Indole as a Dienophile in Inverse Electron Demand Diels–Alder Reactions: Reactions with 1,2,4-Triazines and 1,2-Diazines

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Received November 1, 1989

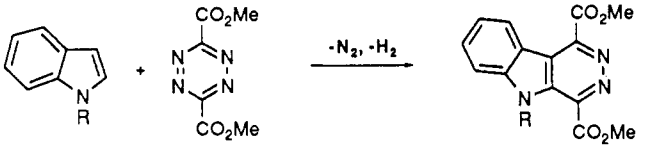
Indole reacts with 1,2,4-triazines in the absence of solvent or in the presence of limited amounts of solvent to produce β- or γ-carbolines, benzo[*f*][1,7]naphthyridines, or the noncyclized 3-[5-(1,2,4-triazinyl)]indoles. The combined yield of cycloadducts with tricarbalkoxytriazines exceeds 90%, with the production of γ-carbolines exceeding 80%. the regiochemistry of the adduct and the ratio of the products is determined mainly by electronic effects of the triazine substituents. Indole also undergoes a cyclocondensation reaction with tetramethyl 1,2-diazine-3,4,5,6-tetracarboxylate to give trimethyl 5*H*-6-oxophenanthridine-2,3,4-tricarboxylate.

Introduction

The inverse electron demand Diels–Alder cycloaddition employing azadienes has become an important tool for the synthesis of biologically active natural[1] and unnatural[2] products.[3] Though the use of indole as a dienophile in both inverse[4] and normal[5] electron demand cycloadditions has been limited, the number of examples is increasing. We recently reported that indole and several of its simple derivatives undergo a facile inverse electron demand Diels–Alder reaction with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (**1**), producing 5*H*-pyridizino[4,5-*b*]indole derivatives (**2**) in excellent yields, Scheme I.[6]

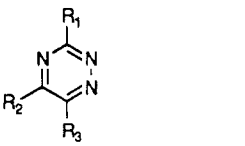
We had hoped to utilize 1,2,4-triazines[7] (**3**) and 1,2-diazines[8] (**4**) in analogous reactions in order to synthesize

Scheme I

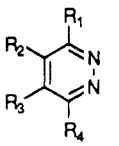


1 **2**

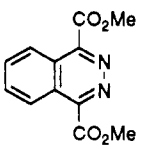
biologically active β-carboline and carbazole natural products, respectively. Such a relatively simple route could be an attractive alternative to the more commonly employed Pictet–Spengler condensation with subsequent aromatization[9] to access β-carbolines substituted in the C ring. Unfortunately, under conditions similar to those employed in the tetrazine reactions, no reaction ensued with triethyl 1,2,4-triazine-3,5,6-tricarboxylate (**3a**) or with 3,6-dichloro-1,2-diazine (**4a**).



3	R_1	R_2	R_3
3a	CO_2Et	CO_2Et	CO_2Et
3b	CO_2Et	CO_2Me	CO_2Me
3c	CO_2Et	CH_3	CO_2Et
3d	CO_2Et	C_6H_5	H
3e	CO_2Et	H	H
3f	CO_2Et	CO_2Et	CH_3
3g	SCH_3	CO_2Me	CO_2Me
3h	CO_2Me	NMe_2	CO_2Me
3i	CO_2Et	CH_3	CH_3
3j	SO_2CH_3	H	H
3k	CO_2Et	H	C_6H_5



4a: $R_1 = R_4 = Cl$; $R_2 = R_3 = H$
4b: $R_1 = R_2 = R_3 = R_4 = CO_2Me$



4c

We have since found that indole does indeed undergo cyclocondensations with 1,2,4-triazines by two regiochemical pathways under neat or highly concentrated conditions, Scheme II. The main products from the cyclo-

(1) Reference 3 for reviews; for some recent examples since these reviews: (a) Boger, D. L.; Coleman, R. S.; Invergo, B. J. *J. Org. Chem.* **1987**, *52*, 1521. (b) Boger, D. L.; Patel, M. *Tetrahedron Lett.* **1987**, *28*, 2499. (c) Boger, D. L.; Patel, M. *J. Org. Chem.* **1988**, *53*, 1405. (d) Melnick, M. J.; Weinreb, S. M. *J. Org. Chem.* **1988**, *53*, 850.

(2) Reference 3 for reviews; for some recent examples since these reviews: (a) Frissen, A. E.; Marcelis, A. T. M.; van der Plas, H. C. *Tetrahedron Lett.* **1987**, *28*, 1589. (b) Taylor, E. C.; Pont, J. L. *Tetrahedron Lett.* **1987**, *28*, 379. (c) Taylor, E. C.; McDaniel, K. F.; Warner, J. C. *Tetrahedron Lett.* **1987**, *28*, 1977. (d) Taylor, E. C.; Macor, J. E. *J. Org. Chem.* **1987**, *52*, 4280. (e) Taylor, E. C.; Pont, J. L. *J. Org. Chem.* **1987**, *52*, 4287. (f) Taylor, E. C.; Warner, J. C.; Pont, J. L. *J. Org. Chem.* **1988**, *53*, 800. (g) Taylor, E. C.; Pont, J. L.; Warner, J. C. *J. Org. Chem.* **1988**, *53*, 3568. (h) Taylor, E. C.; Pont, J. L.; van Engen, D.; Warner, J. C. *J. Org. Chem.* **1988**, *53*, 5093. (i) Taylor, E. C.; French, L. G. *J. Org. Chem.* **1989**, *54*, 1245. (j) Taylor, E. C.; Macor, J. E. *J. Org. Chem.* **1989**, *54*, 1249. (k) Boger, D. L.; Sakya, S. M. *J. Org. Chem.* **1988**, *53*, 1415. (l) Boger, D. L.; Wysocki, R. J., Jr. *J. Org. Chem.* **1989**, *54*, 714.

(3) For reviews of the inverse electron demand Diels–Alder reaction using azadienes: (a) Boger, D. L. *Tetrahedron* **1983**, *39*, 2869. (b) Boger, D. L. *Chem. Rev.* **1986**, *86*, 781. (c) Boger, D. L.; Weinreb, S. N. *Hetero Diels–Alder Methodology in Organic Synthesis*; Organic Chemistry Monograph Series, Vol. 47; Academic: New York, 1987. (d) Kametani, T.; Hibino, S. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic: New York, 1987; Vol. 42, pp 246–335.

