), 6.35 (1 H, m, CD=C*H*), 1.89 (3 H, s, CH_3).

Reaction of 1a with PPA. Hydrazone **1a** (3.0 g) was added portionwise to stirred PPA (45 g) preheated to 80 °C. The reaction was exothermic and the temperature rose to 115 °C; the reaction mixture was stirred at this temperature for 20 min, then poured into H_2O (150 mL). The precipitated solid was extracted with Et_2O and the organic layer washed with H_2O and with a 5% $NaHCO_3$ solution, dried (Na_2SO_4), and evaporated under reduced pressure. The solid residue (2.36 g) was treated with diisopropyl ether, filtered, and crystallized from petroleum ether to give the methyl 3-[2,4-dimethyl-6-(methylamino)phenyl]-4-(4-methoxyphenyl)-2-oxo-3-butenoate (**2a**) (0.96 g): mp 117 °C. Anal. Calcd for $C_{21}H_{23}NO_3$: C, 71.38; H, 6.51; N, 3.96. Found: C, 70.85; H, 6.88; N, 3.76. ^1H NMR δ 7.25 (2 H, d, aromatic in position meta to the OCH_3 group), 7.07 (1 H, s, aromatic in position 3 of xylidine ring), 6.8 (4 H, m, aromatic and vinylic); 4.9 (1 H, d, exchangeable with D_2O, NH), 3.92 (3 H, s, OCH_3), 3.77 (6 H, s, OCH_3 and NCH_3), 2.47 and 2.53 (2 × 3 H, 2 s, 2 CH_3). Mother liquors from crystallization of **2a** were evaporated to dryness to give a residue (1.1 g) which was chromatographed on a silica gel column (eluent $CHCl_3$). The main product eluted, which solidified on treatment with Et_2O, was crystallized from *i*-PrOH to give the methyl 3-[2,4-dimethyl-6-(methylamino)phenyl]-4-(4-methoxyphenyl)-2-oxo-3-butenoate (**2a'**) (second isomer): mp 228 °C. Anal. Calcd for $C_{21}H_{23}NO_3$; C, 71.38; H, 6.51; N, 3.96. Found: C, 71.30; H, 6.50; N, 3.76. ^1H NMR δ 7.23 (2 H, d, aromatic in position meta to the OCH_3 group), 7.02 (1 H, s, aromatic in position 3 of xylidine ring), 6.75 (2 H, d, aromatic in position ortho to the OCH_3 group), 6.73 (1 H, s, aromatic in position 5 of xylidine ring); 6.42 (1 H, s, CH); 3.95 (3 H, s, OCH_3), 3.72 (3 H, s, OCH_3), 3.22 (3 H, s, NCH_3), 2.42 and 2.35 (2 × 3 H, 2 s, 2 CH_3).

Catalytic Hydrogenation of 2a,a': 2-(Methoxycarbonyl)-3-(4-methoxybenzyl)-1,4,6-trimethylindole. A solution of **2a** (0.51 g) in AcOH (10 mL) was hydrogenated at room temperature under 1 atm hydrogen pressure in the presence of 10% Pd on charcoal (0.1 g). Catalyst was filtered off and the solvent removed under reduced pressure; the residue was dissolved in Et_2O and the resulting solution washed with 5% $NaHCO_3$ solution and dried (Na_2SO_4). Removal of the solvent left a residue which was dissolved in diisopropyl ether; a few impurities were filtered off and the clear filtrate evaporated to dryness. The residue (0.41 g) was chromatographed on a silica gel column (eluent $CHCl_3$). The first product eluted was the 2-(methoxycarbonyl)-3-(4-methoxybenzyl)-1,4,6-trimethylindole (0.30 g): mp 127 °C (hexane–cyclohexane); ^1H NMR δ 7.02 and 6.67 (2 × 1 H, 2 s, aromatic of the indole ring), 7.00 (2 H, d of a AA'BB' system, aromatic in position meta to the OCH_3 group), 6.76 (2 H, d of a AA'BB' system, aromatic in position ortho to the OCH_3 group), 4.57 (2 H, s, CH_2), 3.97 (3 H, s, OCH_3), 3.82 (3 H, s, OCH_3), 3.73 (3 H, s, NCH_3), 2.51 and 2.45 (2 × 3 H, 2 s, 2 CH_3). Analogous reaction on **2a'** gave the same final product.

