MeOH. Mp: 171-172 °C (lit.[3f] mp 188-190 °C).

2,3-Dimethoxy-5-methyl-11,12-dihydrobenz[*c*]phenanthridin-6(5*H*)-one (6c). From dimethoxypyrrolinedione **7c** (450 mg, 1.65 mmol), anthranilic acid (**9a**) (1.45 g, 10.64 mmol), and isoamyl nitrite (2.04 g, 17.45 mmol) was obtained the benzophenanthridinone **6c** (250 mg, 49% yield) and crystallized from MeOH. Mp: 184-185 °C (lit.[19] mp 184-186 °C).

5-Methyl-12,13-dihydro-1,3-benzodioxolo[5,6-*c*]-1,3-dioxolo[4,5-*j*]phenanthridine-6(5*H*)-one (6d). Dihydrooxyavicine. From pyrrolinedione **7d** (60 mg, 0.23 mmol), 4,5-methylenedioxyanthranilic acid (**9c**) (426 mg, 2.35 mmol), and isoamyl nitrite (450 mg, 3.86 mmol) was obtained the benzophenanthridinone **6d** (13 mg, 16% yield). Mp: 242-243 °C (benzene-hexane) (lit.[14] mp 237-241 °C).

2-Isopropoxy-5-methyl-3,8,9-trimethoxy-11,12-dihydrobenzo[*c*]phenanthridin-6(5*H*)-one (6f). Dihydrooxyfagaronine. From pyrrolinedione **7e** (200 mg, 0.66 mmol), 4,5-dimethoxyanthranilic acid (**9b**) (1.14 g, 5.81 mmol), and isoamyl nitrite (1.11 g, 9.52 mmol) was obtained the benzophenanthridinone **6f** (81 mg, 30% yield) and crystallized from MeOH. Mp: 218 °C. UV (EtOH) λ_{max}: 234, 266, 344, 358 nm. IR (KBr): 1630, 1500 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.42 (d, J = 6 Hz, 6 H), 2.79 (s, 4 H), 3.80 (s, 3 H), 3.87 (s, 3 H), 4.02 (s, 3 H), 4.03 (s, 3 H), 4.57-4.66 (m, 1 H), 6.85 (s, 1 H), 7.02 (s, 1 H), 7.04 (s, 1 H), 7.88 (s, 1 H). LRMS m/e: 409 (M^+, 88), 367 (100), 352 (51). Anal. Calcd for $C_{24}H_{27}NO_5$: C, 65.92; H, 5.53; N, 5.12. Found: C, 65.85; H, 5.43; N, 5.14.

5-Benzyl-11,12-dihydrobenzo[*c*]phenanthridin-6(5*H*)-one (6h). From pyrrolinedione **7f** (230 mg, 0.79 mmol) in DME (40 mL), anthranilic acid (**9a**) (634 mg, 4.63 mmol), and isoamyl nitrite (888 mg, 7.59 mmol) was obtained the benzophenanthridinone **6h** (136 mg, 50% yield) and crystallized from MeOH. Mp: 128-129 °C (lit.[17] mp 128-131 °C).

Modification of the General Procedure for the Reaction of 7d with Arynes 3b and 3d. To a stirred ice-cooled solution of the appropriate anthranilic acid in EtOH were added concd HCl and isoamyl nitrite, and the mixture was stirred for 45 min at 0 °C, diluted with ether, and stirred for a further 45 min. The diazonium salt, now as hydrochloride, was washed as above and aspirated into a plastic syringe. **Caution! The same precautions as above should be observed!** The suspended diazonium salt was added to a refluxing solution of **7d** containing propylene oxide.

2,3-Dimethoxy-12-methyl-5,6-dihydro[1,3]benzodioxolo[5,6-*c*]phenanthridin-13(12*H*)-one (6e). Dihydrooxynitidine. From pyrrolinedione **7d** (60 mg, 0.233 mmol), propylene oxide (5.3 mL), dichloroethane (40 mL), 4,5-dimethoxyanthranilic acid (**9b**) (766 mg, 3.89 mmol), isoamyl nitrite (842 mg, 7.20 mmol) and concentrated HCl (0.4 mL) was obtained the benzophenanthridinone **6e** (25 mg, 29% yield). Mp: 236-237 °C (EtOH) (lit.[14] mp 242-245 °C (benzene-hexane)).

1,2-Dimethoxy-12-methyl-5,6-dihydro[1,3]benzodioxolo[5,6-*c*]phenanthridin-13(12*H*)-one (6g). Dihydrooxychelerythrine. From pyrrolinedione **7d** (123 mg, 0.48 mmol), propylene oxide (6.3 mL), dichloroethane (30 mL), 3,4-dimethoxyanthranilic acid (**9d**) (914 mg, 4.64 mmol), isoamyl nitrite (1.15 mL, 8.59 mmol), and concd HCl (0.5 mL) was obtained the benzophenanthridinone **6g** (51 mg, 29% yield). Mp: 202-204 °C (lit.[15a] mp 208-209 °C).

Acknowledgment. Financial support from the DGICYT (Project No PB87-0663-C02-01) is gratefully acknowledged.

Registry No. **1c**, 6872-57-7; **1e**, 34316-15-9; **6a**, 51066-35-4; **6b**, 98799-71-4; **6c**, 65332-25-4; **6d**, 56221-63-7; **6e**, 56221-66-0; **6f**, 143237-38-1; **6g**, 65341-23-3; **6h**, 51066-28-5; **7a**, 111865-20-4; **7b**, 111865-21-5; **7c**, 143237-35-8; **7d**, 143237-36-9; **7e**, 143237-37-0; **7f**, 143237-34-7; **8a** (X = O), 529-34-0; **8a** (X = NMe), 111865-18-0; **8a** (X = NBn), 32851-51-7; **8b** (X = O), 1078-19-9; **8b** (X = NMe), 111865-19-1; **8c** (X = O), 13575-75-2; **8c** (X = NMe), 143237-32-5; **8d** (X = O), 41303-45-1; **8d** (X = NMe), 55950-08-8; **8e** (X = O), 98799-45-2; **8e** (X = NMe), 143237-33-6; **9a**, 118-92-3; **9b**, 5653-40-7; **9c**, 20332-16-5; **9d**, 5701-87-1; oxalyl chloride, 79-37-8.

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A New Approach to the Synthesis of Antitumor Benzophenanthridine Alkaloids. Formal Synthesis of Nitidine

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The synthesis of benzophenanthridine alkaloids by an efficient new convergent strategy based on the Diels-Alder reaction between an α-pyrone and an aryne is described. With minor modifications, norbenzophenanthridines and phenanthridines and their 12-amino derivatives were obtained in good overall yields.

The benzophenanthridine alkaloids, a group of isoquinoline alkaloids with more than 60 members,[1] is characterized by the basic skeleton **1**. The most important members of this group from a pharmacological point of view are quaternary salts. In particular, the alkaloids fagaronine (**2a**) and nitidine (**2b**) have marked antitumor properties.[2] Both have shown activity against leukemia in the P-388 test, but the trials of nitidine were interrupted because of toxicity problems.

There are many classical methods[3] for the synthesis of benzophenanthridines using one-bond reactions (formation of one bond/step) but very few involving a two-bond key step; the first to be reported was the formation of ring B by cycloaddition between an *o*-quinodimethane and an alkyne.[4] Our experience with the synthesis of aporphi-

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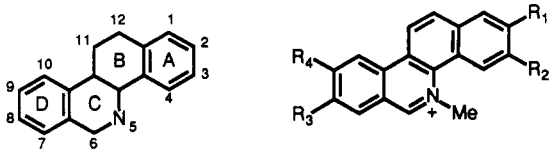
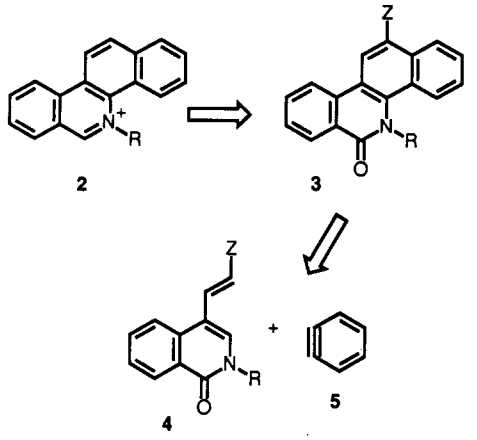


1

2a R_1=OH, R_2=R_3=R_4=OMe
2b R_1+R_2=OCH_2O, R_3=R_4=OMe

Figure 1.

Scheme I



noids,[5] protoberberines,[6] etc., by the intermolecular benzyne cycloaddition (IBC) approach led us to design new strategies for the synthesis of benzophenanthridine alkaloids based on the same ideas, the key steps of these two-bond procedures consisting in intermolecular cycloaddition between an appropriate diene and an aryne. Recently, we reported a route in which ring C was formed by cycloaddition of an azadiene equivalent and an aryne.[7,8] We describe here the results of another new strategy derived from the retrosynthetic analysis shown in Scheme I.