(4) (a) Seitz, G.; Kampchen, T. *Arch. Chem. (Weinheim, Ger.)* **1976**, *309*, 679. (b) Takahashi, M.; Ishida, H.; Kohmoto, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1725. (c) Raasch, M. S. *J. Org. Chem.* **1980**, *45*, 856. (d) Plate, R.; Ottenheijm, H. C. J.; Nivard, R. J. F. *J. Org. Chem.* **1984**, *49*, 540. (e) Omote, Y.; Tomotake, A.; Kashima, C. *Tetrahedron Lett.* **1984**, *25*, 2993. (f) Plate, R.; Hermkens, P. H. H.; Smits, J. M. M.; Ottenheijm, H. C. J. *J. Org. Chem.* **1986**, *51*, 309. (g) Black, D. St. C.; Craig, D. C.; Heine, H. W.; Kumar, N.; Williams, E. A. *Tetrahedron Lett.* **1987**, *28*, 6691. (h) Pinduar, U.; Kim, M. H. *Tetrahedron Lett.* **1988**, *29*, 3927. (i) Backvall, J. E.; Plobeck, N. A.; Juntunen, S. K. *Tetrahedron Lett.* **1989**, *30*, 2589.

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(6) Benson, S. C.; Palabrica, C. A.; Snyder, J. K. *J. Org. Chem.* **1987**, *52*, 4610.

(7) For reviews of 1,2,4-triazine chemistry: (a) Neunhoeffer, H. *Chemistry of 1,2,3-Triazines and 1,2,4-Triazines, Tetrazines, and Pentazines*; The Chemistry of Heterocyclic Compounds Monograph Series, Vol. 33; Wiley-Interscience: New York, 1978; pp 189–1072. (b) Neunhoeffer, H. In *Comprehensive Heterocyclic Chemistry*; Boulton, A. J., McKillop, A., Eds.; Pergamon: Oxford, 1984; Vol. 3, pp 385–456.

(8) For reviews of 1,2-diazine chemistry: (a) Tisler, M.; Stanovnik, B. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Boulton, A. J., Eds.; Academic: New York, 1979; Vol. 24, pp 363–456. (b) Tisler, M.; Stanovnik, B. In *Comprehensive Heterocyclic Chemistry*; Boulton, A. J., McKillop, A., Eds.; Pergamon: Oxford, 1984; Vol. 3, pp 1–56.

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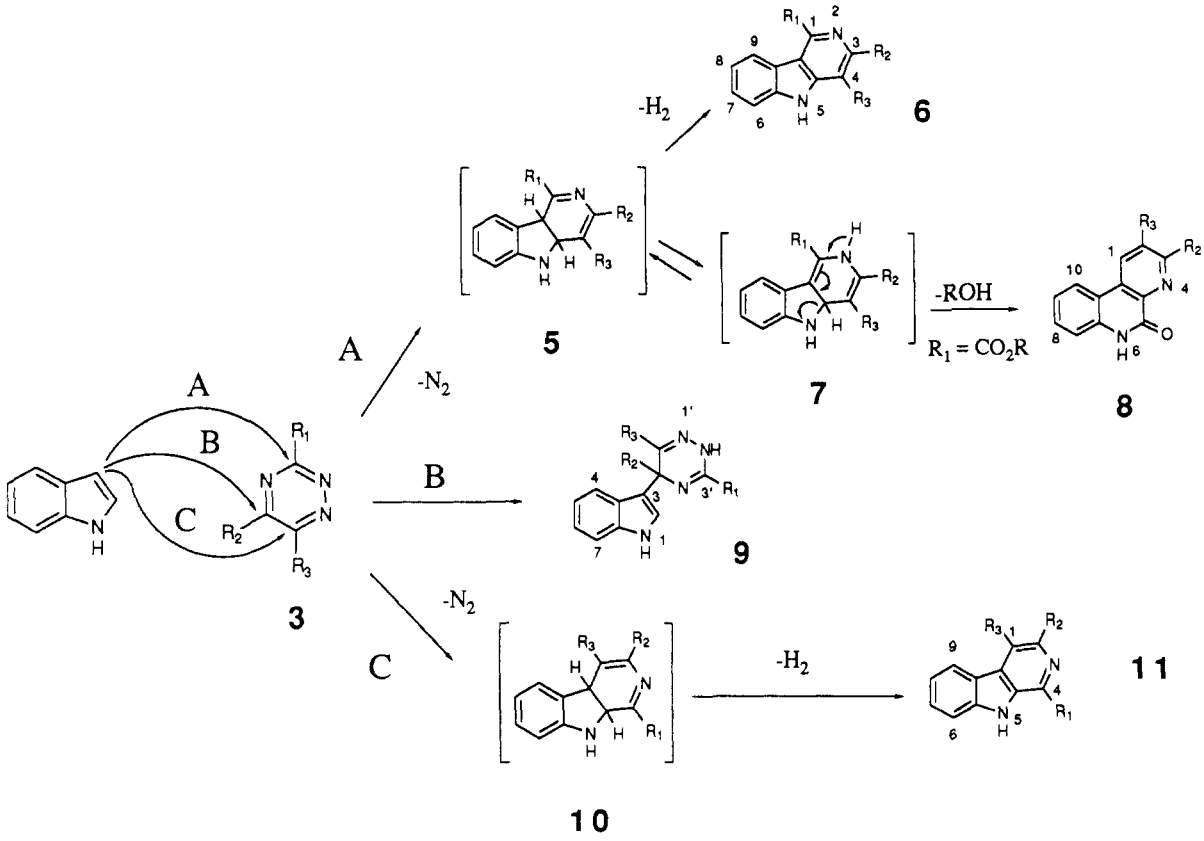
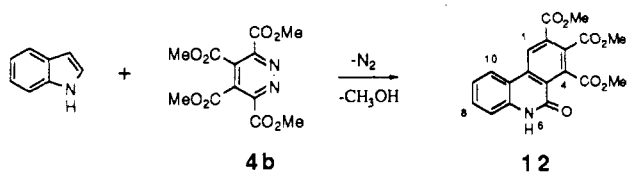
0022-3263/90/1955-3257$02.50/0

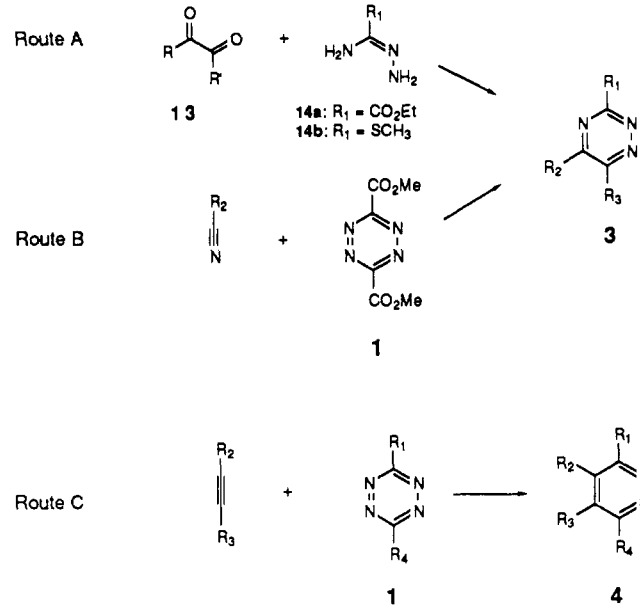
Scheme II



Scheme III



Scheme IV



additions are γ-carbolines and benzo[*f*][1,7]naphthyridines (**6** and **8**, route A) or β-carbolines (**11**, route C). Noncyclized adducts (**9**, route B) were also produced by nucleophilic addition of the indole 3-position to C-5 of the triazine nucleus. The regiochemical course of the reaction and the ratio of products is dependent upon the substituent groups on the triazine ring, as well as the conditions under which the reaction is run.