3-[(4-Methoxyphenyl)methylene]-1,4,6-trimethyl-2-indolinone. A solution of **2a** (0.21 g) and KOH pellets (0.25 g) in EtOH (5 mL) was refluxed for 3 h. Solvent was removed under reduced pressure and the residue dissolved in H_2O; 35% H_2O_2 solution (0.2 mL) was added and the solution refluxed for 20 min. The 3-[(4-methoxyphenyl)methylene]-1,4,6-trimethyl-2-indolinone separated upon neutralization: mp 184 °C dec (*i*-PrOH). Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.78. Found: C, 77.61; H, 6.20; N, 4.28. ^1H NMR δ 7.15 (2 H, d of a AA'BB' system, aromatic in position meta to the OCH_3 group), 6.95 and 6.70 (2 × 1 H, 2 s, aromatic of indole ring), 6.70 (2 H, d of a AA'BB' system, aromatic), 6.37 (1 H, s, =CH), 3.87 and 3.75 (2 × 3 H, 2 s, OCH_3 and NCH_3), 2.44 and 2.07 (2 × 3 H, 2 s, 2 CH_3).

Reaction of 1b with PPA. Hydrazone **1b** (2.5 g) was added portionwise to PPA (50 g) preheated to 80 °C; the temperature was then increased to 110 °C and maintained for 15 min. The reaction mixture was poured into H_2O and, after neutralization with concentrated NH_4OH solution, the separated oil was extracted with $CHCl_3$. The organic layer, washed with H_2O and dried (Na_2SO_4), after removal of the solvent, gave a brown oily residue which was chromatographed on a silica gel column (eluent $CHCl_3$). Fractions first eluted were a complex mixture of products and were discarded; the main product, eluted in the following fractions, was rechromatographed and crystallized from diisopropyl ether (0.58 g) to give the methyl 3-[2,4-dimethyl-6-(methylamino)phenyl]-3-oxo-4-phenyl-3-butenoate (**2b**) in a pure state: mp 127 °C; ^1H NMR δ 7.25 (5 H, m, C_6H_5), 7.0 (1 H, s, aromatic in position 3 of the xylidine ring), 6.74 (2 H, m, aromatic and vinylic), 4.80 (2 H, 2 s, exchangeable with D_2O, NH), 3.55 and 3.64 (2 × 3 H, 2 s, OCH_3 and NCH_3), 2.50 and 2.40 (2 × 3 H, 2 s, 2 CH_3).

Catalytic Hydrogenation of 2b: 3-Benzyl-2-(methoxycarbonyl)-1,4,6-trimethylindole. A solution of **2b** (0.180 g) in EtOH (25 mL) was hydrogenated in the presence of 10% Pd on charcoal (0.05 g) at room temperature under 1 atm hydrogen pressure. Catalyst was filtered off and the solvent removed under reduced pressure. The residue was treated with boiling cyclohexane; unreacted starting product was filtered off and the 3-benzyl-2-(methoxycarbonyl)-1,4,6-trimethylindole separated on cooling (0.10 g): mp 127 °C; ^1H NMR δ 7.20 (5 H, m, C_6H_5), 7.06 and 6.70 (2 × 1 H, 2 s, aromatic of indole ring), 4.67 (2 H, s, CH_2), 4.00 and 3.82 (2 × 3 H, 2 s, NCH_3 and OCH_3), 2.50 and 2.45 (2 × 3 H, 2 s, 2 CH_3). These data were coincident with those obtained from an authentic sample obtained by independent synthesis (see below).

***N*-Methyl-*N*-(3,5-dimethylphenyl)hydrazone of Methyl 2-Oxo-4-phenylbutyrate.** *N*-Methyl-*N*-(3,5-dimethylphenyl)-hydrazine (0.68 g) and methyl 2-oxo-4-phenylbutyrate[16] (1.0 g) were made to react without any solvent; H_2O was removed in vacuo and the orange-colored solid crystallized from hexane to give the title hydrazone: mp 75 °C (0.85 g).