Preliminary studies of our synthetic plan led us to the pioneering work of Dyke's group in this field. In the 1970's they attempted to prepare benzophenanthridines by the reaction of diene 4 (R = H, Z = CO_2Me) and benzyne, but they obtained very disappointing results (1.2% yield).[9] We suspected that this result could be greatly improved by using a more suitable diene. After trials with 1,2-diazines, we focused our attention on the cycloaddition reactions of α-pyrones. It is well-known that α-pyrones react with benzyne to give an adduct which loses CO_2 by a retro Diels–Alder reaction to afford a naphthalene.[10] To obtain the tetracyclic skeleton of benzophenanthridines we needed the tricyclic pyrone **9** as the key intermediate.

Pyrone **9a** was obtained as described in the literature[11] from phthalimide **6a**.

To generate arynes, we chose the method based on the aprotic diazotization of the corresponding anthranilic acid **14**, isolation of the intermediate diazonium 2-carboxylate **15**, and thermal decomposition of **15** by addition to a refluxing solution of the diene.[12] We have used this method extensively for the synthesis of aporphinoids, in which cycloaddition occurs in good yield (approximately 60%) with benzyne and in lower yield (approximately 20%) with alkoxy-substituted arynes.

When benzenediazonium 2-carboxylate (**15a**)[12] was added to a refluxing solution of pyrone **9a** in DME, we obtained an adduct with two additional aromatic rings (MS m/z 379, 14 aromatic protons in ^{1}H NMR). In a preliminary paper[13] we indicated that these data were in keeping with structure **10a**, but the isomeric structure **16** could not be ruled out. We believed that both structures were reasonable from a mechanistic point of view: both could be formed by nucleophilic attack on the benzyne (through oxygen or nitrogen), although alternative ene reactions (with the tautomers) could also take place.[14] To finally establish the structure of the adduct we synthesized compound **10a** as indicated in Scheme II. *N*-Phenylhomophthalimide (**6b**) was transformed into the pyrone **9b** and reacted with benzyne (**5a**) as above to afford, in 88% yield, the adduct **10a**, which was chromatographically and spectroscopically different from that obtained previously. We accordingly assigned structure **16** to the adduct produced in the reaction of **9a** and **5a**.

Since antitumor benzophenanthridines such as fagaronine (**2a**) and nitidine (**2b**) are *N*-methyl derivatives we decided to prepare *N*-methylpyrones, hoping that the methyl group could avoid the formation of phenyl ethers such as **16**. These compounds were prepared from *N*-methylhomophthalimide (**6c**), as above. From the reaction of **9c** with a great excess (approximately 10 equiv) of benzyne (**5a**) in refluxing DME we isolated a compound which showed a molecular ion at m/z 467 in the mass spectrum, 11 protons in the aromatic region of the ^{1}H NMR spectrum, and two quaternary aliphatic carbons in ^{13}C NMR spectrum; these data agree with structure **17a**.

Using approximately 5 equiv of benzyne (**5a**) we obtained a mixture of starting material, adduct **17a** (22% yield, 34% yield from unrecovered starting material), and a new major product (39% yield, 59% from unrecovered starting material) whose spectroscopic data were in keeping with structure **10b**. A systematic study of reaction conditions showed that dioxane is a more suitable solvent for this reaction. When the reaction was carried out as above (10 equiv of benzyne, 80 °C, etc.) but with dioxane as solvent, we obtained the adduct **10b** in 80% yield.

Since natural benzophenanthridines have no carboxyl group at position 12 we attempted the elimination of this group from compound **10b**. Hydrolysis with ethanolic KOH and decarboxylation with Cu/quinoline afforded **3a** in 85% yield.

To obtain the alkaloid nitidine (**2b**) we generated as above 4,5-methylenedioxybenzyne (**5b**) from 4,5-methylenedioxyanthranilic acid (**14b**) in the presence of **9c** to afford the adduct **10c** in 72% yield. Hydrolysis to **10f** (100% yield) and decarboxylation (72% yield) yielded oxonitidine (**3b**). Since this compound has already been transformed into nitidine (**2b**), the formal synthesis of this

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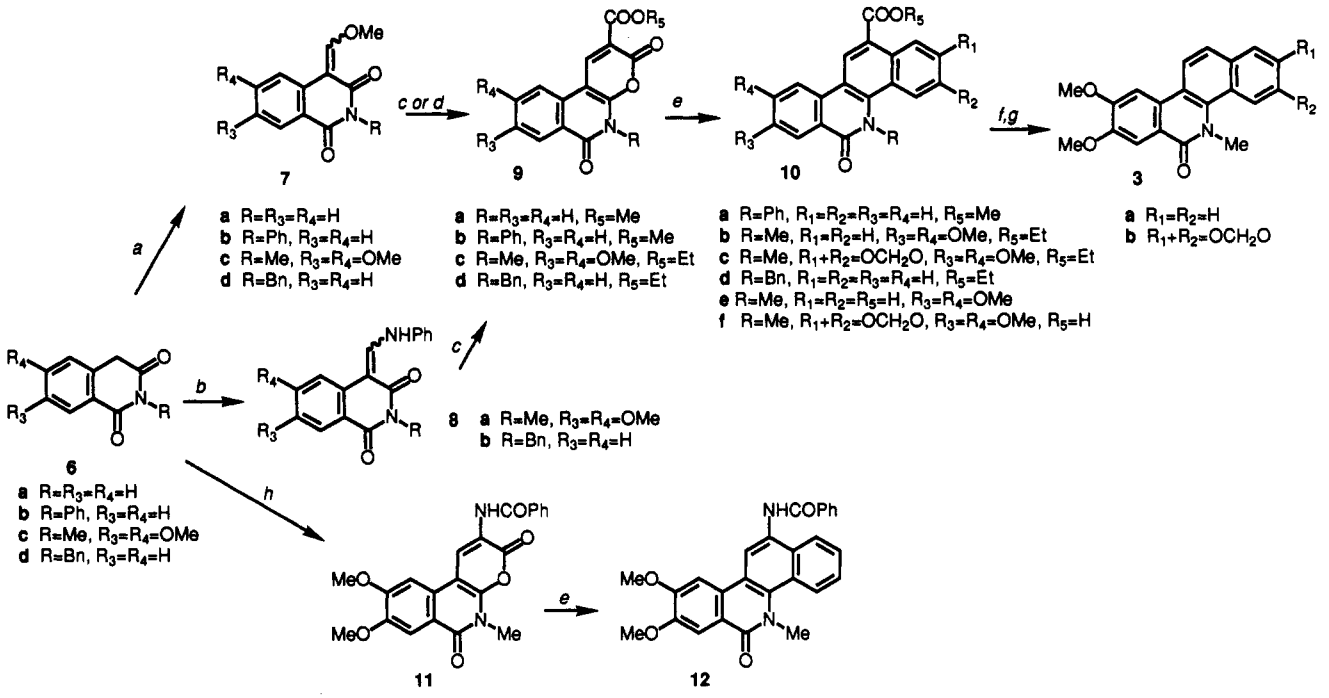
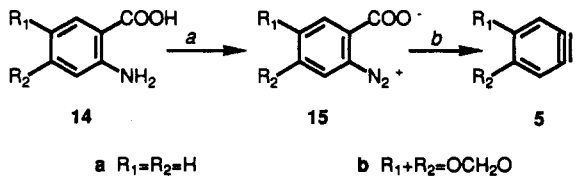
Scheme II[a]



[a] Key: (a) $CH(OMe)_3$, Ac_2O; (b) $CH(OMe)_3$, $PhNH_2$, HOAc, DMF; (c) $NCCH_2CO_2Et$, *t*-BuOK, DMF; (d) $NCCH_2CO_2Et$, NaOMe, DMF; (e) **5**, Δ; (f) KOH, EtOH; (g) Cu, Δ; (h) methyl 2-(benzoylamino)-3-(dimethylamino)propenoate,[21] HOAC.

Scheme III[a]



[a] Key: (a) *i*-AmONO; (b) Δ.

alkaloid was complete.[15] Remarkably, the overall yield for the synthesis of **3b** from the homophthalimide **6c** was 46%.

There are many norbenzophenanthridine alkaloids that can presumably be obtained by the above procedure provided that the group on the nitrogen atom can be replaced by hydrogen after the benzyne cycloaddition. To extend our method to norbenzophenanthridines we chose as protecting group the benzyl group, which can be eliminated by hydrogenolysis. The *N*-benzyl derivative **9d** was prepared following the sequence **6d** → **7d** (88%) → **9d** (78%) as above, and reaction of **9d** with benzyne afforded **10d** in 74% yield. As expected, **10d** was recovered unchanged when hydrogenolysis was carried out under mild conditions. To avoid harsh conditions we decided to reduce the amide to the amine, which ought to undergo hydrogenolysis under milder conditions:[16] amide **10d** was treated with $POCl_3$ with a view to generate the imidoyl chloride (which can be reduced with sodium borohydride), but instead we obtained, in 97% yield, the deprotected chloroimine **18a**. However, catalytic reduction of **18a** afforded the amine **18b** in 80% yield.