Indole also undergoes cycloadditions with the electron-deficient tetramethyl 1,2-diazine-3,4,5,6-tetracarboxylate (**4b**) with subsequent rearrangement leading to the phenanthridone **12**, Scheme III. Other 1,2-diazines (**4a** and **4c**) were unreactive toward indole. The reactions with the diazines and triazines may be run in the presence of small amounts of solvent but are greatly retarded by the addition of excess solvent.

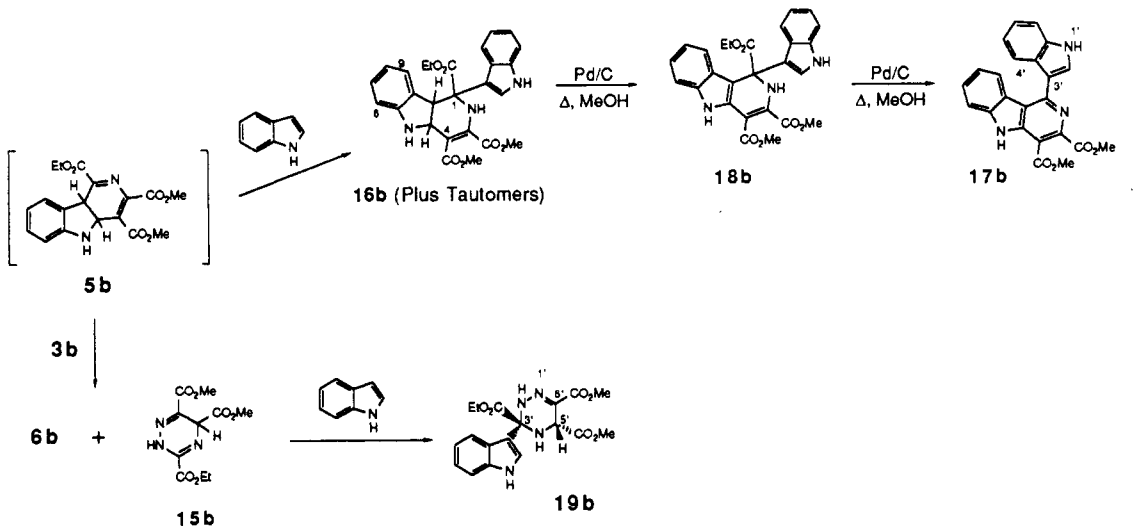
Results

Preparation of 1,2,4-Triazines (3) and 1,2-Diazines (4). The primary route employed to the 1,2,4-triazine skeleton was the condensation of α,β-dioxo compounds (**13**) with ethyl amidrazonate (**14a**) or *S*-methylisothiosemicarbazide (**14b**) (Scheme IV, route A).[7] Thus, triazines **3a–f** were prepared by the condensation of **14a** with the requisite dione according to the procedure of Boger and co-workers.[10,11] Regioisomeric pairs **3c** and **3f** (10.5:1), as well as **3d** and **3k** (34:1), were produced as mixtures in the condensation of **14a** with the α,β-diketones (**13** R = CO_2Et, R′ = CH_3 for **3c** and **3f**; R = C_6H_5, R′ = H for **3d** and **3k**) and subsequently separated to give the pure triazines.

(10) Boger, D. L.; Panek, J. S.; Yasuda, M. *Org. Synth.* **1987**, *66*, 142.

(11) Most of these triazines have appeared in the literature in the past, but with no experimental details concerning their preparation and little or no characterization reported. Consequently, the procedure of Boger et al. (ref 10) on the synthesis of **3a** was adapted for the preparation of most other triazines. For an early report on the preparation of **3a**: (a) Rutz, R.; Schroeder, S. *J. Org. Chem.* **1958**, *23*, 1931. For early reports on the use of amidrazone condensation to prepare 1,2,4-triazines: (b) Neunhoeffer, H.; Hennig, H.; Fruhauf, H.-W.; Mutterer, *Tetrahedron Lett.* **1969**, 3147. (c) Taylor, E. C.; Martin, S. F. *J. Org. Chem.* **1972**, *37*, 3958. For a recent adaptation of this route, see ref 2i.

Scheme V



Dimethyl 3-(methylthio)-1,2,4-triazine-5,6-dicarboxylate, **3g**, was prepared by the condensation of dimethyl 2,3-dioxosuccinate with **14b**.[12] 3-(Methylsulfonyl)-1,2,4-triazine (**3j**)[13] was similarly prepared by the condensation of glyoxal with **14b** to give the (methylthio)triazine, followed by MCPBA oxidation to the sulfone.

The inverse electron demand Diels–Alder cycloaddition of dimethylcyanamide with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (**1**) was utilized to prepare triazine **3h** (Scheme IV, route B).[14] Similarly, the 1,2-diazines (**4b** and **4c**) were prepared by a cycloaddition of the appropriately disubstituted acetylene with **1** (Scheme IV, route C).[15] For example, the cycloaddition of benzyne with **1** gave **4c** in 48% yield.

Reaction of Indole with Trialkyl 1,2,4-Triazine-3,5,6-tricarboxylates (3a and 3b). In preliminary experiments, triazine **3a** reacted with indole (70 °C, 8 h, sealed tube) in the absence of solvent with the initial appearance of a orange red color and subsequent nitrogen evolution, producing **6a** and **8a** as the main products. Confirmation that a cycloaddition had occurred with subsequent aromatization was ascertained by the loss of the signals for the NH, H-2, and H-3 protons of indole, with the appearance of a carboline NH (δ 10.38 vs the indole NH δ ~8 in $CDCl_3$) in the ^1H NMR spectrum of **6a**, and the quinolone NH in the ^1H NMR spectrum of **8a** (δ 12.16), and ultimately by the mass spectra. From the NMR data alone (^1H and ^{13}C) of **6a**, it was difficult to assign the product as either the β- or γ-carboline due to the identity of the alkoxy groups at C-1 and C-4 (both ethoxy). Consequently, triazine **3b** was prepared[16] and reacted with indole under identical conditions. The γ-carboline structure of the major product (**6b**) was then established by the observation of NOE's between the ethoxyl methylene protons (δ 4.61, q, J = 7.2 Hz) and H-9 (δ 8.68, d, J = 8.4 Hz), and between the C-4 methoxyl protons (δ 4.02, s) and H-5 (NH: δ 10.28, bs). Confirmation of **6a** as the γ-carboline was subsequently made by comparison of the ^{13}C NMR spectrum with that of **6b**.