3-Benzyl-2-(methoxycarbonyl)-1,4,6-trimethylindole. A solution of the hydrazone described above (0.9 g) in AcOH (10 mL) was refluxed for 1 h. Solvent was removed under reduced pressure and the residue treated with Et_2O and H_2O; the organic layer was washed with 5% $NaHCO_3$ solution, dried, and evapo-

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rated to dryness. The solid residue was directly crystallized from cyclohexane to give the 3-benzyl-2-(methoxycarbonyl)-1,4,6-trimethylindole (0.52 g), mp 127 °C.

Reaction of 1c with PPA. Hydrazone **1c** (5.5 g) was added portionwise to PPA (100 g) preheated to 85 °C; the resulting mixture was heated at 110 °C for 30 min, then poured into H_2O, and extracted with warm AcOEt. Some insoluble tarry material was filtered off. Removal of the solvent from the organic extract left a residue which was chromatographed on a silica gel column (eluent $CHCl_3$:MeOH 98:2). Fractions first eluted gave a solid (2.5 g) which was crystallized from *i*-PrOH, then treated with Et_2O to remove the last traces of impurities. The methyl 3-[2-(methylamino)phenyl]-4-(4-methoxyphenyl)-2-oxo-3-butenoate (**2c**): mp 193 °C; M_r (mass spectrometry) 324; ^1H NMR δ 8.05 (2 H, d, aromatic in position meta to the OCH_3 group), 7.4 (5 H, m, aromatic of the aniline ring), 6.75 (2 H, d, aromatic in position ortho to the OCH_3 group), 6.23 (1 H, s, vinylic), 4.04 and 3.75 (2 × 3 H, 2 s, 2 OCH_3), 3.47 (3 H, s, NCH_3).

4-(Methoxyphenyl)bis[1-methyl-2-(methoxycarbonyl)indol-3-yl]methane (3c) (from 2c). A solution of **2c** (0.10 g) in 60% AcOH was refluxed for 1 h. The diindolylmethane derivative **3c** separated on cooling as a white solid with mp 180 °C; M_r (mass spectrometry) 496; ^1H NMR δ 7.3 and 6.8 (7 H and 6 H, 2 m, aromatic and CH), 4.0 (6 H, s, 2 $COOCH_3$), 3.84 (3 H, s, OCH_3), 3.75 (6 H, s, 2 NCH_3).

Reaction of 1d with PPA. A mixture of **1d** (2.34 g) and PPA (100 g) was heated, with stirring, on an oil bath at 120 °C for a few minutes. The heating bath was removed and the mixture was left to cool to 80 °C, then poured into H_2O (200 mL), and neutralized with 26% NH_4OH solution. The precipitated oil was exhaustively extracted with $CHCl_3$; the organic solution was washed with H_2O and dried (Na_2SO_4), and the solvent removed under reduced pressure. The residue was treated with *i*-PrOH, to give the phenylbis(1,4,6-trimethylindol-3-yl)methane (**3a**): mp above 200 °C (AcOH). Anal. Calcd for $C_{29}H_{30}N_2$: C, 85.71; H, 7.39; N, 6.90. Found: C, 85.56; H, 7.37; N, 7.00. M_r (mass spectrometry) 406; ^1H NMR δ 7.22 (5 H, s, C_6H_5), 6.91 (2 H, s, aromatic in position 5 of indole ring), 6.22 (2 H, s, aromatic in position 7 of the indole ring), 6.39 (1 H, s, CHC_6H_5), 6.20 (2 H, s, aromatic in position 2 of the indole ring), 3.60 (6 H, s, 2 NCH_3), 2.46 (12 H, s, 4 CH_3).

