Synthesis of 3-Phenylisoquinolones by Reaction of Simple Pyrroline-2,3-diones with Benzyne. New Mechanistic Considerations

Agustín Cobas, Enrique Guitián,* and Luis Castedo

Departamento de Química Orgánica, Universidad de Santiago, and Sección de Alcaloides del CSIC, 15706 Santiago de Compostela, Spain

Received November 23, 1992

3-Phenylisoquinolones were obtained by cycloaddition of benzyne to 5-phenylpyrroline-2,3-diones. New mechanistic hypotheses for these transformations are discussed.

In recent years we have reported new syntheses of protoberberine[1a,b] and benzophenanthridine[2] alkaloids, and of some indole compounds,[1b] based on cycloaddition of pyrroline-2,3-diones **1** and arynes **2**. In these reactions, pyrroline-2,3-diones behaved as equivalents of azadienes **4**,[3] and by reaction with arynes led to isoquinolones **3**. We hypothesized that the mechanism might involve polar or concerted 4 + 2 cycloaddition followed by extrusion of CO. A systematic study of this reaction as a potential tool for the synthesis of simple isoquinolines, which are common building blocks in compounds of pharmaceutical and/or biological importance, has now shed new light on its mechanism. The study was carried out using pyrrolinediones **5a–c**[4] and **6a–j**.

Pyrrolinediones **6a–h** were prepared starting from the corresponding ketone **7** as shown in Scheme I. Treatment with amine **8** and $TiCl_4$ afforded imine **9**, which without purification was reacted with oxalyl chloride to yield the desired pyrrolinediones **6**. The results were acceptable in all cases except those of **6d** and **6f**, for which better results were obtained using methyl chlorooxalate instead of oxalyl chloride. Treatment of imines **9d** and **9f** with methyl chlorooxalate afforded amides **10d** (68%) and **10f** (85%), which were cyclized to **6d** (62%) and **6f** (72%), respectively, by heating with silica gel in dichloroethane. The yield of the cyclization was improved using $AlCl_3$ instead of silica gel. Reaction of **10f** with $AlCl_3$ afforded **6f** in 81% yield.

Pyrrolinediones **6i** and **6j** were obtained by halogenation of **6c** (Scheme III). Chlorination to **6i** was achieved in 54% yield with NaOCl. Bromination to **6j** was carried out (99% yield) with Br_2.

Benzyne was generated in the presence of the pyrrolinediones **5** and **6** by decomposition of benzendiazonium 2-carboxylate, which was obtained by aprotic diazotization of anthranilic acid (2-aminobenzoic acid) in THF or DME.[5]

When isatin (**5a**) was treated with benzenediazonium 2-carboxylate prepared from anthranilic acid in THF, the cycloadduct was not observed; instead, **13** was isolated in 38% yield. We explain the formation of **13** as occurring via the oxonium salt **14** (Scheme IV). Isatins **5b** and **5c** were recovered unchanged from reactions carried out under the same conditions.

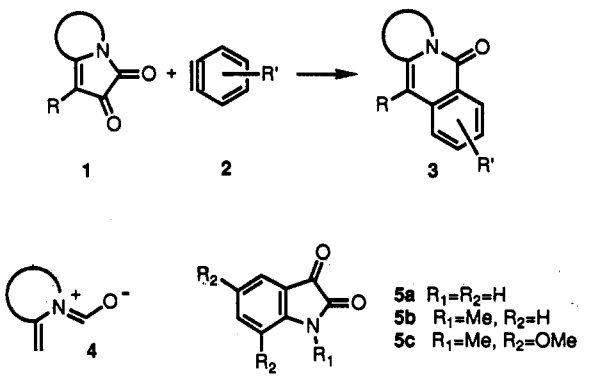


Figure 1.

The reactions of the simple pyrrolinediones **6a–i** with benzyne were then investigated. From the first series of experiments we obtained the adducts indicated in Scheme I.

Pyrrolinediones **6a**, **c**, and **d**, which are unsubstituted at position 4, reacted with two benzyne molecules to afford the 4-phenylisoquinolones **15a**, **c**, and **d**, respectively. Under the same conditions, pyrrolinedione **6b** was recovered unchanged. Pyrrolinediones **6e–i**, which have an alkyl group or a chlorine atom at position 4, reacted with one benzyne molecule to afford the adducts **15e–i**, the substituent at position 4 preventing reaction with a second benzyne molecule.

The reaction of bromopyrrolinedione **6j** led to the bromoadduct **15j** (54%), the phenylated adduct **15c** (20%), and a minor unexpected compound (17%) whose spectroscopic data are in keeping with structure **16c** (Scheme V).

The ^1H NMR spectrum for compound **16c** (Figure 2) shows a signal for an aromatic proton at 5.21–5.17 (m, 1 H), and COSY experiments showed that this proton belongs to ring A of **16c** (Figure 2). We attributed the anomalous shift of this proton to the anisotropic effect of ring C (Figure 2). To test this hypothesis we calculated a minimum energy conformation of **16c**, using force field calculations.[6] The calculated angle abcd is 74.84°, which places a ring A hydrogen in the diamagnetic field of the phenyl ring.

Bromoisoquinolone **15j** was transformed into isoquinolone **15k** by hydrogenolysis.

The above results showed the effectiveness of the cycloaddition for the synthesis of 3-phenylisoquinolones

(1) (a) Saá, C.; Guitián, E.; Castedo, L.; Suau, R.; Saá, J. M. *J. Org. Chem.* **1986**, *51*, 2781. (b) Cobas, A.; Guitián, E.; Castedo, L. *J. Org. Chem.* **1992**, *57*, 6765.

(2) Martín, G.; Guitián, E.; Castedo, L.; Saá, J. M. *J. Org. Chem.* **1992**, *57*, 5907.

(3) Boger, D. L.; Weinreb, S. *Hetero Diels–Alder Methodology in Organic Synthesis*; Academic Press: New York, 1987.

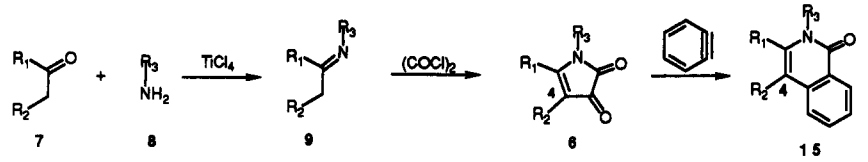
(4) **5a,b** are commercially available. **5c** was prepared according to: Taylor, A. *J. Chem. Res., Miniprint* **1980**, 4154.