Formation of benzonaphthyridines **8a** and **8b** via rearrangement of the intermediate dihydrocycloadducts, Scheme II, route A, is analogous to the reaction of indole with tetrazines.[4a,6,17] These products were identified by the loss of the ethoxy group originally at the C-3 position of the triazine as detected in the mass spectra and ^1H NMR spectra. In addition, these compounds revealed a characteristically low field, nonexchangeable singlet in the ^1H NMR spectra (**8b**: δ 9.35) which showed strong NOE's to H-10 (**8b**: δ 8.52, d, J = 8.0 Hz), and a quinolone carbonyl in the ^{13}C NMR (**8b**: δ 158.5) and FTIR (**8b**: $\nu_{C=O}$ 1684 cm^{-1}) spectra.

2,5-Dihydrotriazine **15b** was also isolated from the reaction with **3b**. Apparently triazine **3b** is also functioning as the dehydrogenation agent for dihydro intermediate, **5b** (Scheme V). Identification of **15b** as the 2,5-dihydro tautomer was indicated by the appearance of two singlets in the ^1H NMR spectrum (δ 9.69 and 5.62). The lower field broad singlet exchanged immediately upon addition of D_2O, suggesting a nitrogen-bonded proton. The ^{13}C NMR spectrum and an Attached Proton Test (APT) confirmed the presence of an sp^3 methine (δ 55.0) and only two substituted sp^2 carbons (δ 144.1, 131.6) in the triazine ring. Selective INEPT studies revealed enhancements of C-3 (δ 144.1) and a methyl ester carbonyl carbon (δ 167.3) via 3-bond polarization transfer upon saturation of the carbon-bound proton, thus confirming the methine location at C-5. The low field frequency of δ 144.1 (in comparison to the C-6 signal at δ 131.6) can best be accounted for by an sp^2 carbon bonded to two nitrogens. Enhancement of C-6 (δ 131.6) by two-bond polarization transfer was also observed in this experiment. (If the methine was located at either C-3 or C-6, enhancement to only one sp^2 hybridized carbon would have been observed in the selective INEPT experiment.) Confirmation of the enhanced carbonyl as the conjugated methyl ester (rather than the ethyl ester) was confirmed by selective INEPT studies upon

(12) Triazine **3g** has previously appeared in the literature, though without characterization: (a) Seitz, G.; Dietrich, S.; Gorge, L.; Richter, J. *Tetrahedron Lett.* **1986**, *27*, 2747. For the use of *S*-alkylisothiosemicarbazide condensations to prepare 1,2,4-triazines: (b) Paudler, W. W.; Chen, T. K. *J. Heterocycl. Chem.* **1970**, *7*, 767. Also, see ref 2d.

(13) Triazine **3j** has appeared in the literature, but details of its preparation and characterization were not included in that report: (a) Chenard, B. L.; Ronau, R. T.; Schulte, G. K. *J. Org. Chem.* **1988**, *53*, 5175. For original preparation: (b) Macor, J. E. Ph.D. Thesis, Princeton University, 1986.

(14) Seitz, G.; Overheu, W. *Chem. Zeit.* **1979**, *103*, 230.

(15) Preparation of **4b**: (a) Neunhoeffer, H.; Werner, G. *Justus Liebigs Ann. Chem.* **1973**, 437. For other examples of the preparation of 1,2-diazines from the cycloaddition of acetylenes with 1,2,4,5-tetrazines: (b) Carboni, R. A.; Lindsey, R. V. *J. Am. Chem. Soc.* **1959**, *81*, 4342. (c) Seitz, G.; Gorge, L.; Dietrich, S. *Tetrahedron Lett.* **1985**, *26*, 4355. (d) Maggiora, L.; Mertes, M. P. *J. Org. Chem.* **1986**, *51*, 950.

(16) Martin, J. C. *J. Org. Chem.* **1982**, *47*, 3761.

(17) For an earlier report of this type of a rearrangement: Acheson, R. M.; Bridson, J. N.; Cecil, T. R.; Hands, A. R. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1569.

Table I. Optimization Conditions for Cycloaddition of 3b with Indole

conditions	temp, °C	time, h	yield, % cycloadducts[a]	6b	8b	16b	19b	15b
1. neat, O_2, 1.2 equiv of indole	80	48	65	47	9	9	10	22
2. neat, Ar, 1.2 equiv of indole	80	48	74	33	20	21	6	19
3. dioxane (3 equiv), O_2, 1.2 equiv of indole	80	48	61	39	22	0	6	21
4. dioxane (3 equiv), O_2, Pd–C, 1.2 equiv of indole	80	48	66	44	22	0	7	26
5. dioxane (5 equiv), O_2, Pd–C, 1.2 equiv of **3b**	80	18	60	50	8	2	3	28
6. dioxane (5 equiv), O_2, Pd–C, 1.8 equiv **3b**	80	18	91	77	14	0	3	37
7. diglyme (5 equiv), Ar, 1.8 equiv of **3b**	80	16	95	86	9	0	0	73
8. diglyme (5 equiv), Ar, 1.8 equiv of **3b**	120	16	95	89	6	0	0	70
9. diglyme (5 equiv), Ar, 1.8 equiv of **3b**	150	16	97	84	13	0	0	55

[a] Total isolated yields of all products via cycloaddition route A, Schemes II and V.

saturation of the methoxy singlet (δ 3.73). The absence of observable coupling in any solvent between the methine proton and the exchangeable, nitrogen-bound proton supported the 2,5-dihydro structure, but does not unambigously rule out the 4,5-dihydro tautomeric form.[18] It is of interest to note that the methylene protons of the ethoxy group appear as a narrowly separated AB system (δ 4.43 and 4.38, J_{AB} = 10.4 Hz) in the ^{1}H NMR spectrum, though this ester group is not attached to a chiral center.[19] Presumably intramolecular hydrogen bonding between this ester carbonyl oxygen and the 2-NH proton sufficiently restricts rotation to induce magnetic nonequivalence.