We were also interested in the possibility of improving antitumor properties by endowing the benzophenanthridine nucleus with chains able to link to DNA.

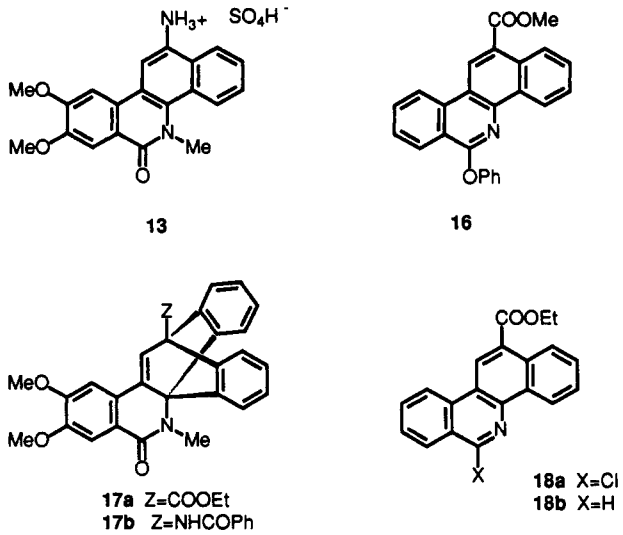


Figure 2.

Since previous studies of structure–activity relationships among benzophenanthridine alkaloids have shown that minor modifications of the substitution pattern of rings A or D lead to less active compounds,[2] and since substitution on ring C (especially the nitrogen atom) can be carried out by classical procedures we decided to attach appropriate chains to ring B, for which our synthetic procedure seemed to be particularly well suited. We in fact investigated the synthesis of the amine **13** by two alternative routes. Schmidt reaction of the acid **10e** afforded the amine **13** in 80% yield. Pyrone **11**, which was prepared in 79% yield from the homophthalimide **6c**, reacted with benzyne (**5a**) (approximately 3 equiv) in DME to afford **12** and **17b** in 79% and 5% yields, respectively. When **11** was treated with benzyne (**5a**) (approximately 10 equiv) in dioxane we isolated **12** in 63% yield.

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In conclusion, the method described above is a short, simple, efficient, new approach to the synthesis of benzophenanthridine alkaloids and their analogues, especially to those with antitumor activity.

Experimental Section

General Procedures. Melting points are uncorrected. Nuclear magnetic resonance spectra were recorded at 250 MHz with $CDCl_3$ as solvent (unless otherwise noted) and $SiMe_4$ as internal standard. Low-resolution mass spectra (LRMS) and high-resolution mass spectra (HRMS) were recorded operating at 70 eV. Combustion analyses were performed at the Servei de Microanalisi de la Universitat de Barcelona and at the Servicio de Microanálisis de la Universidad de Málaga. Solvents were dried by standard procedures.[17,18]

1,2,3,4-Tetrahydro-6,7-dimethoxy-4-(methoxymethylene)-2-methylisoquinoline-1,3-dione (7c). Trimethyl orthoformate (110 mg, 1.02 mmol) was added to a suspension of **6c**[19] (240 mg, 1.02 mmol) in Ac_2O (2 mL), and the mixture was refluxed. When the reaction was over (10 min), one half of the solvent was evaporated off in vacuo, and hot MeOH (1 mL) was added. The mixture was stirred for 15 min and cooled, and the brown precipitate formed was recovered by filtration to afford **7c** (265 mg, 94%), mp 205–206 °C (EtOH): ^{1}H NMR δ 7.97 (s, 1 H, ArH), 7.76 (s, 1 H, ArH), 7.70 (s, 1 H, ArH), 4.19 (s, 3 H, OMe), 3.97 (s, 6 H, 2 × OMe), 3.40 (s, 3 H, NMe); ^{13}C NMR (DEPT) δ 166.42 (C), 164.42 (C), 163.42 (CH), 153.45 (C), 148.37 (C), 126.62 (C), 116.75 (C), 109.92 (CH), 108.00 (CH), 105.39 (C), 63.93 (CH_3), 56.04 (CH_3), 55.95 (CH_3), 26.89 (CH_3); IR (KBr) 1690, 1650, 1600 cm^{-1}; UV (EtOH) λ_{max} 228, 242, 272, 350 nm; LRMS m/z 277 (M^+, 100), 262 (49), 248 (24); HRMS calcd for $C_{13}H_{15}NO_5$ 277.0950, found 277.0946. Anal. Calcd for $C_{14}H_{15}NO_5$: C, 60.65; H, 5.45; N, 5.05. Found: C, 60.42; H, 5.39; N, 5.26.

2-Benzyl-1,2,3,4-tetrahydro-4-(methoxymethylene)isoquinoline-1,3-dione (7d). Compound **7d** was obtained (1.050 g, 88% yield) from Ac_2O (8 mL), DMF (2 mL), **6d**[20] (1.025 g, 4.084 mmol), and trimethyl orthoformate (760 mg, 7.17 mmol) (TLC: alumina; hexane/CH_2Cl_2 (4:1)): mp 156–157 °C; ^{1}H NMR δ 8.31–8.25 (m, 2 H, ArH), 8.05 (s, 1 H, CC*H*OMe), 7.63–7.56 (m, 1 H, ArH), 7.48–7.22 (m, 6 H, ArH), 5.26 (s, 2 H, NC*H*$_2$Ph), 4.18 (s, 3 H, OMe); IR (KBr) 1750, 1720, 1655 cm^{-1}; UV (EtOH) λ_{max} 242, 330 nm; LRMS m/z 293, 262, 233, 137, 91 (100); HRMS calcd for $C_{18}H_{15}NO_3$ 293.1052, found 293.1062.

4-(Anilinomethylene)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline-1,3-dione (8a). A few drops of acetic acid were added to a solution of **6c**[19] (70 mg, 0.298 mmol), trimethyl orthoformate (63 mg, 0.594 mmol), aniline (37 mg, 0.398 mmol), and DMF (2 mL), and the mixture was stirred at 95 °C until the imine had disappeared (approximately 1.5 h). The solution was cooled to rt and treated with EtOH (5 mL), the precipitated **8a** was filtered off (83 mg), and the filtrate was concentrated and chromatographed on silica gel plates to afford a further 15 mg of **8a**; combined yield, 98%: mp 182–183 °C (MeOH); ^{1}H NMR δ 12.33 (d, J = 12.5 Hz, 1 H, NH), 8.22 (d, J = 12.5 Hz, 1 H, CC*H*NHPh), 7.64 (s, 1 H, ArH), 7.48–7.37 (m, 2 H, ArH), 7.22–7.13 (m, 3 H, ArH), 6.90 (s, 1 H, ArH), 4.01 (s, 3 H, OMe), 3.93 (s, 3 H, OMe), 3.45 (s, 3 H, NMe); ^{13}C NMR δ 166.96, 163.81, 154.08, 147.67, 142.19, 139.74, 130.01, 129.73, 124.90, 117.40, 114.88, 109.86, 99.63, 96.72, 56.10, 56.07, 26.32; IR (KBr) 1670, 1630, 1610, 1595, 1580 cm^{-1}; UV (EtOH) λ_{max} 234, 248, 312, 402 nm; LRMS m/z 338 (M^+, 100), 323 (67.5), 293 (13), 264 (16), 77 (42), 69 (45); HRMS calcd for $C_{19}H_{18}N_2O_4$ 338.1266, found 338.1264. Anal. Calcd for $C_{19}H_{18}N_2O_4 \cdot {}^1/_4H_2O$: C, 66.60; H, 5.44; N, 8.17. Found: C, 66.27; H, 5.07; N, 8.59.

4-(Anilinomethylene)-2-benzyl-1,2,3,4-tetrahydroisoquinoline-1,3-dione (8b). Compound **8b** (305 mg, 87% yield, yellow needles) was obtained as above from imide **6d**[20] (251 mg, 1.0 mmol), trimethyl orthoformate (160 mg, 1.509 mmol), aniline (100 mg, 1.075 mmol), and acetic acid (a few drops) in dry DMF (10 mL): mp 201–202 °C; ^{1}H NMR δ 12.29 (d, J = 12.6 Hz, 1 H, NH), 8.45 (d, J = 12.7 Hz, 1 H, CC*H*NHPh), 8.32–8.29 (m, 1 H, ArH), 7.64–7.16 (m, 13 H, ArH), 5.35 (s, 2 H, ArC*H*$_2$); ^{13}C NMR δ 166.56, 164.13, 143.35, 139.57, 137.77, 135.26, 133.28, 130.00, 129.56, 128.43, 128.38, 127.22, 125.11, 124.73, 121.58, 117.72, 117.50, 96.43, 43.00; IR (KBr) 1665, 1625, 1591, 1575 cm^{-1}; UV (EtOH) λ_{max} 224, 248, 260, 394 nm; LRMS m/z 354 (M^+, 100); HRMS calcd for $C_{23}H_{18}N_2O_2$ 354.1368, found 354.1349. Anal. Calcd for $C_{23}H_{18}N_2O_2 \cdot {}^2/_7H_2O$: C, 76.83; H, 5.21; N, 7.79. Found: C, 76.73; H, 5.06; N, 8.02.