(5) Logullo, F. M.; Seitz, A. H.; Friedman, L. *Org. Synth.* **1968**, *48*, 12.

(6) PC Model from Serena Software was used on a Macintosh SE30 computer.

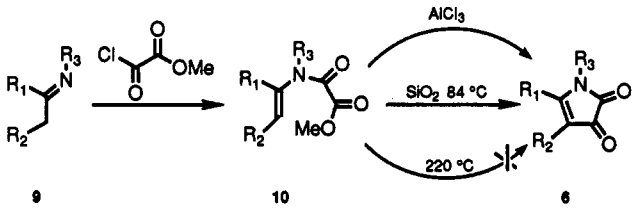
0022-3263/93/1958-3113$04.00/0

Scheme I

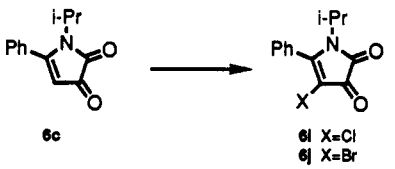


Ketone 7	Amine 8	Imine 9	%	Pyrrolinedione 6	%	Adduct 15		%
a R_1=Ph, R_2=H	a R_3=Ph	a	40	a	74	a	R_1=R_2=R_3=Ph	57
b R_1=t-Bu, R_2=H	b R_3=i-Pr	b	57	b	89	b	R_1=t-Bu, R_2=H or Ph, R_3=i-Pr	0
a R_1=Ph, R_2=H	b R_3=i-Pr	c	64	c	56	c	R_1=R_2=Ph, R_3=i-Pr	82
a R_1=Ph, R_2=H	c R_3=Me	d	86	d	26	d	R_1=R_2=Ph, R_3=Me	91
c R_1=Ph, R_2=Et	b R_3=i-Pr	e	87	e	42	e	R_1=Ph, R_2=Et, R_3=i-Pr	46
d R_1=Ph, R_2=Me	c R_3=Me	f	98	f	17	f	R_1=Ph, R_2=R_3=Me	94
d R_1=Ph, R_2=Me	b R_3=i-Pr	g	85	g	60	g	R_1=Ph, R_2=Me, R_3=i-Pr	86
d R_1=Ph, R_2=Me	a R_3=Ph	h	62	h	58	h	R_1=R_3=Ph, R_2=Me	70
				I R_1=Ph, R_2=Cl, R_3=i-Pr		I	R_1=Ph, R_2=Cl, R_3=i-Pr	52

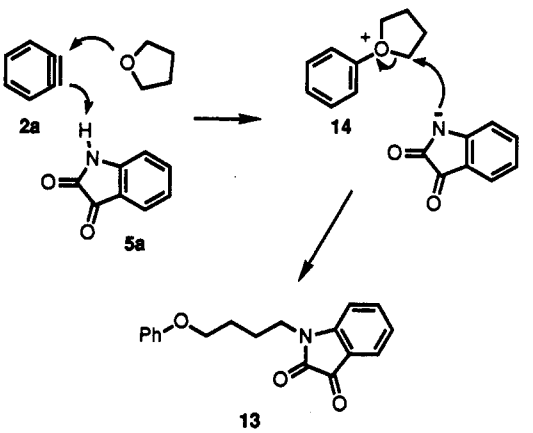
Scheme II



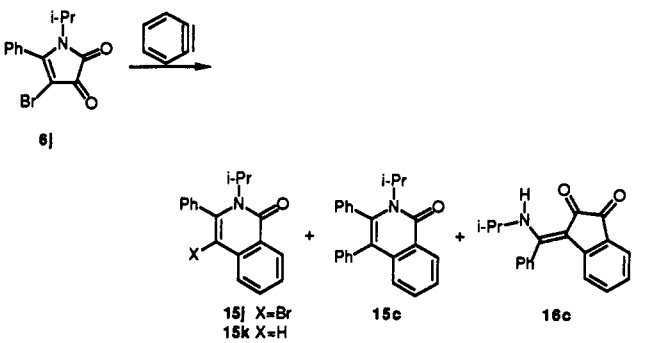
Scheme III



Scheme IV



Scheme V



and suggested that a more complex mechanism should be considered than had hitherto been hypothesized.

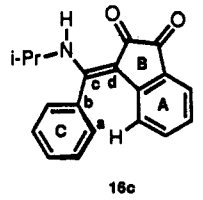
From a mechanistic point of view, the first question to answer was whether **16c** was a byproduct or an intermediate in the formation of adduct **15c**. To investigate this question, compound **16c** was treated with benzyne under the same reaction conditions as above. The isolation of adduct **15c** in 94% yield strongly suggests that **16c** is an intermediate in the formation of adduct **15c** from pyrrolinedione **6j**.

Adduct **15c** was also obtained from the reaction of pyrrolinedione **6c** and benzyne, suggesting that **16c** might also be an intermediate in this reaction. To test the hypothesis that pyrrolinedione **6c** reacts with benzyne to afford intermediate **16c**, which then reacts with a second benzyne molecule to afford the adduct **15c**, we carried out the reaction of pyrrolinedione **6c** with benzyne using only 1 equiv. of benzenediazonium 2-carboxylate. The reaction mixture afforded starting pyrrolinedione **6c** (60%), adduct **15c** (25%), and intermediate **16c** (7%). The phenylated adduct **15c** was not formed when adduct **15k** was treated with benzyne.

We have previously hypothesized[1a] that the mechanism of these reactions involves the formation of cycloadduct **17** (Scheme VI), followed by the extrusion of CO to afford **15**. In view of the experimental results reported here we now suggest that (a) if R_2 = Cl, Me, or Et, pyrrolinediones **6e–i** react with benzyne to afford **17**, which after extrusion of CO yields isoquinolones **15e–i**; (b) if R_2 = H, pyrrolinediones **6a–d** react with benzyne to afford **16** (most probably via **17** and **18**), after which the most likely reaction sequence is ene reaction of **16** with benzyne to yield **19**, cyclization to **20**, and extrusion of CO to the final products, **15a–d**; and (c) if R_2 = Br, **6j** reacts with benzyne to afford the intermediate **17**, which can both extrude CO to yield **15j** and undergo opening to **18**, which by debromination[7] and protonation affords **16** and thence **15c** as above.