In addition to these main products, a diadduct (**16b**) and a tautomerically pure noncyclized monoadduct (**19b**) were also isolated. From the integration of the methoxy singlets and the indole-2′ resonances in the ^{1}H NMR spectrum, **16b** appeared to be a mixture of three tautomeric forms in a 1/1.2/1.4 ratio, which were inseparable despite repeated attempts under numerous chromatographic conditions. The appearance of two mutually coupled, nonexchangeable protons in the ^{1}H NMR spectra (**16b**: δ 5.03 and 4.83, H-4a and H-9b, respectively, $^3J_{4a,9b}$ = 8.6 Hz) with the lower field signal (H-4a) also coupled to the 5-NH proton (**16b**: δ 5.45, bs) indicated that the dihydro bridgehead tautomer was one of the tautomers. A similar diadduct was produced in the reaction of indole with tetrazine **1**, with similar spectral properties.[6] Confirmation of the diadduct structure came from the mass spectrum, which showed a molecular ion at 475.1748 (HRMS: $[M]^+$, calcd for $C_{26}H_{25}N_3O_6$, 475.1743). This compound apparently arises from the nucleophilic addition of a second molecule of indole onto the dihydro intermediate **5b** produced by the cycloaddition after the release of nitrogen, but before dehydrogenation can occur (Scheme V).

Refluxing this tautomeric mixture in methanol in the presence of Pd/C and O_2 produced the fully aromatized γ-carboline **17b**. Using an older, less active supply of Pd/C enabled detection of the dehydrogenated intermediate **18b**, which also could be converted to **17b** by further refluxing. With **17b** in hand, the site of substitution of the second indole addition was confirmed by NOE's. Thus, reciprocal NOE's were observed between H-9 and the H-4′ proton of the C-1 indole substituent, thereby eliminating the remote possibility that a dihydro intermediate on the way to a β-carboline was trapped by a second indole molecule.

The structure of **19b** was initially suggested by the ^{1}H NMR spectrum, revealing resonances typical for a 3-substituted indole (H-2 δ 7.18, d, J = 2.4 Hz; N-H δ 8.33). Two other exchangeable protons were also observed (δ 6.15 and 6.19) along with a nonexchangeable doublet (δ 4.71, J = 2.4). This latter signal, shown to be due to a carbon-bound proton by a HETCOR experiment correlating with a methine carbon at δ 58.6, was coupled to the lower field exchangeable proton. Selective INEPT studies revealed three-bond polarization transfers to a quaternary carbon (C-3′, δ 59.6) and a methyl ester carbonyl carbon (δ 170.5) upon saturation of the methine signal. Enhancement of the second methyl ester carbonyl (δ 169.0) due to two-bond polarization transfers were also observed in this experiment. Thus, the methine must be located at C-5, and the site of indole substitution occurred at C-3′. This was confirmed by three-bond polarization transfers from the N4′-H exchangeable proton to the indole C-3 (δ 112.2), the triazine C-6′ (δ 134.9) and a methyl ester carbonyl (δ 169.0) by a selective INEPT experiment, while no enhancement was observed in the carbonyl resonance at δ 170.5 (four bonds removed from the N-4′ proton).

The stereochemistry was established by the observation of an NOE between the methine proton and the methylene and methyl protons of the ethyl ester group. The ethoxy methylene protons appeared as an AB system in the ^{1}H NMR spectrum (δ 4.34 and 4.32, J_{AB} = 11.2 Hz), due to the attachment of the ester group to a chiral center.

Presumably **19b** arises by the nucleophilic attack of indole at C-3 of **15b** formed in the dehydrogenation of the dihydro intermediate **5b**. In support of this suggestion, **19b** was formed in 91% yield when **15b** and indole were subjected to the identical reaction conditions, Scheme V.

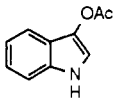
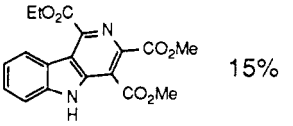
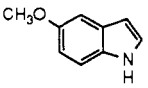
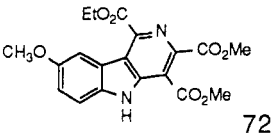
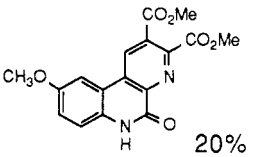
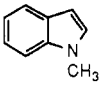
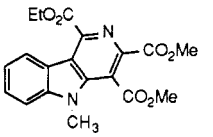
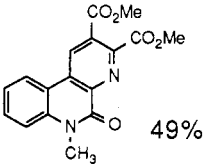
The best conditions for obtaining γ-carboline **6b** (89%) employed small amounts of diglyme (4.5–5 equiv) with 1.8 equiv of triazine (the excess triazine promotes the dehydrogenation). Under these solvated conditions, none of **16b** or **19b** was detected. Increasing amounts of solvent severely slowed the reaction. Using an excess of indole, or only a slight excess of **3b** (rather than 1.8 equiv of **3b**) gave more rearranged products (**8b**), at the expense of the γ-carbolines (**6b**), Table I.

Since an increased rate of dehydrogenation of the dihydro intermediate **5** should increase production of γ-carbolines over the rearrangement pathway, attempts were made to promote the dehydrogenation pathway. The reaction of indole with **3b** in diglyme under argon was compared to the products obtained under oxygen. Little variation in the ratio of products **6b**/**8b** was observed under the different atmospheres when excess **3b** was used, including experiments wherein oxygen was bubbled directly through the reaction medium. Adding Pd/C to the reaction mixture under an oxygen atmosphere also had no effect on the **6b**/**8b** ratio when an excess of triazine (1.8 equiv) was employed. Use of a slight excess of **3b** under an oxygen atmosphere in the presence of Pd/C gave only a slight increase in the **6b**/**8b** ratio, with **15b** still being

(18) The 2,5-dihydro tautomer is the dominant form for most dihydro-1,2,4-triazines: (a) Sasaki, T.; Minamoto, K.; Harada, K. *J. Org. Chem.* **1980**, *45*, 4587. (b) Sasaki, T.; Minamoto, K.; Harada, K. *J. Org. Chem.* **1980**, *45*, 4594. For a report of the 4,5-dihydro tautomer: (c) Daunis, J.; Pigiere, C. *Bull. Chim. Soc. Fr.* **1973**, 2493.

(19) For an example of a similar magnetic nonequivalence of the ethoxy methylene protons of an ethyl ester which is not attached to a chiral center: Plate, R.; Ottenheijm, H. C. J. *Tetrahedron Lett.* **1986**, *27*, 3755.