Methyl 5,6-Dihydro-3,6-dioxo-5-phenyl-3*H*-pyrano[2,3-*c*]isoquinoline-2-carboxylate (9b). *t*-BuOK (350 mg, 3.125 mmol) was added to a suspension of **7b**[11] (700 mg, 2.51 mmol) and methyl cyanoacetate (310 mg, 3.13 mmol) in DMF (5 mL), and the mixture was stirred under an Ar atmosphere for 1.5 h at 90 °C. The reaction mixture was poured into 5% HCl (25 mL) and stirred at rt for a further 30 min. The yellow precipitate formed was filtered out and washed with hot MeOH to yield **9b** (725 mg, 83%) as yellow crystals: mp 278–279 °C; ^{1}H NMR δ 9.14 (s, 1 H, H_{11}), 8.46–8.42 (m, 1 H, ArH), 8.03–8.00 (m, 1 H, ArH), 7.90–7.83 (m, 1 H, ArH), 7.64–7.55 (m, 4 H, ArH), 7.33–7.29 (m, 2 H, ArH), 3.94 (s, 3 H, OMe); ^{13}C NMR δ 164.00, 161.40, 155.09, 154.23, 146.68, 134.56, 133.02, 131.32, 129.78, 129.28, 127.97, 127.68, 122.79, 120.80, 107.17, 95.79, 52.46. IR (KBr) 1765, 1705, 1685, 1620 cm^{-1}; UV (EtOH) λ_{max} 232, 258, 280, 292, 390 nm; LRMS m/z 347 (M^+, 100), 319 (78), 232 (79).

Ethyl 5,6-Dihydro-8,9-dimethoxy-5-methyl-3,6-dioxo-3*H*-pyrano[2,3-*c*]isoquinoline-2-carboxylate (9c). (a) From Enamine **8a**. *t*-BuOK (35 mg, 0.313 mmol) was added to a solution of **8a** (100 mg, 0.296 mmol) and ethyl cyanoacetate (40 mg, 0.354 mmol) in dry DMF (2 mL), as a result of which the temperature rose slightly. The mixture was heated at 100 °C for 2 h, cooled to rt, treated with H_2O (1 mL) and 10% HCl, stirred for 15 min, and brought to pH 3 by addition of solid $NaHCO_3$. The white precipitate formed was filtered off and recrystallized from EtOH to afford **9c** (60 mg, 56%).

(b) From Enol Ether **7c**. NaOMe (65 mg, 1.204 mmol) was added to a solution of **7c** (250 mg, 0.903 mmol) and ethyl cyanoacetate (125 mg, 1.106 mmol) in DMF (2 mL), and the mixture was stirred for 1 h at 90 °C, poured over H_2O (3 mL), acidified with 10% HCl, and stirred at rt for 30 min. The orange precipitate formed was filtered out and dissolved in MeOH (50 mL), a few drops of 10% HCl were added, and the solution was stirred for 12 h. The yellow precipitate formed was collected by filtration to afford 245 mg of **9c**. The aqueous and methanolic filtrates were concentrated in vacuo and chromatographed on silica gel to yield further **9c** (60 mg); 94% combined yield: mp 235–236 °C (EtOH); ^{1}H NMR δ 8.99 (s, 1 H, Ar), 7.78 (s, 1 H, ArH), 7.22 (s, 1 H, Ar), 4.45 (q, J = 7.1 Hz, 2 H, OC*H*$_2$CH$_3$), 4.09 (s, 3 H, OMe), 4.01 (s, 3 H, OMe), 3.77 (s, 3 H, NMe), 1.44 (t, J = 7.1 Hz, 3 H, OCH$_2$C*H*$_3$); ^{1}H NMR (CMSO-d_6) δ 9.16 (s, 1 H, ArH), 7.62 (s, 1 H, ArH), 7.56 (s, 1 H, ArH), 4.30 (q, J = 7.1 Hz, 2 H, OC*H*$_2$CH$_3$), 4.01 (s, 3 H, OMe), 3.86 (s, 3 H, OMe), 3.54 (s, 3 H, NMe), 1.31 (t, J = 7.1 Hz, 3 H, OCH$_2$C*H*$_3$); ^{13}C NMR δ 164.16, 160.33, 155.03, 154.49, 149.56, 146.13, 126.24, 115.97, 108.79, 106.38, 101.23, 95.81, 61.81, 56.44, 56.22, 28.54, 14.26; IR (KBr) 2970, 2780, 1775, 1690, 1680, 1580 cm^{-1}; UV (EtOH) λ_{max} 226, 254, 284, 400 nm; LRMS m/z 359 (M^+, 100), 331 (48), 316 (21); HRMS calcd for $C_{18}H_{17}NO_7$ 359.1005, found 359.1004. Anal. Calcd for $C_{18}H_{17}NO_7 \cdot {}^1/_4H_2O$: C, 59.42; H, 4.89; N, 3.85. Found: C, 59.44; H, 4.63; N, 4.14.

Ethyl 5-Benzyl-5,6-dihydro-3,6-dioxo-3*H*-pyrano[2,3-*c*]-isoquinoline-2-carboxylate (9d). (a) From Enol Ether **7d**. Freshly prepared NaOMe (230 mg, 4.259 mmol) was added under an Ar atmosphere to a suspension of **7d** (950 mg, 3.242 mmol) and ethyl cyanoacetate (475 mg, 4.204 mmol) in dry DMF (8 mL), and the suspension was stirred for 1 h at 90 °C, poured into water (25 mL), acidified with concd HCl until acidic, and stirred at rt for 1 h. Filtration afforded **9d** (865 mg) as a yellow solid. The filtrate was extracted with CH_2Cl_2 (3 × 25 mL), the organic phase was dried over Na_2SO_4, the solvent was evaporated off in vacuo, and the residue was crystallized from MeOH as **9d** (80 mg). Overall yield 78%, mp 217–219 °C.

(b) From Enamine **8b**. *t*-BuOK (52 mg, 0.464 mmol) was added to a suspension of **8b** (120 mg, 0.339 mmol) and ethyl cyanoacetate

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

(18) Many of these compounds, especially pyrones **8** and benzophenanthridines **3**, are very insoluble in common organic solvents.

(19) Elliot, J. W., Jr. *J. Heterocycl. Chem.* **1972**, *9*, 853.

(20) Pulvermacher, G. *Ber.* **1887**, *20*, 2497.

(52 mg, 0.460 mmol) in dry DMF (2 mL), and the mixture was stirred for 1 h at 90 °C under an Ar atmosphere. Workup as above afforded **9d** (120 mg, 94% yield): ^{1}H NMR δ 9.04 (s, 1 H, H_1), 8.46 (dd, J_1 = 8.1 Hz, J_2 = 0.7 Hz, 1 H, ArH), 7.94–7.91 (m, 1 H, ArH), 7.84–7.77 (m, 1 H, ArH), 7.62–7.52 (m, 3 H, ArH), 7.36–7.28 (m, 3 H, ArH), 5.53 (s, 2 H, $ArCH_2$), 4.42 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 1.46 (t, J = 7.1 Hz, 3 H, OCH_2CH_3); ^{13}C NMR δ 163.56, 161.00, 155.32, 154.14, 146.24, 135.20, 134.20, 131.19, 129.36, 129.32, 128.80, 128.35, 127.40, 122.68, 120.56, 107.11, 95.75, 61.68, 45.09, 14.21; IR (KBr) 1780, 1670, 1620, 1570, 1520 cm^{-1}; UV (EtOH) λ_{max} 230, 250, 282, 292, 394 nm; LRMS m/z 375 (M^+, 31), 91 (100). Anal. Calcd for $C_{21}H_{17}NO_5$: C, 69.42; H, 4.71; N, 3.85. Found: C, 69.66; H, 4.71; N, 3.78.