We believe that similar mechanisms may be postulated for previously reported reactions of pyrrolinediones with benzyne.[1,2]

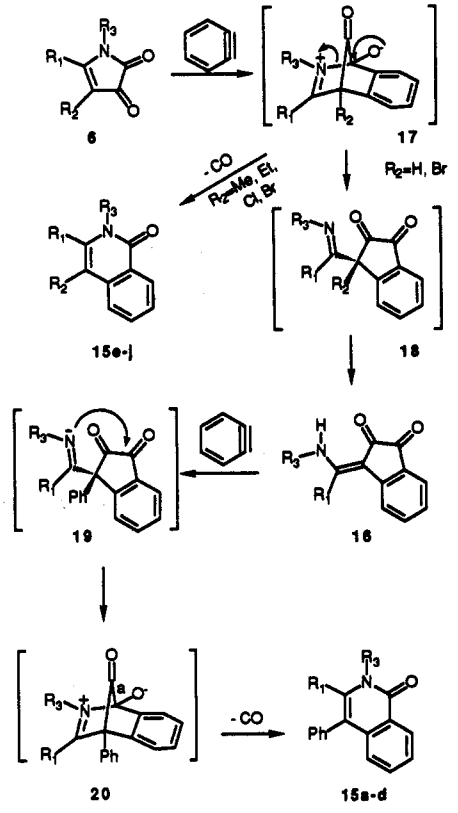
(7) A bromine atom placed in a position flanked by carbon–heteroatom multiple bonds undergoes a substitution reaction very easily.



16c

Figure 2.

Scheme VI



Experimental Section

General Procedures. Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded at 250 and 62.83 MHz in $CDCl_3$. Low-resolution mass spectra (LRMS) and high-resolution mass spectra (HRMS) were recorded at an ionization voltage of 70 eV. Combustion analyses were performed at the Microanalysis Services of the University of Barcelona. Solvents were dried by standard procedures.[8]

General Procedure for the Synthesis of Imines 9b–h. Ketone 7 was added to a solution of amine 8 in dry $CHCl_3$, and the reaction flask was purged with argon and cooled. $TiCl_4$ was introduced by syringe, the cooling bath was removed, and the solution was stirred at rt. After reaction the mixture was filtered through Celite, the solvent was evaporated in vacuo, and the residue was partially dissolved in ether (50 mL). Filtration through Celite and evaporation of the solvent in vacuo afforded 9 as an oil that was used in the next reaction without purification.

***N*-(α-Methyl-*tert*-butylidene)isopropylamine (9b).** $TiCl_4$ (1.32 mL, 12.02 mmol) was added to a mixture of *tert*-butyl methyl ketone (**7b**, 2.185 g, 21.85 mmol) and isopropylamine (**8b**, 8.43 mL, 98.80 mmol) in dry $CHCl_3$ (40 mL) at −40 °C. Stirring for 3 days at rt and workup afforded **9b** (1.747 g, 57%) as an oil: ^1H NMR δ 3.57 (h, J = 6.2 Hz, 1 H), 1.75 (s, 3 H), 1.06–1.04 (m, 15 H); ^{13}C NMR δ 170.8, 49.8, 39.9, 27.8, 23.4, 11.9.

***N*-(α-Methylbenzylidene)isopropylamine (9c).** To acetophenone (**7a**, 5.00 g, 41.61 mmol) and isopropylamine (**8b**, 12.45 mL, 146.00 mmol) in dry $CHCl_3$ (125 mL) at −20 °C was added $TiCl_4$ (4.56 mL, 41.61 mmol) in dry $CHCl_3$ (30 mL). Stirring for 4 days at rt and workup afforded **9c** as an oil (4.325 g, 64%): ^1H NMR δ 7.77–7.74 (m, 2 H), 7.38–7.35 (m, 3 H), 3.86 (h, J = 6.3 Hz, 1 H), 2.25 (s, 3 H), 1.23 (d, J = 6.2 Hz, 6 H).

***N*-(α-Methylbenzylidene)methylamine (9d).** $TiCl_4$ (0.85 mL, 7.74 mmol) was added to acetophenone (**8a**, 1.85 g, 14.34 mmol) and methylamine (**8c**, 2.00 g, 64.52 mmol) in $CHCl_3$ (40 mL) at −40 °C. Stirring at rt for 3 days and workup afforded **9d** as an oil (1.887 g, 86%): ^1H NMR δ 7.76–7.73 (m, 2 H), 7.39–7.36 (m, 3 H), 3.34 (s, 3 H), 2.23 (s, 3 H).

***N*-(α-Propylbenzylidene)isopropylamine (9e).** To butyrophenone (**7c**, 5.055 g, 34.11 mmol) and isopropylamine (**8b**, 11.7 mL, 136.43 mmol) in $CHCl_3$ (125 mL) at −20 °C was added $TiCl_4$ (2.24 mL, 20.46 mmol) in $CHCl_3$ (30 mL). Stirring for 4 days at rt and workup afforded **9e** as an oil (5.635 g, 87%). The ^1H NMR spectrum shows a 1:1.8 mixture of Z and E isomers. (*E*)-**9e**: ^1H NMR δ 7.70–7.66 (m, 2 H), 7.38–7.32 (m, 3 H), 3.90 (h, J = 6.2 Hz, 1 H), 2.66 (t, J = 7.8 Hz, 2 H), 1.60–1.40 (m, 2 H), 1.21 (d, J = 6.2 Hz, 6 H), 0.97–0.89 (m, 3 H). (*Z*)-**9e**: ^1H NMR δ 7.38–7.32 (m, 3 H), 7.09–7.05 (m, 2 H), 3.40 (h, J = 6.2 Hz, 1 H), 2.49 (t, J = 7.8 Hz, 2 H), 1.60–1.40 (m, 2 H), 1.07 (d, J = 6.2 Hz, 6 H), 0.97–0.89 (m, 3 H).