Table II. Reaction of Indole Derivatives with Triazine 3b

indole derivative	temp, °C	time, h	products[a]
 Neat, Ar 1.8 eq **3b**	120	18	 15%
 Dioxane (5 eq), Ar 1.8 eq **3b**	80	19	 72%  20%
 Dioxane (5 eq), Ar 1.8 eq **3b**	80	19	 42%  49%

[a] Isolated yields.

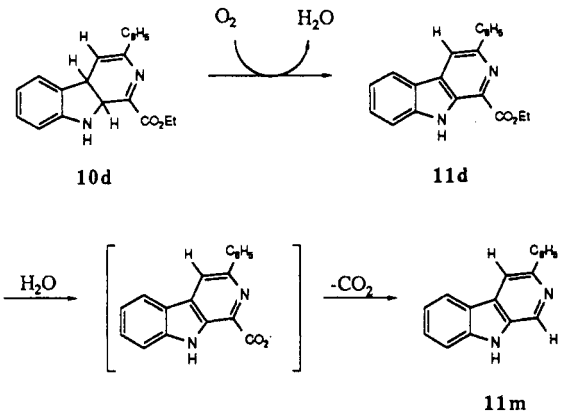
produced and a decrease in the overall yield of cycloadducts. Thus, dehydrogenation of the dihydro intermediate **5b** by the excess triazine is the main route to the γ-carbolines. The importance of the excess triazine in promoting the dehydrogenation of intermediate **5b** is also seen in the lower yields of **6b** and longer reaction times required when indole is used in excess, or only a slight excess of **3b** (1.2 equiv) is employed (compare items 1–5 with 6–9).

In an effort to promote the cycloaddition with the triazines by increasing the energy level of the dienophilic HOMO with electron-donating substituents, the reactions of **3b** with 3-acetoxyindole, 5-methoxyindole, and 1-methylindole were examined, Table II. The reaction with 3-acetoxyindole gave only a poor yield (15%) of γ-carboline **6b**, the only cycloadduct detected, and required neat conditions and relatively high temperature. When solvent was present, no reaction occurred. In contrast, both 5-methoxyindole and 1-methylindole yielded cycloadducts in excellent yields, with the latter reaction producing more rearranged product, **8**.

Reaction of Indole with Other 1,2,4-Triazines. In order to determine whether substituent control could manipulate the regioselectivity of the cycloaddition to produce β-carbolines as the cycloadducts, other triazines were examined, Table III. Most reactions were run in the presence of a small amount of solvent, and all proceeded with the initial appearance of a deep red color and the evolution of nitrogen. Some triazines (**3e–g**) reacted with indole only under neat conditions. γ-Carboline **6c** and quinolone **8c** were identified from the reactions with triazine **3c** by their ^{1}H NMR and ^{13}C NMR spectra. The lower reactivity of **3c** toward indole is illustrated by the higher temperature necessary to optimize the yield via cycloaddition route A.

Only triazine **3d** reacted with indole via more than one pathway, pathways A and C. Thus, rearranged adduct **8d** was isolated along with β-carbolines **11d** and 2-phenyl-β-carboline (**11m**, $R_1 = R_3 = H$, R_2 = phenyl). Quinoline **20** was also consistently obtained in about 20% isolated yield (see Discussion). β-Carboline **11b** was presumed to have been formed by the hydrolysis of the ester in **11d** with subsequent decarboxylation. The hydrolysis may be a consequence of the water produced by the oxygen-promoted dehydrogenation of the dihydro precursor cycloadduct, **10d** (Scheme VI). Indeed, under nonanhydrous conditions, the yield of **11m** increased to 9%. The structure of **11m** was confirmed by hydrolysis of the ester in **11d** (ethanolic KOH), with subsequent decarboxylation of the acid (Cu^0/quinoline) yielding **11m**.

Scheme VI



Scheme VII

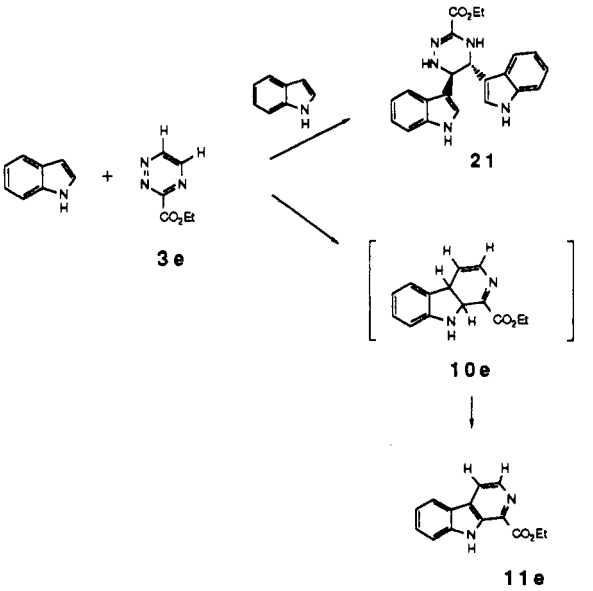
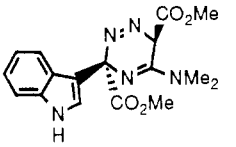


Table III. Cycloadditions of Indole with 1,2,4-Triazines and 1,2-Diazine 4b

azadiene	conditions	cycloadducts,[a] %	pathway:[b] products
3b	diglyme (5.0 equiv), 120 °C, 16 h[c]	95	A: **6b** (89), **8b** (6)
3c	diglyme (4.5 equiv), 120 °C, 20 h[c]	58	A: **6c** (17), **8c** (41)
3d	diglyme (4.5 equiv), 180 °C, 20 h[d]	78	A and C: **8d** (5), **11d** (50), **11l** (2), **20** (21)
3d	wet diglyme (4 equiv), 180 °C, 20 h[d]	74	A and C: **8d** (5), **11d** (37), **11l** (9), **20** (23)
3e	neat, 120 °C, 18 h[e]	15	C: **11e** (15), **21** (13)
3f	neat, 80 °C, 14 h[e]	0	B: **9f** (64)
3g	neat, 110 °C, 14 h[e]	0	B: **9g** (60)
3h	neat 120 °C, 48 h[e]	0	 **23** (16)
4b	diglyme (4.5 equiv), 180 °C, 48 h[d]	41	**12** (41)

[a] Combined, isolated yields of all products from cycloaddition pathways. [b] Refer to Scheme II; isolated yield of each product in parentheses. [c] 1.8 equiv of triazine. [d] 1.5 equiv of triazine or diazine. [e] 1.5 equiv of indole.