2-(Benzoylamino)-5,6-dihydro-8,9-dimethoxy-5-methyl-3,6-dioxo-3*H*-pyrano[2,3-*c*]isoquinoline (11). A suspension of imide **6c**[19] (600 mg, 2.55 mmol) and methyl 2-(benzoylamino)-3-(dimethylamino)propenoate[21] (634 mg, 2.56 mmol) in glacial acetic acid (15 mL) was refluxed for 3 h and cooled to rt. The yellow precipitate was filtered out and washed with MeOH to afford **11** (820 mg, 79% yield), which crystallized from $CHCl_3$/MeOH as yellow crystals: mp 310 °C dec; ^{1}H NMR δ 9.37 (s, 1 H, ArH), 8.57 (bs, 1 H, NH), 7.94 (d, J = 8.0 Hz, 2 H, ArH), 7.81 (s, 1 H, ArH), 7.62–7.52 (m, 3 H, ArH), 7.24 (s, 1 H, ArH), 4.11 (s, 3 H, OMe), 4.02 (s, 3 H, OMe), 3.79 (s, 3 H, NMe); ^{13}C NMR δ 166.53, 160.20, 156.76, 154.75, 149.43, 145.62, 133.42, 132.46, 128.94, 127.04, 126.81, 122.95, 118.53, 116.59, 108.57, 101.85, 95.50, 56.49, 56.03, 28.21; IR (KBr) 1705, 1655, 1610, 1585 cm^{-1}; UV (EtOH) λ_{max} 245, 280, 295, 328, 380 nm; LRMS m/z 406 (M^+, 100), 273 (68), 105 (79); HRMS calcd for $C_{22}H_{18}N_2O_6$ 406.1165, found 406.1147. Anal. Calcd for $C_{22}H_{18}N_2O_6$: C, 65.02; H, 4.46; N, 6.89. Found: C, 64.77; H, 4.41; N, 6.74.

General Procedure for the Intermediate Benzyne Cycloaddition. This general procedure has been described previously.[5a]

Reaction of Methyl 5,6-Dihydro-3,6-dioxo-3*H*-pyrano[2,3-*c*]isoquinoline-2-carboxylate (9a) with Benzyne A. A solution of pyrone **9a**[11] (300 mg, 1.11 mmol) in a mixture of DME and dioxane (2:1, 100 mL) was reacted (see general procedure) with a suspension of benzenediazonium 2-carboxylate (**15a**), prepared from anthranilic acid (**14a**) (967 mg, 7.06 mmol) and isoamyl nitrite (1.322 g, 11.30 mmol). The solvent was evaporated off in vacuo and the residue chromatographed on silica gel (CH_2Cl_2/hexane (4:1)) to afford 180 mg (43%) of **16**: mp 156–157 °C (EtOH); ^{1}H NMR δ 9.23 (s, 1 H, H_{11}), 8.96 (m, 1 H, ArH), 8.81 (m, 1 H, ArH), 8.67 (m, 2 H, ArH), 7.96 (m, 1 H, ArH), 7.78 (m, 1 H, ArH), 7.67 (m, 1 H, ArH), 7.59–7.43 (m, 5 H, ArH), 7.37 (m, 1 H, ArH), 4.09 (s, 3 H, OCH_3); ^{13}C NMR δ 168.12, 160.03, 153.67, 142.49, 135.89, 131.81, 131.70, 131.15, 129.46, 128.40, 127.70, 126.68, 125.68, 125.49, 125.35, 125.19, 124.25, 122.38, 122.34, 119.68, 117.45, 52.22; IR (KBr) 1710, 1615 cm^{-1}; UV (EtOH) λ_{max} 272, 332, 345, 364 nm; LRMS m/z 379 (100, M^+), 348 (14), 319 (10), 77 (9). Anal. Calcd for $C_{25}H_{17}NO_3$: C, 79.14; H, 4.51; N, 3.69. Found: C, 78.85; H, 4.90; N, 3.59.

Reaction of Methyl 5,6-Dihydro-3,6-dioxo-5-phenyl-3*H*-pyrano[2,3-*c*]isoquinoline-2-carboxylate (9b) with Benzyne. Compound **9b** (150 mg, 39.58 mmol) was reacted in dioxane (20 mL) with benzenediazonium 2-carboxylate (**15a**) prepared from anthranilic acid (**14a**) (430 mg, 3.14 mmol) and isoamyl nitrite (585 mg, 5.79 mmol). The reaction was stopped when the addition of further salt failed to cause a clear advance of the reaction. Workup and chromatography (silica gel, CH_2Cl_2) afforded **10a** (142 mg, 88%) as white needles: mp 248–249 °C (EtOH); ^{1}H NMR δ 9.01 (s, 1 H, H_{11}), 8.87 (d, J = 7.9 Hz, 1 H, ArH), 8.55 (dd, J_1 = 1.1 Hz, J_2 = 7.9 Hz, 1 H, ArH), 8.37 (d, J = 8.3 Hz, 1 H, ArH), 7.86 (dt, J_1 = 1.3 Hz, J_2 = 7.7 Hz, 1 H, ArH), 7.67–7.56 (m, 2 H, ArH), 7.47–7.30 (m, 6 H, ArH), 7.08–7.01 (m, 1 H, ArH), 4.08 (s, 3 H, OMe); ^{13}C NMR δ 167.43, 163.23, 142.81, 138.25, 133.93, 133.45, 132.69, 129.29, 129.08, 128.86, 128.59, 127.68, 127.41, 126.41, 125.97, 125.81, 125.14, 124.90, 123.41, 122.30, 116.13, 52.26; IR (KBr) 1708, 1652, 1595 cm^{-1}; UV (EtOH) λ_{max} 226, 244, 272, 282, 324, 338, 348, 366 nm; LRMS m/z 379 (M^+, 100), 348 (15), 291 (24); HRMS calcd for $C_{25}H_{17}N_2O_3$ 379.1208, found 379.1203. Anal. Calcd for $C_{25}H_{17}N_2O_3$: C, 79.14; H, 4.51; N, 3.59. Found: C, 79.38; H, 4.49; N, 3.47.

Reaction of Ethyl 5,6-Dihydro-8,9-dimethoxy-5-methyl-3,6-dioxo-3*H*-pyrano[2,3-*c*]isoquinoline-2-carboxylate (9c) with Benzyne. Benzenediazonium 2-carboxylate (**15a**) prepared from anthranilic acid (**14a**) (467 mg, 3.4 mmol) and isoamyl nitrite (650 mg, 5.45 mmol) was added to a solution of **9c** (100 mg, 0.278 mmol) in dioxane (25 mL) heated in an oil bath at 85 °C. Workup and chromatography (silica gel, CH_2Cl_2/hexane 20%; CH_2Cl_2; CH_2Cl_2/MeOH (1%)) afforded **10b** (87 mg, 80% yield), which crystallized from EtOH as white needles (mp 195–196 °C), **17a** (3 mg, 2% yield, mp 169–170 °C, EtOH), and **9c** (3–4 mg).

Spectroscopic data for ethyl 5,6-dihydro-8,9-dimethoxy-5-methyl-6-oxobenzo[*c*]phenanthridine-12-carboxylate (**10b**): ^{1}H NMR δ 8.94 (dd, J_1 = 1.1 Hz, J_2 = 8.4 Hz, 1 H, ArH), 8.85 (s, 1 H, ArH), 8.32 (m, 1 H, ArH), 7.94 (s, 1 H, ArH), 7.64 (s, 1 H, ArH), 7.67–7.52 (m, 2 H, ArH), 4.57 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 4.15 (s, 1 H, OMe), 4.07 (s, 1 H, OMe), 4.02 (s, 1 H, NMe), 1.53 (t, J = 7.1 Hz, 3 H, OCH_2CH_3); ^{13}C NMR δ 166.94, 163.64, 153.50, 149.96, 131.78, 127.83, 127.29, 126.01, 125.49, 124.61, 124.53, 122.31, 119.04, 115.05, 108.27, 102.54, 61.05, 55.95, 40.90, 14.26; IR (KBr) 2950, 1715, 1650, 1610, 1510 cm^{-1}; UV (EtOH) λ_{max} 265, 295, 350, 368 nm; LRMS m/z 391 (M^+, 100), 390 (74.5), 362 (31), 346 (15), 318 (9); HRMS calcd for $C_{23}H_{21}NO_5$ 391.1420, found 391.1404. Anal. Calcd for $C_{23}H_{21}NO_5$: C, 70.56; H, 5.41; N, 3.58. Found: C, 70.38; H, 5.09; N, 3.34.

Spectroscopic data for ethyl 4b,5,6,12-tetrahydro-8,9-dimethoxy-5-methyl-6-oxo-4b,12-*o*-benzenobenzo[*c*]phenanthridine-12-carboxylate (**17a**): ^{1}H NMR δ 7.80 (s, 1 H, ArH), 7.65 (s, 1 H, ArH), 7.53–7.50 (m, 2 H, ArH), 7.49–7.41 (m, 2 H, ArH), 7.16–7.10 (m, 4 H, ArH), 6.87 (s, 1 H, CH), 4.73 (q, J = 7.2 Hz, 2 H, OCH_2CH_3), 3.96 (s, 3 H, OMe), 3.86 (s, 3 H, OMe), 3.70 (s, 3 H, NMe), 1.60 (t, J = 7.1 Hz, 3 H, OCH_2CH_3); ^{13}C NMR δ 169.59, 164.22, 152.78, 150.16, 145.32, 143.84, 140.69, 129.93, 128.37, 125.93, 125.27, 124.47, 122.48, 118.86, 109.97, 103.45, 74.25, 62.11, 61.11, 56.14, 36.90, 14.51; IR (KBr) 2965, 2940, 1740, 1650, 1600 cm^{-1}; UV (EtOH) λ_{max} 240, 316, 332 nm; LRMS m/z 467 (M^+, 100), 394 (45), 366 (64.5), 338 (21); HRMS calcd for $C_{29}H_{25}NO_5$ 467.1733, found 467.1725. Anal. Calcd for $C_{29}H_{25}NO_5 \cdot {}^1/_2H_2O$: C, 73.00; H, 5.50; N, 2.94. Found: C, 72.83; H, 5.31; N, 2.86.