***N*-(α-Ethylbenzylidene)methylamine (9f).** $TiCl_4$ (0.85 mL, 7.74 mmol) was added to propiophenone (**7d**, 2.1 g, 15.67 mmol) and methylamine (**8c**, 2.00 g, 64.52 mmol) in $CHCl_3$ (50 mL) at −40 °C. Stirring at rt for 4 days and workup afforded **9f** (oil, 2.25 g, 98%) as a 2.3:1 mixture of E and Z isomers. (*E*)-**9f**: ^1H NMR δ 7.76–7.72 (m, 2 H), 7.44–7.43 (m, 2 H), 3.39 (s, 3 H), 2.73 (q, J = 7.7 Hz, 2 H), 1.14–1.06 (m, 3 H). (*Z*)-**9f**: ^1H NMR δ 7.44–7.43 (m, 2 H), 7.11–7.07 (m, 2 H), 3.05 (t, J = 1.3 Hz, 3 H), 2.53 (m, 2 H), 1.14–1.06 (m, 3 H).

***N*-(α-Ethylbenzylidene)isopropylamine (9g).** To propiophenone (**7d**, 5.037 g, 37.54 mmol) and isopropylamine (**8b**, 15 mL, 175.00 mmol) in $CHCl_3$ (125 mL) at −20 °C was added $TiCl_4$ (2.6 mL, 23.70 mmol) in $CHCl_3$ (30 mL). Stirring at rt for 4 days and workup afforded **9g** as an oil (5.586 g, 85%), Z:E ratio 1:1.7. (*Z*)-**9g**: ^1H NMR δ 7.39–7.33 (m, 3 H), 7.09–7.05 (m, 2 H), 3.39 (h, J = 6.2 Hz, 1 H), 2.27 (s, 3 H), 1.08 (d, J = 6.2 Hz, 6H). (*E*)-**9g**: ^1H NMR δ 7.74–7.71 (m, 2 H), 7.39–7.33 (m, 3 H), 3.91 (h, J = 6.2 Hz, 1 H), 2.15 (s, 3 H), 1.23 (d, J = 6.2 Hz, 6 H).

***N*-(α-Ethylbenzylidene)aniline (9h).** To propiophenone (**7d**, 5.00 g, 37.22 mmol) and aniline (**8a**, 11.90 mL, 130 mmol) in toluene (125 mL) cooled to −20 °C was added $TiCl_4$ (2.45 mL, 22.35 mmol) in dry toluene (30 mL). Stirring at rt for 6 days and workup afforded **9h** (4.805 g, 62%), which was crystallized from petroleum ether as white crystals: mp 150 °C (lit.[9] mp 151–153 °C); ^1H NMR δ 7.96–7.92 (m, ArH), 7.49–7.06 (m, ArH), 6.83–6.79 (m, ArH), 2.67 (q, J = 7.6 Hz, 2 H), 1.10 (t, J = 7.6 Hz, 3 H).

1,5-Diphenyl-2,3-pyrrolinedione (6a). Oxalyl chloride (2.92 mL, 33.79 mmol) in dry CCl_4 (20 mL) was added dropwise to a solution of **9a**[10] (6.59 g, 33.79 mmol) and pyridine (5.34 mL, 67.59 mmol) in dry CCl_4 (60 mL) cooled at 0 °C. The temperature was raised to 40 °C, and the mixture was stirred for 5 min. The syrup formed was treated with CCl_4 (30 mL) and stirred at 40 °C for 1 h. The red precipitate was collected by filtration, dissolved in CH_2Cl_2, and treated with 10% HCl. The organic phase was decanted, washed with 10% HCl and then with water, dried over Na_2SO_4, and concentrated to afford **6a** (6.22 g, 74%), which crystallized from hexane as red crystals: mp 197–198 °C (lit.[11] mp 179 °C); ^1H NMR δ 7.50–7.28 (m, 8 H), 7.08–7.04 (m, 2 H), 5.81 (s, 1 H); ^{13}C NMR δ 182.25, 171.5, 158.7, 133.8, 132.3, 129.0, 128.70, 128.5, 128.4, 127.8, 126.8, 101.39; UV (EtOH) λ_{max} 234, 302, 414 nm; IR (KBr) 1765, 1710 cm^{-1}; LRMS m/z 221 (M^+, 100), 193 (84), 180 (59), 77 (73).

General Procedure for the Synthesis of Pyrrolinediones. Oxalyl chloride in dry CCl_4 was added dropwise to a solution of imine 9 and pyridine in dry CCl_4 cooled at 0 °C under Ar atmosphere. The mixture was stirred at 0 °C for 15 min and 8

(8) Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon Press: New York, 1988.

(9) Montgomery, F. C.; Saunders, W. H., Jr. *J. Org. Chem.* **1976**, *41*, 2368.

(10) Saunders, W. H., Jr.; Caress, E. A. *J. Am. Chem. Soc.* **1964**, *86*, 861.

(11) Eistert, B.; Müller, G. W.; Arackal, T. J. *Liebigs Ann. Chem.* **1976**, 1021.

h at rt and was then washed with 10% HCl and with H_2O, dried over Na_2SO_4, and concentrated.

5-*tert*-Butyl-1-isopropyl-2,3-pyrrolinedione (6b). From imine **9b** (1.015 g, 7.20 mmol), pyridine (1.14 mL, 14.40 mmol), and oxalyl chloride (0.62 mL, 7.20 mmol) was obtained **6b** (1.253 g, 89%) as red crystals: ^{1}H NMR δ 5.20 (s, 1 H), 4.24 (h, J = 6.8 Hz, 1 H), 1.50 (d, J = 6.8 Hz, 6 H), 1.38 (s, 9 H); ^{13}C NMR δ 184.4, 184.3, 160.30, 97.9, 48.4, 34.04, 28.1, 19.4; IR (KBr) 1740, 1715 cm^{-1}; LRMS m/z 195 (M$^+$, 31), 152 (30), 110 (36), 81 (20), 68 (100).