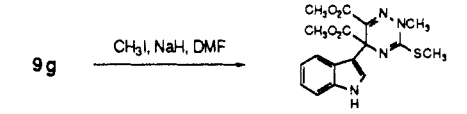
Triazine **3e** gave only poor yields (15%) of β-carboline **11e**, identified by mass spectra and ^1H and ^{13}C NMR spectra, Scheme VII. The regiochemistry of the adduct was established by the observations of NOE's between the H-5 (N-H) proton (δ 11.65, bs) and the methylene group of the ethyl ester (δ 4.48, q, J = 7.2 Hz), and between H-1 (δ 8.39, d, J = 4.8 Hz) and H-9 (δ 8.28, d, J = 8.0 Hz).

The main byproduct from the reaction with **3e** was the noncyclized diadduct, **21** (13%). The mass spectrum was crucial in establishing the diadduct nature of **21**. Thus, the molecular formula, (HRMS, $[M]^+$: 387.1695 $C_{22}H_{21}N_5O_2$) could be accounted for by the addition of two indole nucleophiles to the triazine skeleton. The structure was suggested by the appearance of two indole units in the ^1H and ^{13}C NMR spectra, with both H-2 signals (δ 6.77, d, J = 2.4 Hz, and 6.67, d, J = 2.4 Hz) showing coupling only to the two indole N-H protons (δ 8.31 and 8.21, respectively, both bs). The ^1H NMR spectrum also revealed two other exchangeable protons (δ 5.67 and 5.57, both bs) and two coupled nonexchangeable protons (δ 4.39 and 5.06, both d, J = 7.2 Hz). An APT experiment confirmed the presence of two methine carbons at δ 52.3 and 55.6. A COSY spectrum revealed coupling between one of the triazinyl N-H protons (δ 5.67) and the higher field methine (J = 1.2 Hz), while the lower field methine proton was coupled to the other triazinyl N-H proton (δ 5.57). These observations suggested the contiguous nature of the four protons on the triazine ring, consistent with structure **21**.

Assignment of the triazine C-5′ and C-6′ as the sites of nucleophilic addition initially suggested by vicinal coupling between the methine protons was confirmed by selective INEPT studies. Thus, saturation of each of the methines resulted in enhancements of the geminal indole C-2 (δ 125.2 from 5.06, and δ 126.2 from 4.39) and the vicinal indole C-3 (δ 112.6 from 4.39, and δ 113.6 from 5.06) carbons via three-bond polarization transfers, respectively. Two-bond polarization transfers to the geminal indole C-3 carbons were also observed in these experiments. These studies also confirmed that one of the methines (δ 5.06) was three bonds removed from the triazinyl sp^2 carbon (δ 137.0). Thus the indole nucleophiles must have added to vicinal sites, C-5′ and C-6′, on the triazine. The coupling constant between H-5′ and H-6′ of 7.2 Hz supports a trans orientation of the two indole substituents, as one would expect on the basis of steric reasoning for the addition of two indole units to vicinal sites.

The reactions with triazines **3f** and **3g** differed from those of **3a–e** in that the noncyclized adducts **9f** and **9g** were isolated as the main products (Scheme II). The "survival" of the original indole H-2 proton in the ^1H NMR spectrum (**9f**: δ 6.95, d, J = 2.4 Hz. **9g**: δ 7.00, d, J = 2.4 Hz) of these adducts, coupled only to the indole N-H protons (**9f**: δ 8.53, bs in $CDCl_3$. **9g**: δ 11.04, bs in DMSO-d_6) indicated the noncyclized structure of the adducts, further supported by the molecular formula established by the high-resolution mass spectra. The ^1H NMR spectra also revealed a second exchangeable proton signal (**9f**: δ 9.21, bs in $CDCl_3$. **9g**: δ 11.69, bs in DMSO-d_6) due to an N-H group on the triazine ring. The ^{13}C NMR studies revealed in addition to the indole carbons, two sp^2 carbons and a quaternary sp^3 carbon for both adducts.

Scheme VIII

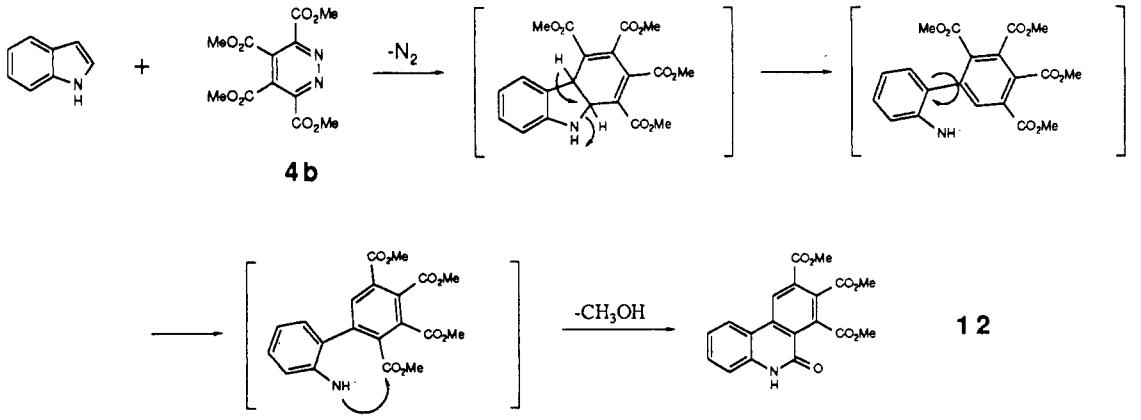


22

The site of the nucleophilic addition to the C-5 position of the triazine nucleus was established by detailed selective INEPT experiments. Thus, for **9f**, the chemical shift of δ 1.97 for the triazine ring methyl substituent strongly suggests that this group be bonded to an sp^2 carbon, thus eliminating C-6′ as the site of substitution. Enhancement of the quaternary carbon (δ 64.2) upon saturation of either this methyl or the indole H-2 resonance via three-bond polarization transfer confirms the site of indole substitution as C-5′ on the triazine ring. Enhancement of the sp^2 carbon at δ 144.4 via two-bond polarization transfer was also observed during the former experiment. The 2′,5′-dihydro tautomeric structure was supported by selective INEPT studies. Thus, polarization transfer from the triazine NH were observed to the sp^2 carbons at δ 144.4 and 144.3, but not to the quaternary carbon nor the indole C-3. (These results, however do not unambiguously rule out the 4′,5′-dihydro tautomeric structure.) As observed with **15b** and **19b**, the methylene protons of the ethoxy group attached to C-5 formed an AB system in the ^1H NMR spectrum (δ 4.27, and 4.26, J_{AB} = 11.0 Hz), while the methylene protons of the ethoxy group at C-3 were magnetically equivalent (δ 4.33).