Reaction of 1e with PPA. A stirred mixture of **1e** (5.34 g) and PPA (70 g) was heated on an oil bath at 120 °C for 20 min. The heating bath was then removed and the mixture left to cool to 80 °C, then it was poured into H_2O (300 mL) and made alkaline with a 26% NH_4OH solution. The brown solid separated was extracted with $CHCl_3$, the resulting solution washed with H_2O and dried (Na_2SO_4), and the solvent removed under reduced pressure. The residue (3.2 g) was chromatographed on a silica gel column (eluent $CHCl_3$). The fractions initially eluted gave the phenylbis(1-methylindol-3-yl)methane (**3b**)[5]: mp 192 °C (AcOH). Anal. Calcd for $C_{25}H_{22}N_2$: C, 85.71; H, 6.28; N, 8.00. Found: C, 85.03; H, 6.44; N, 8.21. ^1H NMR δ 7.5–6.85 (13 H, m, aromatic in position 4, 5, 6, and 7 of the indole ring and C_6H_5), 6.53 (2 H, s, aromatic in position 2 of the indole ring), 5.88 (1 H, s, CHC_6H_5), 3.70 (6 H, s, 2 NCH_3). Final fractions of the chromatography gave the 3-phenyl-3-(*N*-methylanilino)propanenitrile (**4a**) (0.2 g), as an oil which solidified on standing. Anal. Calcd for $C_{16}H_{16}N_2$: C, 81.36; H, 6.78; N, 11.86. Found: C, 81.40; H, 7.12; N, 11.30. ^1H NMR δ 7.45–6.75 (10 H, m, 2 C_6H_5), 5.35 (1 H, t, CH, J = 7), 3.02 (2 H, d, CH_2), 2.72 (3 H, s, CH_3).

1-Methylindol-3-yl Phenyl Ketone. A solution of 3-indolyl phenyl ketone[17] (8.5 g) in DMF (40 mL) was cautiously dropped into a slurry of NaH (55% suspension in mineral oil) (1.85 g) in DMF (50 mL); the temperature was controlled at 20 °C by an ice bath. The mixture was warmed at 30–35 °C for 30 min, cooled again to 10–15 °C during the addition of CH_3I (7.7 g), then warmed to 30–40 °C for 15 min, and finally diluted with H_2O. Separated product was extracted with Et_2O and the organic layer washed with H_2O and dried (Na_2SO_4). Removal of the solvent left the 1-methylindol-3-yl phenyl ketone as a solid residue (7.8 g), which was used without any further purification.

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(1-Methylindol-3-yl)phenylmethanol. A solution of 1-methylindol-3-yl phenyl ketone (2.0 g) in dry THF (10 mL) was dropped into a slurry of $LiAlH_4$ (0.1 g) in dry THF (10 mL). The temperature was kept under 40 °C by a cooling bath; the mixture was left to stand for 15 min, then cooled to 10 °C, and cautiously treated first with H_2O (0.5 mL) and then with a 35% NaOH solution; evaporation of the solvent gave the (1-methylindol-3-yl)phenylmethanol with mp 73 °C (diisopropyl ether); ^1H NMR δ 6.75 (1 H, s, aromatic in position 2 of the indole ring), 7.7–6.9 (10 H, m, aromatic), 3.7 (3 H, s, CH_3), 2.2 (1 H, s, OH).

Phenylbis(1-methylindol-3-yl)methane (3b) from (1-Methylindol-3-yl)phenylmethanol. A solution of the carbinol described above (0.50 g) in 50% AcOH (8 mL) was refluxed for a few minutes. The diindolylmethane derivative **3b** separated on cooling (0.33 g) as a white solid with mp 193 °C. The (4-nitrophenyl)hydrazone of benzaldehyde (2.2 g) (mp 192 °C) could be isolated by adding (4-nitrophenyl)hydrazine to the mother liquors.

Reaction of 1f with PPA. Hydrazone **1f** (1.6 g) was added portionwise to PPA (26 g) preheated to 100 °C. The reaction was exothermic; the mixture was stirred at 100 °C for 20 min, then cooled to 70 °C, and poured onto H_2O. After neutralization with 26% NH_4OH solution, the separated products were extracted with Et_2O. Organic layer, after removal of the solvent, left a residue (1.2 g) which was chromatographed on a silica gel column (eluent $CHCl_3$). The main product eluted was the oily 2-methyl-3-(*N*-methylanilino)-3-phenylpropanenitrile (**4b**) (0.35 g): ^1H NMR δ 7.5–6.4 (10 H, m, aromatic), 4.97 (1 H, d, CHC_6H_5, J = 9), 3.50 (1 H, m, CHCN), 2.76 (3 H, s, NCH_3), 1.29 (3 H, d, $CHCH_3$, J = 8).