1-Isopropyl-5-phenyl-2,3-pyrrolinedione (6c). From imine **9c** (2.00 g, 12.42 mmol), pyridine (1.83 mL, 23.12 mmol), and oxalyl chloride (1.02 mL, 11.56 mmol) was obtained a residue which was chromatographed (silica gel, CH_2Cl_2/ethyl ether (4:1)) and crystallized from hexane to yield **6c** (1.506 g, 56%) as red crystals: mp 90–91 °C; ^{1}H NMR δ 7.64–7.46 (m, 5 H), 5.40 (s, 1 H), 3.98 (h, J = 6.9 Hz, 1 H), 1.45 (d, J = 6.9 Hz, 6 H); ^{13}C NMR δ 183.1, 174.8, 160.0, 131.9, 129.8, 129.3, 127.4, 101.2, 47.5, 20.00; UV (EtOH) λ_{max} 243, 281, 418 nm; IR (KBr) 1745, 1715 cm^{-1}; LRMS m/z 215 (M$^+$, 38), 187 (27), 172 (100).

1-Methyl-5-phenyl-2,3-pyrrolinedione (6d). From imine **9d** (2.30 g, 17.29 mmol), pyridine (2.73 mL, 34.59 mmol), and oxalyl chloride (1.49 mL, 17.29 mmol) was obtained a residue, which was chromatographed (silica gel, CH_2Cl_2) and crystallized from hexane to yield **6d** (0.831 g, 26%) as red crystals: mp 122–123 °C; ^{1}H NMR δ 7.59–7.56 (m, 5 H), 5.51 (s, 1 H), 3.17 (s, 3 H); ^{13}C NMR δ 183.2, 173.3, 160.00, 132.4, 129.2, 129.00, 127.9, 99.9, 28.5; UV (EtOH) λ_{max} 239, 298, 422 nm; IR (KBr) 1765, 1700 cm^{-1}; LRMS m/z 187 (M$^+$, 53), 159 (45), 118 (100).

4-Ethyl-1-isopropyl-5-phenyl-2,3-pyrrolinedione (6e). From imine **9e** (5.64 g, 30.13 mmol), pyridine (4.76 mL, 60.26 mmol), and oxalyl chloride (2.68 mL, 30.13 mmol) was obtained a residue which was chromatographed (silica gel, CH_2Cl_2) and crystallized from hexane to yield **6e** (3.258 g, 42%) as red crystals: mp 65 °C, ^{1}H NMR δ 7.58–7.54 (m, 3 H), 7.36–7.32 (m, 2 H), 3.63 (h, J = 6.9 Hz, 1 H), 2.03 (q, J = 7.5 Hz, 2 H), 1.34 (d, J = 6.9 Hz, 6 H), 0.94 (t, J = 7.5 Hz, 3 H); ^{13}C NMR δ 185.5, 168.0, 159.2, 130.8, 129.2, 128.9, 127.6, 114.5, 47.1, 20.00, 15.6, 13.7; UV (EtOH) λ_{max} 270, 428 nm; IR (KBr) 1740, 1705 cm^{-1}; LRMS m/z 243 (M$^+$, 94), 200 (78), 172 (100), 104 (75).

1,4-Dimethyl-5-phenyl-2,3-pyrrolinedione (6f). From imine **9f** (4.24 g, 28.83 mmol), pyridine (4.55 mL, 57.66 mmol), and oxalyl chloride (2.50 mL, 28.90 mmol) was obtained a residue which was chromatographed (silica gel, CH_2Cl_2) and crystallized from hexane to yield **6f** (1.00 g, 17%) as red crystals: mp 158–159 °C; ^{1}H NMR δ 7.59–7.56 (m, 3 H), 7.45–7.43 (m, 2 H), 2.98 (s, 3 H), 1.73 (s, 3 H); ^{13}C NMR δ 185.6, 166.5, 159.6, 131.2, 129.1, 128.4, 128.1, 108.1, 28.1, 6.7; UV (EtOH) λ_{max} 266, 432 nm; IR (KBr) 1750, 1715 cm^{-1}; LRMS m/z 201 (M$^+$, 62), 173 (14), 144 (71), 118 (100).

4-Methyl-1-isopropyl-5-phenyl-2,3-pyrrolinedione (6g). **6g** (6.603 g, 60%) was obtained from imine **9g** (5.58 g, 32.27 mmol), pyridine (5.09 mL, 64.54 mmol), and oxalyl chloride (2.79 mL, 32.27 mmol): mp 135–137 °C (hexane); ^{1}H NMR δ 7.58–7.55 (m, 3 H), 7.39–7.34 (m, 2 H), 3.69 (h, J = 6.9 Hz, 1 H), 1.61 (s, 3 H), 1.35 (d, J = 6.9 Hz, 6 H); ^{13}C NMR δ 185.5, 168.2, 159.6, 130.9, 129.1, 128.8, 127.8, 108.7, 47.2, 20.00, 6.8; UV (EtOH) λ_{max} 214, 272, 432 nm; IR (KBr) 1740, 1705 cm^{-1}; LRMS m/z 229 (M$^+$, 100), 201 (21), 186 (84), 158 (82), 130 (41), 104 (80).

4-Methyl-1,5-diphenyl-2,3-pyrrolinedione (6h). From imine **9h** (3.67 g, 17.58 mmol), pyridine (2.92 mL, 36.92 mmol), and oxalyl chloride (1.60 mL, 18.46 mmol) was obtained **6h** (2.69 g, 58%) as red crystals: mp 185–186 °C (hexane); ^{1}H NMR δ 7.45–7.21 (m, 8 H), 7.00–6.96 (m, 2 H), 1.92 (s, 3 H); ^{13}C NMR δ 184.8, 165.3, 158.30, 133.9, 131.3, 128.9, 128.5, 128.2, 127.3, 126.6, 109.7, 7.1; UV (EtOH) λ_{max} 240, 300, 432 nm; IR (KBr) 1750, 1710 cm^{-1}; LRMS m/z 263 (M$^+$, 30), 235 (47), 206 (100), 180 (52), 77 (65).

***N*-(α-Methylenebenzyl)-*N*-methoxalylmethylamine (10d).** Methyl chlorooxalate (0.24 mL, 2.85 mmol) was added to a solution of imine **9d** (3.50 g, 26.31 mmol) and dry pyridine (0.21 mL, 2.60 mmol) in dry THF (20 mL) cooled at −20 °C. The mixture was stirred ar rt for 3 h and filtered. The solvent was evaporated in vacuo from the mixture, and the residue was chromatographed (silica gel, CH_2Cl_2) to afford **10d** (394 mg, 68%): ^{1}H NMR δ 7.47–7.44 (m, 2 H), 7.42–7.38 (m, 3 H), 5.42 (s, 1 H), 5.17 (s, 1 H), 3.69 (s, 3 H), 3.01 (s, 3 H); ^{13}C NMR δ 163.0, 161.9, 147.4, 134.2, 129.4, 128.6, 126.8, 111.4, 52.0, 33.0; UV (EtOH) λ_{max} 240 nm; IR (KBr) 1745, 1670 cm^{-1}; LRMS m/z 219 (M$^+$, 21), 160 (29), 118 (48), 103 (100), 77 (25).