Reaction of Ethyl 5-Benzyl-5,6-dihydro-3,6-dioxo-3*H*-pyrano[2,3-*c*]isoquinoline-2-carboxylate (9d) with Benzyne. To a solution of **9d** (375 mg, 1 mmol) in dioxane (75 mL) was added, as above, a suspension of benzenediazonium 2-carboxylate prepared from anthranilic acid (2.175 g, 15.896 mmol) and isoamyl nitrite (2.975 g, 25.4 mmol). Workup as above afforded ethyl 5-benzyl-5,6-dihydro-6-oxobenzo[*c*]phenanthridine-12-carboxylate (**10d**) (300 mg, 74% yield): ^{1}H NMR (19.7×10^{-3} M) δ 9.04 (s, 1 H, ArH), 9.00 (d, J = 8.7 Hz, 1 H, ArH), 8.52 (d, J = 7.9 Hz, 1 H, ArH), 8.37 (d, J = 8.2 Hz, 1 H, ArH), 8.20 (d, J = 8.7 Hz, 1 H, ArH), 7.90–7.84 (m, 1 H, ArH), 7.67–7.57 (m, 2 H, ArH), 7.38–7.22 (m, 6 H, ArH), 4.56 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 1.54 (t, J = 7.1 Hz, 3 H, OCH_3CH_3); ^{13}C NMR δ 167.04, 164.67, 140.35, 138.04, 133.58, 133.25, 132.61, 129.00, 128.75, 128.51, 127.98, 127.14, 126.43, 126.38, 125.79, 125.71, 125.30, 125.25, 124.95, 123.09, 122.20, 116.12, 61.29, 56.01, 14.43; IR (KBr) 3065, 2990, 1715, 1655, 1610, 1595 cm^{-1}; UV (EtOH) λ_{max} 228, 250, 272, 282, 298, 322, 336, 364 nm; LRMS m/z 407 (16), 149 (56), 120 (34), 105 (100), 77 (62); HRMS calcd for $C_{27}H_{21}NO_3$ 407.1521, found 407.1541. Anal. Calcd for $C_{27}H_{21}NO_3 \cdot {}^1/_3H_2O$: C, 78.43; H, 5.28; N, 3.39. Found: C, 78.33; H, 4.90; N, 3.75.

Reaction of 2-(Benzoylamino)-5,6-dihydro-8,9-dimethoxy-5-methyl-3,6-dioxo-3*H*-pyrano[2,3-*c*]isoquinoline (11) with Benzyne. (a) In 1,2-Dichloroethane. To a refluxing solution of **11** (100 mg, 0.246 mmol) in 1,2-dichloroethane (20 mL) was added dropwise a suspension of benzenediazonium 2-carboxylate (**15a**) prepared from anthranilic acid (**14a**) (390 mg, 2.854 mmol) and isoamyl nitrite (535 mg, 4.573 mmol). When the reaction was complete (after the addition of 2.5–3 equiv of the diazonium salt), the solvent was evaporated off in vacuo and the residue was chromatographed on a silica gel column (CH_2Cl_2/hexane (9:1), CH_2Cl_2 and CH_2Cl_2/MeOH (5%)) and then on neutral alumina (activity III) to afford **12** (85 mg, 79%) and the double addition adduct **17b** (6 mg, 5%).

(b) In 1,4-Dioxane. To a refluxing solution of **11** (100 mg, 0.246 mmol) in dioxane (20 mL) was added, as above, benzene-

(21) Stanovnik, B.; Svete, J.; Tisler, M.; Zorz, L.; Hvala, I.; Simonik, I. *Heterocycles*, **1988**, *27*, 903.

diazonium 2-carboxylate (**15a**) prepared from anthranilic acid (**14a**) (392 mg, 2.861 mmol) and isoamyl nitrite (536 mg, 4.581 mmol). All the sale prepared was added. Evaporation of the solvent in vacuo and chromatographic purification as above afforded **12** (68 mg, 63%) which crystallized from acetone as white needles: mp 250 °C.

Spectroscopic data for 2-(benzoylamino)-5,6-dihydro-8,9-dimethoxy-5-methyl-3,6-dioxo-3*H*-pyrano[2,3-*c*]isoquinoline (**12**) (^{1}H NMR data were obtained from a 22.8 × 10^{-3} M solution in $CDCl_3$):[22] ^{1}H NMR δ 8.51 (bs, 1 H, NH), 8.36 (m, 2 H, ArH), 8.08 (d, *J* = 6.4 Hz, 2 H, ArH), 8.00–7.96 (m, 1 H, ArH), 7.91 (s, 1 H, ArH), 7.64–7.54 (m, 5 H, ArH), 7.50 (s, 1 H, ArH), 4.06 (s, 3 H, OMe), 4.03 (s, 3 H, OMe), 3.99 (s, 3 H, NMe); ^{13}C NMR (DEPT) δ 166.76 (C), 163.73 (C), 153.22 (C), 149.81 (C), 134.20 (C), 133.83 (C), 132.05 (CH), 129.38 (C), 128.78 (CH), 128.38 (C), 128.08 (C), 127.41 (CH), 126.33 (CH), 125.71 (CH), 124.75 (CH), 122.12 (CH), 119.07 (C), 116.93 (CH), 116.29 (C), 108.16 (CH), 102.84 (CH), 55.94 (CH_3), 40.76 (CH_3); IR (KBr) 1640, 1605 cm^{-1}; UV (EtOH) λ_{max} 230, 256, 266, 290, 338, 352, 368 nm; LRMS *m/z* 438 (M^+, 87), 333 (90), 105 (100); HRMS calcd for $C_{27}H_{22}N_2O_4$ 391.1420, found 391.1404. Anal. Calcd for $C_{27}H_{22}N_2O_4 \cdot {}^1/_2H_2O$: C, 72.47; H, 5.18; N, 6.26. Found: C, 72.76; H, 5.08; N, 6.34.

Spectroscopic data for 12-(benzoylamino)-4b,5,6,12-tetrahydro-8,9-dimethoxy-5-methyl-6-oxo-4b,12-*o*-benzenobenzo[*c*]-phenanthridine (**17b**): ^{1}H NMR δ 8.14 (dd, J_1 = 9.0 Hz, J_2 = 1.5 Hz, 2 H, ArH), 7.79 (s, 1 H, H_7), 7.68–7.57 (m, 4 H, ArH), 7.48–7.45 (m, 2 H, ArH), 7.39–7.36 (m, 2 H, ArH), 7.21–7.13 (m, 3 H, ArH), 6.85 (s, 1 H, H_{11}), 3.96 (s, 3 H, OMe), 3.81 (s, 3 H, OMe), 3.72 (s, 3 H, NMe); ^{13}C NMR (DEPT) δ 167.61 (C), 164.32 (C), 152.83 (C), 150.08 (C), 144.46 (C), 141.15 (C), 140.38 (C), 134.62 (C), 132.66 (CH), 132.48 (CH), 129.18 (CH), 127.37 (CH), 125.71 (CH), 125.38 (CH), 124.62 (C), 122.58 (CH), 119.59 (CH), 118.77 (C), 109.94 (CH), 103.71 (CH), 73.44 (C), 65.58 (C), 56.13 (CH_3), 56.09 (CH_3), 37.01 (CH_3); IR (KBr) 2945, 1730, 1655, 1645, 1590 cm^{-1}; UV (EtOH) λ_{max} 256, 264, 322, 338, 360, 380 nm; LRMS *m/z* 514 (46), 409 (100), 393 (12), 105 (43); HRMS calcd for $C_{33}H_{26}N_2O_4$ 514.1892, found 514.1876.