Reaction of Hydrazone 1g (and 8) with PPA. Hydrazone **1g** (12.2 g) was added to PPA (38 g) preheated to 80 °C. After 20 min the mixture was poured into H_2O and the resulting solution neutralized with 26% NH_4OH solution. The separated oil was extracted with Et_2O; the organic layer was dried (Na_2SO_4), the solvent removed under reduced pressure, and the residue (2.2 g) chromatographed on a silica gel column (eluent $CHCl_3$). Initial and final fractions were discarded; intermediate fractions gave the 3-methyl-3-(*N*-methylanilino)propanenitrile (**4c**) (1.1 g), which was distilled in vacuo: bp 140 °C (0.5 mmHg). Anal. Calcd for $C_{11}H_{14}N_2$: C, 75.86; H, 8.04; N, 16.09. Found: C, 75.55; H, 8.20; N, 16.20. ^1H NMR δ 7.25 and 6.85 (2 and 3 H, 2 m, C_6H_5), 4.27 (1 H, sx, CH, J = 7), 2.82 (3 H, s, NCH_3), 2.53 (2 H, d, CH_2CN), 1.40 (3 H, d, CH_3CH). An identical procedure was employed for the reaction with PPA of hydrazone **8** and of an equimolar mixture of **8** and **1g**. In the former case the 3-[*N*-(trideuteriomethyl)-anilino]butanenitrile-3-*d* (**9**) was isolated in a pure state. Anal. Calcd for $C_{11}H_{10}D_4N_2$: C, 74.16; H/D, 7.87; N, 15.73. Found: C, 74.54; H/D, 8.21; N, 16.02. M_r (mass spectrometry) 178; ^1H NMR δ 7.3 (3 H, m, aromatic), 2.55 (2 H, s, CH_2), 1.4 (3 H, s, CH_3). In the case of the reaction of the mixture of **8** and **1g**, the mass spectrometry data of the aminonitrile recovered after column chromatography showed two molecular peaks at 174 and 178, intermediate peaks at 177 and 175 being completely absent.

Registry No. **1a**, 91632-74-5; **1b**, 91632-75-6; **1c**, 91632-76-7; **1d**, 91632-77-8; **1e**, 23718-97-0; **1f**, 76344-26-8; **1g**, 66400-72-4; **2a**, 91632-78-9; **2a'**, 91632-79-0; **2b**, 91632-80-3; **2c**, 91632-81-4; **3a**, 91632-82-5; **3b**, 29670-54-0; **3c**, 56297-44-0; **4a**, 91632-83-6; **4b**, 91670-48-3; **4c**, 91632-84-7; **8**, 91632-88-1; **9**, 91632-93-8; 4-toluenesulfonanilide, 68-34-8; trideuteriomethyl iodide, 865-50-9; *N*-(trideuteriomethyl)-4-toluenesulfonanilide, 91632-85-8; *N*-(trideuteriomethyl)aniline, 36622-84-1; *N*-nitroso-*N*-(trideuteriomethyl)aniline, 91632-86-9; *N*-(trideuteriomethyl)-*N*-phenylhydrazine, 91632-87-0; crotonic-3-*d* aldehyde *N*-(trideuteriomethyl)-*N*-phenylhydrazone, 91632-88-1; 2-(methoxycarbonyl)-3-(4-methoxybenzyl)-1,4,6-trimethylindole, 91632-89-2; 3-[(4-methoxyphenyl)methylene]-1,4,6-trimethyl-2-indolinone, 91632-90-5; 3-benzyl-2-(methoxycarbonyl)-1,4,6-trimethylindole, 91632-91-6; *N*-methyl-*N*-(3,5-dimethylphenyl)hydrazine, 80398-80-7; methyl 2-oxo-4-phenylbutyrate, 83402-87-3; methyl 2-oxo-4-phenylbutyrate *N*-methyl-*N*-(3,5-dimethylphenyl)hydrazone, 91632-92-7; 3-indolyl phenyl ketone, 15224-25-6; 1-methylindol-3-yl phenyl ketone, 19012-01-2; (1-methylindol-3-yl)phenylmethanol, 1908-67-4.