Pyrrolinedione 6d from Enamide 10d. A mixture of amide **10d** (154 mg, 0.731 mmol), silica gel (2 g), and dichloroethane (40 mL) was refluxed under Ar for 48 h. Evaporation of the solvent and chromatography (silica gel, CH_2Cl_2) afforded **6d** as a red solid (82 mg, 62%).

***N*-(α-Ethylidenebenzyl)-*N*-methoxalylmethylamine (10f).** Methyl chlorooxalate (1.4 mL, 15.31 mmol) was added to a solution of imine **9f** (2.25 g, 17.28 mmol) and dry pyridine (1.20 mL, 15.31 mmol) in dry THF (50 mL) at −40 °C. The mixture was stirred at rt for 8 h. Workup as above afforded **10f** (2.862 g, 85%) as an oil. Solid **10f** was obtained by crystallization from hexane: mp 55–57 °C; ^{1}H NMR δ 7.21–7.07 (m, 5 H), 5.51 (q, J = 7.2 Hz, 1 H), 3.48 (s, 3 H), 2.58 (s, 3 H), 1.50 (d, J = 7.2 Hz, 3 H); ^{13}C NMR δ 163.2, 161.3, 139.3, 132.6, 128.7, 128.2, 127.9, 123.0, 51.4, 31.6, 13.3; UV (EtOH) λ_{max} 216, 238 nm; IR (KBr) 1740, 1645 cm^{-1}; LRMS m/z 233 (M$^+$, 19), 218 (42), 174 (84), 118 (70), 117 (100), 115 (34), 91 (25).

Pyrrolinedione 6f from 10f. (a) Silica Gel. A mixture of **10f** (152 mg, 0.652 mmol), silica gel (2 g), and dichloroethane (50 mL) was refluxed for 7 days. Workup as above (chromatography on silica gel, 3:1 hexane–ether) afforded **6f** (95 mg, 72%).

(b) $AlCl_3$. $AlCl_3$ (170 mg, 1.259 mmol) was added to a solution of enamide **10f** (100 mg, 0.429 mmol) in dry dichloroethane (2 mL), and the mixture was stirred for 10 min. CH_2Cl_2 (10 mL) and H_2O (10 mL) were added, and the organic phase was decanted, dried over Na_2SO_4, and concentrated in vacuo. The red residue was chromatographed (silica gel, 3:1 hexane–ether) to afford **6f** (70 mg, 81%).

4-Chloro-1-isopropyl-5-phenyl-2,3-pyrrolinedione (6i). A solution of **6c** (118 mg, 0.549 mmol) in CH_2Cl_2 (15 mL) was treated with 10% HCl and stirred vigorously. An aqueous solution of NaOCl (0.2 M, pH 12) was added dropwise until **6c** disappeared (TLC). The organic phase was decanted and concentrated in vacuo, and the residue was chromatographed (silica gel, CH_2Cl_2) to afford **6i** (74 mg, 54%): mp 139–140 °C (hexane); ^{1}H NMR δ 7.61–7.57 (m, 3 H), 7.50–7.46 (m, 2 H), 3.82 (h, J = 6.8 Hz, 1 H), 1.40 (d, J = 6.8 Hz, 6 H); ^{13}C NMR δ 177.5, 167.9, 157.8, 132.1, 129.2, 128.2, 126.7, 104.2, 48.5, 20.0; UV (EtOH) λ_{max} 286, 444 nm; IR (KBr) 1750, 1730 cm^{-1}; LRMS m/z 251 (M$^+$, 32), 249 (M$^+$, 95), 206 (79), 172 (55), 104 (100).

4-Bromo-1-isopropyl-5-phenyl-2,3-pyrrolinedione (6j). Br_2 (1.00 g, 6.25 mmol) in CH_2Cl_2 (20 mL) was added to a solution of **6c** (1.344 g, 6.25 mmol) in CH_2Cl_2 (50 mL0, and the solution was stirred at rt for 5 min. the mixture was washed with 20% sodium metabisulfite and H_2O, and the organic phase was dried over Na_2SO_4 and concentrated in vacuo to afford **6j** (1.830 g, 99%): mp 143–145 °C (hexane); ^{1}H NMR δ 7.62–7.58 (m, 3 H), 7.50–7.46 (m, 2 H), 3.83 (h, J = 6.8 Hz, 1 H), 1.41 (d, J = 6.8 Hz, 6 H); ^{13}C NMR δ 178.1, 170.1, 157.8, 132.0, 129.2, 128.1, 127.8, 91.6, 48.8, 20.1; UV (EtOH) λ_{max} 288, 448 nm; IR (KBr) 1745, 1730 cm^{-1}; LRMS m/z 295 (M$^+$, 48), 293 (M$^+$, 50), 252 (43), 250 (44), 186 (24), 129 (45), 104 (100).

Reaction of Pyrrolinediones 6 with Benzyne. General Procedure. Excess isoamyl nitrite was added over 1–2 min to a stirred ice-cooled solution of the appropriate anthranilic acid in dry DME containing a catalytic amount of trichloroacetic acid. The ice bath was removed after 15 min, and the mixture turned red brown as it reached room temperature. The mixture was stirred for an additional 90 min. The following is the recommended procedure for appropriate handling: *after dilution with DME, most of the solvent was aspirated by means of a plastic syringe with Teflon tubing (instead of the standard metallic needle) and discarded.* **Caution! when dry, benzenediazonium-2-carboxylate detonates violently on being scraped or heated.** *The remaining material was washed several times with DME as above until the washing liquors were neutral, and the resulting brownish precipitate was suspended in solvent (1,2-dichloroethane). This suspension was aspirated portionwise into a plastic syringe through a Teflon tube (instead of the standard metallic needle) and added dropwise to a refluxing solution of pyrrolinediones in 1,2-dichloroethane.* When the addition was complete (TLC monitoring), the reaction mixture was refluxed until the starting material had disappeared, and

the solvent was evaporated in vacuo. The residue thus obtained was purified by chromatography on column (silica gel, CH_2Cl_2).