Reaction of 9c with 4,5-(Methylenedioxy)benzyne (5b). To a stirred refluxing solution of **9c** (165 mg, 0.460 mmol) in dioxane (30 mL) was added, as above, 4,5-(methylenedioxy)-benzenediazonium 2-carboxylate (**15b**) prepared from 4,5-(methylenedioxy)anthranilic acid (**14b**) (780 mg, 4.30 mmol) and isoamyl nitrite (810 g, 6.92 mmol). Refluxing and stirring were maintained overnight due to the slow decomposition of this diazonium salt. Evaporation of the solvent in vacuo and chromatographic purification (silica gel, 12% $CHCl_3$/ether) afforded ethyl 5,6-dihydro-8,9-dimethoxy-5-methyl-2,3-(methylenedioxy)-6-oxobenzo[*c*]phenanthridine-12-carboxylate (**10c**) (130 mg, 72% yield), which crystallized from 2:1 EtOH/CH_2Cl_2. Crystallization from $CHCl_3$/EtOH afforded white needles: mp 257–259 °C; ^{1}H NMR δ 8.70 (s, 1 H, H_{11}), 8.37 (s, 1 H, ArH), 7.89 (s, 1 H, ArH), 7.57 (s, 1 H, ArH), 7.55 (s, 1 H, ArH), 6.13 (s, 2 H, OCH_2O), 4.53 (q, *J* = 7.1 Hz, 2 H, OCH_2CH_3), 4.13 (s, 3 H, MeO), 4.06 (s, 3 H, MeO), 3.92 (s, 3 H, NMe), 1.51 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3); ^{13}C NMR δ 167.38, 164.37, 153.88, 150.13, 148.91, 146.67, 129.94, 128.40, 123.36, 122.06, 121.60, 119.17, 115.37, 108.72, 103.55, 102.86, 102.69, 101.80, 61.24, 56.23, 41.33, 14.40; IR (KBr) 2980, 2930, 1715, 1655, 1610, 1500, 1475 cm^{-1}; UV (EtOH) λ_{max} 222, 268, 298 nm; LRMS *m/z* 435 (M^+, 100), 406 (11.5), 390 (8), 380 (9), 69 (6); HRMS calcd for $C_{24}H_{21}NO_7$ 435.1318, found 435.1315. Anal. Calcd for $C_{24}H_{21}NO_7 \cdot H_2O$: C, 63.57; H, 5.11; N, 3.09. Found: C, 63.72; H, 4.75; N, 3.01.

5,6-Dihydro-8,9-dimethoxy-5-methyl-6-oxobenzo[*c*]-phenanthridine-12-carboxylic Acid (10e). To a solution of **10b** (50 mg, 0.126 mmol) in refluxing EtOH (5 mL) was added a 10% ethanolic solution of KOH (6 mL). After 5 min the solution was cooled by stirring in an ice/water bath, acidified with 10% HCl (10 mL), and stirred in the cooling bath for a further 2 h. **10e** (47 mg, 100%) was collected by filtration as a white precipitate: mp 280 °C (H_2O); ^{1}H NMR (DMSO-d_6) δ 8.94 (s, 1 H, H_{11}), 8.87 (d, *J* = 8.4 Hz, 1 H, ArH), 8.46 (d, *J* = 8.4 Hz, 1 H, ArH), 7.82 (s, 1 H, ArH), 7.75 (s, 1 H, ArH), 7.70–7.56 (m, 2 H, ArH), 4.06 (s, 3 H, OMe), 3.93 (s, 3 H, OMe), 3.89 (s, 3 H, NMe); ^{13}C NMR (Py-c_5) δ 170.05, 164.03, 154.64, 151.08, 139.61, 133.16, 128.87, 127.62, 127.36, 126.31, 125.70, 125.42, 125.06, 120.09, 115.98, 109.38, 104.13, 55.99, 55.81, 41.16; IR (KBr) 1670, 1635, 1610, 1590 cm^{-1}; UV (EtOH) λ_{max} 222, 260, 264, 290, 322, 348, 368 nm; LRMS *m/z* 363 (M^+, 100), 69 (89); HRMS calcd for $C_{21}H_{17}NO_5$ 363.1107, found 363.1123. Anal. Calcd for $C_{21}H_{17}NO_5 \cdot {}^3/_2H_2O$: C, 64.61; H, 5.16; N, 3.58. Found: C, 64.22; H, 5.09; N, 3.58.

5,6-Dihydro-8,9-dimethoxy-5-methyl-2,3-(methylenedioxy)-6-oxobenzo[*c*]phenanthridine-12-carboxylic Acid (10f). A 10% ethanolic solution of KOH (5 mL) was added dropwise to a solution of **10c** (25 mg, 0.063 mmol) in dioxane (10 mL), and the mixture was refluxed for 15 min. The solvent was evaporated off in vacuo, and the residue was dissolved in water (5 mL) and washed with ether (3 × 5 mL). The aqueous phase was treated with 10% HCl, and the white precipitate formed was collected by filtration and washed with water (2 × 5 mL) to afford **10f** (23 mg, 100% yield): mp 327–329 °C (H_2O); ^{1}H NMR (DMSO-d_6) δ 8.79 (s, 1 H, H_{11}), 8.32 (s, 1 H, H_7), 7.78 (s, 1 H, H_{10}), 7.73 (s, 1 H, ArH), 7.70 (s, 1 H, ArH), 6.22 (s, 2 H, OCH_2O), 4.04 (s, 3 H, OMe), 3.91 (s, 3 H, OMe), 3.81 (s, 3 H, NMe); ^{13}C NMR (DMSO-d_6) δ 168.35, 162.95, 153.62, 149.72, 148.44, 146.67, 138.58, 129.31, 127.74, 123.02, 122.06, 120.85, 118.19, 114.49, 108.02, 103.4, 102.83, 102.35, 101.95, 55.94, 55.58, 40.76; IR (KBr) 3390, 1700, 1630 cm^{-1}.

8,9-Dimethoxy-5-methylbenzo[*c*]phenanthridin-6-one (3a) by Decarboxylation of 10e. A suspension of **10e** (45 mg, 0.124 mmol) and a catalytic amount of copper powder in quinoline (3 mL) was heated in a Kugelrohr apparatus for 15 min at 170 °C. The mixture was diluted with CH_2Cl_2 (25 mL) and washed with 10% HCl (4 × 25 mL) and water (25 mL). The organic phase was dried (Na_2SO_4), the solvent was evaporated off in vacuo, and the residue was chromatographed on a silica gel plate (CH_2Cl_2) to afford **3a** (35 mg, 85% yield), which crystallized from EtOH as pink needles: mp 147–149 °C; ^{1}H NMR δ 8.39–8.35 (m, 1 H, ArH), 8.14 (d, *J* = 8.8 Hz, 1 H, ArH), 7.96 (s, 1 H, ArH), 7.92–7.88 (m, 1 H, ArH), 7.74 (d, *J* = 8.7 Hz, 1 H, ArH), 7.64 (s, 1 H, ArH), 7.55–7.51 (m, 2 H, ArH), 4.12 (s, 3 H, OMe), 4.07 (s, 6 H, OMe + NMe); ^{13}C NMR δ 164.15 (C), 153.66 (C), 150.06 (C), 135.89 (C), 134.52 (C), 128.86 (C), 128.52 (CH), 126.24 (CH), 125.49 (CH), 125.01 (CH), 124.84 (C), 123.91 (CH), 119.82 (CH), 119.59 (C), 117.05 (C), 108.74 (CH), 103.03 (CH), 56.24 (CH_3), 56.14 (CH_3), 41.07 (CH_3); IR (film) 1638, 1608 cm^{-1}; UV (EtOH) λ_{max} 226, 254, 264, 276, 286, 318, 332, 350 nm; LRMS *m/z* 319 (M^+, 100), 274 (8), 260 (7). Anal. Calcd for $C_{20}H_{17}NO_3$: C, 75.22; H, 5.37; N, 4.39. Found: C, 75.14; H, 5.40; N, 4.52.

5,6-Dihydro-2,3-dimethoxy-12-methyl[1,3]benzodioxolo-[5,6-*c*]phenanthridin-13(12*H*)-one (6-Oxonitidine, 3b) by Decarboxylation of 10f. A mixture of **10f** (14 mg, 0.034 mmol), copper powder (5 mg), $Cu(OCH_3COCH_3)$ (2 mg), 2,2′-dipyridine (50 mg, 0.34 mmol), and quinoline (3 mL) was heated for 30 min at 180 °C under an Ar atmosphere. After being cooled to rt, the mixture was diluted with ether and washed with 2 N NaOH (1 × 25 mL), 10% HCl (3 × 25 mL), and H_2O (25 mL). The organic phase was dried over Mg_2SO_4 and concentrated in vacuo, and the residue was purified by column chromatography (silica gel, CH_2Cl_2/MeOH (0.5%)) to afford oxonitidine (**3b**)[15] (9 mg, 72% yield): mp 280–282 °C (EtOH) (lit.[15] mp 284–285 °C): ^{1}H NMR δ 8.01 (d, *J* = 9.2 Hz, 1 H, H_{11}), 7.94 (s, 1 H, H_7), 7.66 (s, 1 H, H_{10}), 7.60 (s, 1 H, ArH), 7.58 (d, *J* = 9.2 Hz, 1 H, H_{12}), 7.20 (s, 1 H, ArH), 6.11 (s, 2 H, OCH_2O) 4.11 (s, 3 H, OMe), 4.07 (s, 3 H, OMe), 4.00 (s, 3 H, NMe); LRMS *m/z* 363 (18), 305 (5), 205 (7), 119 (24), 44 (100).