2,3,4-Triphenyl-1-isoquinolone (15a). From **6a** (100 mg, 0.401 mmol) was obtained 2,3,4-triphenyl-1-isoquinolone (**15a**) (86 mg, 57%): mp 134–136 °C (hexane); ^{1}H NMR δ 8.59–8.56 (m, 1 H), 7.59–7.56 (m, 2 H), 7.28–7.09 (m, 12 H), 6.89 (m, 4 H); ^{13}C NMR δ 162.6, 141.0, 139.5, 137.7, 136.4, 134.8, 132.5, 131.6, 131.0, 129.5, 128.5, 128.2, 128.0, 127.5, 127.2, 127.1, 126.9, 125.6, 118.8; UV (EtOH) λ_{max} 222, 295, 334 nm; IR (KBr) 1655 cm^{-1}; LRMS *m/z* 373 (M$^+$, 100), 372 (77).

2-Isopropyl-3,4-diphenyl-1-isoquinolone (15c). From **6c** (120 mg, 0.558 mmol) was obtained 3,4-diphenyl-2-isopropyl-1-isoquinolone (**15c**) (153 mg, 82%): mp 250–251 °C (hexane); ^{1}H NMR δ 8.55–8.51 (m, 1 H), 7.51–7.46 (m, 2 H), 7.23–7.01 (m, 11 H), 4.11 (h, J = 7.8 Hz, 1 H), 1.58 (d, J = 7.8 Hz, 6 H); ^{13}C NMR δ 162.4, 141.8, 137.0, 135.8, 131.9, 131.6, 129.8, 128.1, 127.9, 127.5, 126.7, 126.5, 125.2, 119.1, 114.6, 53.5, 19.4; UV (EtOH) λ_{max} 297, 334 nm; IR (KBr) 1650 cm^{-1}; LRMS *m/z* 339 (M$^+$, 58), 338 (32), 297 (11), 296 (55).

2-Methyl-3,4-diphenyl-1-isoquinolone (15d). From **6d** (100 mg, 0.535 mmol) was obtained 2-methyl-3,4-diphenyl-1-isoquinolone (**15d**) (151 mg, 91%): mp 245 °C (EtOH–H_2O); ^{1}H NMR δ 8.59–8.55 (m, 1 H), 7.53–7.48 (m, 2 H), 7.25–7.05 (m, 11 H), 3.37 (s, 3 H); ^{13}C NMR δ 162.8, 141.3, 137.2, 136.5, 135.1, 132.0, 131.6, 130.0, 128.2, 127.9, 127.9, 126.8, 126.6, 125.4, 125.0, 118.9, 34.3; UV (EtOH) λ_{max} 296, 444 nm; IR (KBr) 1650 cm^{-1}; LRMS *m/z* 311 (M$^+$, 88), 310 (100).

4-Ethyl-2-isopropyl-3-phenyl-1-isoquinolone (15e). From **6e** (100 mg, 0.411 mmol) was obtained 4-ethyl-2-isopropyl-3-phenyl-1-isoquinolone (**15e**) (55 mg, 46%): mp 156–157 °C (hexane); ^{1}H NMR δ 8.56–8.53 (m, 1 H), 7.71–7.65 (m, 2 H), 7.55–7.47 (m, 4 H), 7.34–7.29 (m, 2 H), 3.97 (h, J = 6.8 Hz, 1 H), 2.38 (q, J = 7.4 Hz, 2 H), 1.53 (d, J = 6.7 Hz, 6 H), 1.04 (t, J = 7.4 Hz, 3 H); ^{13}C NMR δ 162.4, 159.39, 140.6, 136.3, 135.7, 131.9, 128.9, 128.6, 128.1, 126.2, 123.0, 116.5, 53.2, 21.7, 19.2, 14.6; UV (EtOH) λ_{max} 298, 336 nm; IR (KBr) 1645 cm^{-1}; LRMS *m/z* 291 (M$^+$, 56), 249 (32), 234 (100).

2,4-Dimethyl-3-phenyl-1-isoquinolone (15f). From **6f** (100 mg, 0.535 mmol) was obtained 2,4-dimethyl-3-phenyl-1-isoquinolone (**15f**) (116 mg, 94%): mp 105 °C (EtOH–H_2O); ^{1}H NMR δ 8.56–8.53 (m, 1 H), 7.71–7.69 (m, 2 H), 7.54–7.49 (m, 4 H), 7.29–7.25 (m, 2 H), 3.27 (s, 3 H), 2.02 (s, 3 H); ^{13}C NMR δ 162.7, 140.3, 137.2, 135.9, 132.1, 129.4, 129.0, 128.7, 128.2, 126.5, 125.3, 123.2, 110.5, 34.2, 14.7; UV (EtOH) λ_{max} 296, 334 nm; IR (KBr) 1645 cm^{-1}; LRMS *m/z* 249 (M$^+$, 89), 248 (100), 233 (34).

4-Methyl-2-isopropyl-3-phenyl-1-isoquinolone (15g). From **6g** (100 mg, 437 mmol) was obtained 4-methyl-2-isopropyl-3-phenyl-1-isoquinolone (**15g**) (104 mg, 86%): mp 125–126 °C (EtOH–H_2O); ^{1}H NMR δ 8.53–8.50 (m, 1 H), 7.70–7.62 (m, 2 H), 7.52–7.46 (m, 4 H), 7.29–7.26 (m, 2 H), 3.99 (h, J = 6.7 Hz, 1 H), 1.93 (s, 3 H), 1.51 (d, J = 6.7 Hz, 6 H); ^{13}C NMR δ 162.5, 140.7, 136.8, 136.7, 132.0, 129.0, 128.9, 128.5, 127.8, 126.8, 126.3, 122.9, 110.3, 53.3, 19.3, 15.0; UV (EtOH) λ_{max} 296, 336 nm; IR (KBr) 1640 cm^{-1}; LRMS *m/z* 277 (M$^+$, 47), 276 (25), 235 (100), 234 (76).

4-Methyl-2,3-diphenyl-1-isoquinolone (15h). From **6h** (100 mg, 0.380 mmol) was obtained 4-methyl-2,3-diphenyl-1-isoquinolone (**15h**) (82 mg, 70%): mp 178–181 °C (hexane); ^{1}H NMR δ 8.57–8.53 (m, 1 H), 7.78–7.76 (m, 2 H), 7.60–7.50 (m, 1 H), 7.19–7.01 (m, 10 H), 2.10 (s, 3 H); ^{13}C NMR δ 162.6, 140.3, 139.8, 137.7, 135.5, 132.7, 130.6, 129.6, 128.6, 127.8, 127.5, 126.8, 125.9, 123.4, 110.4, 14.8; UV (EtOH) λ_{max} 294, 334 nm; IR (KBr) 1650 cm^{-1}; LRMS *m/z* 311 (M$^+$, 100), 310 (91).

4-Chloro-2-isopropyl-3-phenyl-1-isoquinolone (15i). From **6i** (100 mg, 0.401 mmol) was obtained 4-chloro-2-isopropyl-3-phenyl-1-isoquinolone (**15i**) (62 mg, 52%): mp 134–136 °C (hexane); ^{1}H NMR δ 8.49–8.46 (m, 1 H), 7.94–7.91 (m, 1 H), 7.77–7.70 (m, 1 H), 7.59–7.51 (m, 4 H), 7.36–7.32 (m, 2 H), 4.04 (h, J = 6.8 Hz, 1 H), 1.53 (d, J = 6.8 Hz, 6 H); ^{13}C NMR δ 161.9, 141.0, 135.2, 134.3, 132.7, 129.2, 129.1, 128.8, 127.9, 127.5, 126.8, 123.6, 111.3, 54.4, 19.3; UV (EtOH) λ_{max} 302, 334 nm; IR (KBr) 1655 cm^{-1}; LRMS *m/z* 299 (M$^+$, 10), 297 (M$^+$, 29), 257 (33), 255 (100).

4-Bromo-2-isopropyl-3-phenyl-1-isoquinolone (15j). From **6j** (100 mg, 0.340 mmol) were obtained 4-bromo-2-isopropyl-3-phenyl-1-isoquinolone (**15j**) (42 mg, 36%), isoquinolone (**15c**) (43 mg, 37%), and 3-[α-(isopropylamino)benzylidene]-1,2-indandione (**16c**) (10 mg, 10%). Data for **15j**: mp 141–142 °C (EtOH–H_2O); ^{1}H NMR δ 8.47–8.44 (m, 1 H), 7.94–7.90 (m, 1 H), 7.74–7.67 (m, 1 H), 7.57–7.48 (m, 4 H), 7.35–7.30 (m, 2 H), 4.05 (h, J = 6.8 Hz, 1 H), 1.51 (d, J = 6.8 Hz, 6 H); ^{13}C NMR δ 162.0, 142.7, 137.3, 135.3, 132.9, 129.2, 129.0, 128.7, 127.8, 127.5, 127.0, 126.3, 102.3, 54.9, 19.3; UV (EtOH) λ_{max} 302, 334 nm; IR (KBr) 1650 cm^{-1}; LRMS *m/z* 343 (M$^+$, 29), 341 (M$^+$, 30), 301 (86), 299 (100).

3-[α-(Isopropylamino)benzylidene]-1,2-indandione (16c). From **6c** (100 mg, 0.465 mmol) and anthranilic acid (64 mg, 0.465 mmol) were obtained **16c** (10 mg, 7%), isoquinolone **15c** (40 mg, 25%), and starting pyrrolinedione **6c** (60 mg, 60%).

Data for **16c**: mp 224 °C (EtOH); ^{1}H NMR δ 10.57 (bs, 1 H), 7.62–7.59 (m, 3 H), 7.46–7.43 (m, 1 H), 7.34–7.33 (m, 2 H), 6.97–6.91 (m, 1 H), 6.87–6.81 (m, 1 H), 5.40–5.37 (m, 1 H), 3.50–3.46 (m, 1 H), 1.22 (d, J = 6.4 Hz, 6 H); ^{13}C NMR δ 192.0, 185.4, 160.5, 148.7, 136.3, 132.3, 130.2, 129.9, 127.2, 127.0, 124.6, 123.9, 119.1, 104.7, 46.2, 23.9; UV (EtOH) λ_{max} 224, 272, 278, 322, 520 nm; IR (KBr) 1730, 1640 cm^{-1}; LRMS *m/z* 291 (M$^+$, 62), 248 (27), 178 (31), 104 (100).

Reaction of 16c with Benzyne. From **16c** (10 mg, 0.037 mmol) was obtained **15c** (11 mg, 94%).

Hydrogenolysis of Isoquinolone 15j. A mixture of isoquinolone **15j** (68 mg), NaOH (70 mg), 10% Pd–C (26 mg), and MeOH (25 mL) was stirred for 12 h in a flask connected to a balloon filled with hydrogen. The mixture was filtered through Celite, and the filtrate was concentrated in vacuo. The residue was treated with H_2O (15 mL) and CH_2Cl_2 (15 mL), and the organic phase was decanted, dried over Na_2SO_4, and concentrated in vacuo. Purification by column chromatography (silica gel, CH_2Cl_2) afforded **15k** (36 mg, 69%): ^{1}H NMR δ 8.43–8.40 (m, 1 H), 7.64–7.57 (m, 1 H), 7.48–7.37 (m, 7 H), 6.33 (s, 1 H), 4.21 (h, J = 6.8 Hz, 1 H), 1.57 (d, J = 6.8 Hz, 6 H); ^{13}C NMR δ 163.3, 144.4, 137.3, 136.1, 132.1, 128.7, 128.6, 127.6, 126.7, 126.5, 125.5, 108.0, 53.0, 19.6; UV (EtOH) λ_{max} 294, 332 nm; IR (KBr) 1645, 1635 cm^{-1}; LRMS *m/z* 263 (M$^+$, 32), 262 (23), 221 (100).

Acknowledgment. Financial support from the DGICYT (Projects PB87-0663 and PB90-0764) is gratefully acknowledged. We also acknowledge the Spanish Ministry of Education for the award of a research grant to A.C. We thank Prof. J. Saá for helpful discussions.

Supplementary Material Available: Combustion analysis data for new compounds (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.