5,6-Dihydro-8,9-dimethoxy-5-methyl-6-oxobenzo[*c*]-phenanthridine-12-ammonium Sulfate (13). Sodium azide (8 mg, 0.213 mmol) was added in three portions to a suspension of **10e** (40 mg, 0.110 mmol) and concd H_2SO_4 (0.15 mL) in $CHCl_3$ (1 mL) heated at 45 °C. Heating was maintained for 2 h, and then the solvent was evaporated and the residue treated with crushed ice. The white precipitate was collected by filtration to afford **13** (38 mg, 80% yield): mp 257–259 °C (H_2O); ^{1}H NMR (free amine) δ 8.34–8.30 (m, 1 H, ArH), 7.94 (s, 1 H, ArH), 7.93–7.89 (m, 1 H, ArH), 7.55–7.50 (m, 3 H, ArH), 7.40 (s, 1 H, ArH), 4.10 (s, 3 H, OMe), 4.05 (s, 3 H, OMe), 3.99 (s, 3 H, NMe); IR (KBr) 3400, 2880, 2580 (broad signals), 1605, 1510 cm^{-1}; IR (film) free amine 3325, 2960, 1730, 1605, 1570. UV (EtOH) λ_{max} 256, 290, 350, 366 nm; LRMS *m/z* 334, 276, 233, 43 (100); HRMS calcd

(22) Chemical shifts depend on the concentration.

for $C_{20}H_{18}N_2O_3$ 334.1317, found 334.1317. Anal. Calcd for $C_{20}H_{18}N_2O_3 \cdot H_2SO_4 \cdot {}^1/_2H_2O$: C, 54.42; H, 4.79; N, 6.35. Found: C, 54.68; H, 4.38; N, 6.17.

Ethyl 6-Chlorobenzo[*c*]phenanthridine-12-carboxylate (18a). A mixture of **10d** (50 mg, 0.122 mmol) and $POCl_3$ (1 mL) was stirred for 3 h at 60 °C, cooled to 0 °C, diluted with ice/water (5 mL), treated with NH_4OH, and extracted with CH_2Cl_2 (3 × 15 mL). The organic phase was washed with H_2O (1 × 15 mL) and dried (Na_2SO_4). Evaporation in vacuo afforded imine **18a** (40 mg, 97% yield): mp 145–146 °C (hexane); ^1H NMR δ 9.43–9.39 (m, 1 H, ArH), 9.22 (s, 1 H, H_{11}), 8.99–8.95 (m, 1 H, ArH), 8.75 (d, J = 8.3 Hz, 1 H, ArH), 8.59 (d, J = 8.3 Hz, 1 H, ArH), 8.04–7.97 (m, 1 H, ArH), 7.87–7.79 (m, 3 H, ArH), 4.61 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 1.58 (t, J = 7.1 Hz, 3 H, OCH_2CH_3); ^{13}C NMR δ 167.50, 152.86, 142.68, 135.00, 132.13, 131.62, 130.90, 128.89, 128.51, 127.92, 127.75, 127.47, 125.85, 125.59, 125.34, 124.52, 122.72, 119.48, 61.55, 14.44; IR (film) 1720, 1605 (mild) cm^{-1}; UV (EtOH) λ_{max} 226, 268, 332, 336, 352, 370 nm; LRMS m/z 335 (100), 307 (17), 290 (60), 227 (53); HRMS calcd for $C_{20}H_{14}NO_2Cl$ 335.0713, found 335.0711. Anal. Calcd for $C_{20}H_{14}NO_2Cl$: C, 71.54; H, 4.20; N, 4.17. Found: C, 71.18; H, 4.09; N, 4.23.

Ethyl Benzo[*c*]phenanthridine-12-carboxylate (18b). To a solution of **18a** (35 mg, 0.104 mmol) in 1:1 benzene/ethanol (4 mL) was added 10% Pd/C (4 mg) and NaOAc (10 mg, 0.122 mmol). Air was removed from the reaction flask and replaced with hydrogen using a balloon, and the mixture was stirred for 3 h at rt and then filtered over Celite. The filtrate was concentrated in vacuo, and the resulting residue was dissolved in CH_2Cl_2 (15 mL) and washed with H_2O (1 × 15 mL). The organic phase was dried over Na_2SO_4, concentrated, and chromatographed on a silica gel column (4:1 CH_2Cl_2/hexane) to afford **18b** (25 mg, 80% yield) as a white solid: mp 95–97° C; ^1H NMR δ 9.52 (s, 1 H, ArH), 9.51–9.48 (m, 1 H, ArH), 9.25 (s, 1 H, ArH), 8.99–8.95 (m, 1 H, ArH), 8.72 (d, J = 8.2 Hz, 1 H, ArH), 8.17–8.14 (m, 1 H, ArH), 7.97–7.90 (m, 1 H, ArH), 7.84–7.73 (m, 3 H, ArH), 4.60 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 1.56 (t, J = 7.1 Hz, 3 H, OCH_2CH_3); ^{13}C NMR δ 167.69, 154.09, 143.52, 133.02, 132.53, 131.44, 130.64, 128.92, 128.43, 127.62, 127.33, 127.20, 127.02, 125.84, 125.17, 124.95, 122.19, 119.40, 61.42, 14.42; IR (film) 2920, 1715, 1620 cm^{-1}; UV (EtOH) λ_{max} 224, 268, 334, 368 nm; LRMS m/z 301 (100), 273 (22), 256 (55), 228 (42), 201 (39); HRMS calcd for $C_{20}H_{15}NO_2$ 301.1108, found 301.1077. Anal. Calcd for $C_{20}H_{15}NO_2 \cdot {}^1/_3H_2O$: C, 78.16; H, 5.14; N, 4.56. Found: C, 78.54; H, 4.88; N, 4.59.

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Registry No. 2b, 6872-57-7; **3a**, 143370-25-6; **3b**, 548-31-2; **5a**, 462-80-6; **5b**, 70429-31-1; **6c**, 38973-42-1; **6d**, 21640-31-3; **7b**, 78363-90-3; **7c**, 128637-93-4; **7d**, 143370-33-6; **8a**, 143370-26-7; **8b**, 143370-34-7; **9a**, 78379-92-7; **9b**, 143370-35-8; **9c**, 128637-90-1; **9d**, 143370-36-9; **10a**, 128637-89-8; **10b**, 128637-92-3; **10c**, 143370-38-1; **10d**, 143370-42-7; **10e**, 143370-39-2; **10f**, 143370-40-5; **11**, 143370-27-8; **12**, 143370-28-9; **13**, 143370-30-3; **14a**, 118-92-3; **14b**, 20332-16-5; **15a**, 1608-42-0; **15b**, 143370-43-8; **16**, 143370-31-4; **17a**, 128637-91-2; **17b**, 143370-37-0; **18a**, 143370-32-5; **18b**, 143370-41-6; $Me_2NCH{=}C(NHCOPh)COOMe$, 56952-04-6; $NCCH_2CO_2Et$, 105-56-6.

Synthesis of Genotoxic Heterocyclic Amines Trp-P-1 and Trp-P-2

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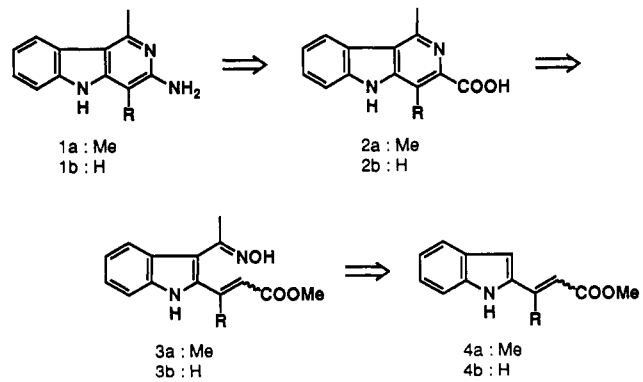
Trp-P-1 (**1a**) and Trp-P-2 (**1b**) possessing a pyrido[4,3-*b*]indole system have been newly synthesized. The key reaction step in the synthetic sequence has been the thermal electrocyclic reaction of the 1-azahexa-1,3,5-triene system **3** involving the indole [*b*] bond derived from 2-vinylindoles **4**. 2-Vinylindole **4a** has been derived from *N*-(benzenesulfonyl)indole (**5**) in a four-step sequence. 2-Vinylindole **4b** has been synthesized by two routes using either ethoxymethylidene Meldrum's acid (**6b**) or diethyl ethoxymethylidenemalonate (**10**) as Michael acceptors to the 2-lithio-*N*-(benzenesulfonyl)indole.

A variety of genotoxic heterocyclic amines are known to be formed when amino acids are pyrolyzed or protein-containing foods are cooked at high temperature.[1-4] Among these amines, Trp-P-1 (**1a**) and Trp-P-2 (**1b**) were isolated from tryptophan pyrolysate,[5] whose structures were determined by X-ray analysis and spectroscopic evidence as 3-amino-1,4-dimethyl-5*H*-pyrido[4,3-*b*]indole (**1a**) and 3-amino-1-methyl-5*H*-pyrido[4,3-*b*]indole (**1b**).[6] Synthetic routes to Trp-P-2 (**1b**) have been reported simultaneously by the Takeda[7] and Akimoto[8] groups, the latter of whom have also completed a synthesis of Trp-P-1 (**1a**).[8]

Scheme I



We are currently interested in the synthesis of condensed heterocyclic compounds, especially fused pyridine

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