The structure of noncyclized adduct **9g** was established by analogous methods. Selective INEPT enhancement of the resonance at δ 151.3 upon polarization transfer from the S-methyl resonance (δ 2.31) requires this substituent to be bonded to an sp^2 carbon, while polarization transfer from the indole H-2 proton to the quaternary carbon, δ 61.4, confirms this carbon as the site of indole addition. Thus, substitution must have occurred either at C-5′ or C-6′. Methyl iodide monomethylation[18] of **9g** yielded **22**, Scheme VIII, the N-2′ site supported as the location of the

Scheme IX



N-methyl group by selective INEPT enhancement of the C-3′ resonance (δ 153.4), and an NOE enhancement of the *S*-methyl resonance upon saturation of the *N*-methyl singlet (δ 3.48). No enhancement of the C-5′ resonance was observed, as should have been the case if methylation had occurred at N-4′. The site of the indole substitution was thus established as C-5′ since a C-6′ substitution would only allow for the location of the N-H (and hence the N-methylation site) at N-1′.

While this data confirms the C-5′ site of the indole addition, it does not identify the tautomeric form of the original adduct. Methylation at N-2′ could be argued to proceed from a less populated but more reactive N-2′,C-5′-dihydro structure. The close correspondance of the ^{13}C chemical shifts of the triazine carbons of **9g** and **22** suggests that this is not the case. This assumption is further supported by the inability to observe an enhancement of either the indole C-3 carbon or the methyl ester carbonyl carbon attached to the quaternary center upon saturation of the N-H resonance in the selective INEPT studies on **9g**. Though a dihedral angle of 90° may account for the reduced coupling between the N–H proton and one of these two carbons, such a conformation should enable coupling to the other carbon to be observable by selective INEPT. Enhancements in these studies were observed only to C-3′ and C-6′.

The reaction of the 5-(dimethylamino)triazine **3h** required high temperatures and was therefore accompanied by a significant amount of intractable decomposition material. A 16% yield of the noncyclized 3-position adduct **23** was obtained (Table III), however, and its structure was confirmed by NMR analysis. The *N*-methyl resonances appeared as two broadened singlets in the ^1H NMR spectrum (δ 3.02 and 2.85), but the ^{13}C NMR spectrum at ambient temperature showed only a single resonance (δ 36.5) for the *N*-methyl groups, suggesting that the hindered rotation observed in the ^1H NMR spectrum could be easily overcome by mild heating. Indeed, the methyl resonances coalesced into a broad singlet at 50 °C. The nonequivalence of the *N*-methyl groups in the ^1H NMR spectrum at ambient temperature suggested that the C-5 carbon of the triazine was sp^2 hybridized. This was confirmed by selective INEPT studies: enhancement of the signal at δ 140.7 upon polarization transfer from the coalesced *N*-methyl singlet (60 °C).

Assignment of the triazine C-3 position as the site of indole addition was further supported by the appearance of a quaternary carbon originating from the triazine skeleton at δ 105.9. Such a low field shift can only be accounted for by a carbon bonded to two sp^2 nitrogens (compare with the shifts of the triazine C-5 in **9f**, δ 64.2, and **9g**, δ 61.4, and those of diadduct **21** C-5, 52.3; C-6, 55.6). Confirmation of this resonance as that belonging to the site of indole attachment was obtained by a selective INEPT experiment which showed three-bond polarization transfer from the indole H-2 proton. The appearance of a nonexchangeable proton singlet (δ 5.58) and a methine carbon at δ 46.1 established the 1,4-dihydro nature of the dihydrotriazine unit. The methyl resonance of the ester group at C-3 appeared as a strongly shielded singlet in the ^1H NMR spectrum (δ 2.90) and was also strongly shielded in the ^{13}C NMR spectrum (δ 41.5). This shielding in both the ^1H and ^{13}C NMR spectra is presumably due to the location of the C-3 methyl ester group immediately above the indole benzenoid ring. Such shielding was not observed in the C-5 adducts **9f** and **9g**.

Triazine **3i** with two electron-donating methyl groups did not react with indole even after 48 h at 150 °C under neat conditions. Increasing the temperature to 210 °C caused slow decomposition of **3i** with no trace of adduct with indole. Triazines **3j** and **3k** decomposed prior to affecting cycloadditions with indole (**3j**, 70 °C and 100 °C; **3k**, 190 °C).

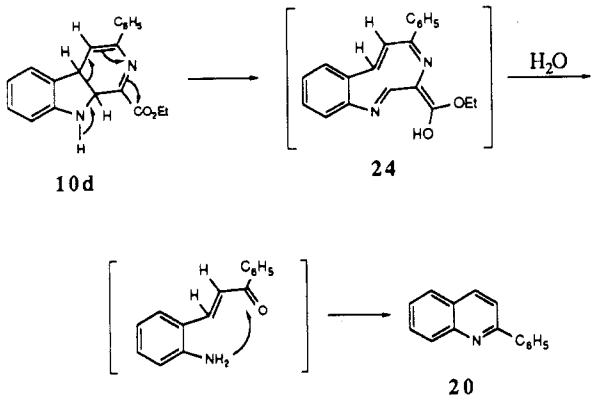
Reaction of Indole with 1,2-Diazines (4). With conditions optimized for the reaction of indole with 1,2,4-triazines, the reaction with 1,2-diazines was briefly reexamined.[6] 3,6-Dichloro-1,2-diazine (**4a**) and dimethyl 2,3-diazanaphthalene-1,4-dicarboxylate (**4c**) did not react with indole under any conditions. Increasingly elevated temperatures led to decomposition of the diazines. Tetramethyl 1,2-diazine-3,4,5,6-tetracarboxylate (**4b**) did undergo a cycloaddition with subsequent rearrangement of the dihydro intermediate to produce phenanthridone **12** in 41% yield (Scheme IX). The rearranged structure **12** was suggested by the presence of the quinolone carbonyl (IR 1670 cm^{-1}; ^{13}C NMR δ 158.6) and confirmed by the mass spectrum and ^1H NMR spectrum (low field N-H proton δ 12.05; low field aromatic singlet δ 8.95; loss of a methoxyl resonance). These observations were similar to those made for the rearranged products, 8, obtained in the reactions with the triazines.

Discussion

These results clearly demonstrated that indole participates in cycloaddition reactions with 1,2,4-triazines, yielding cycloadducts by two regiochemical pathways and a noncyclized adduct by a third route. The observed regioselectivity can be rationalized by a highly nonsynchronous cycloaddition mechanism or by a stepwise, cyclocondensation route.[20] The site of the initial nucleophilic addition of indole on the triazine skeleton is thus controlled

(20) Dewar, M. J. S.; Olivella, S.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1986**, *108*, 5771.

Scheme X



primarily by the relative electrophilicities of C-3, C-5, and C-6 of the triazine nucleus, and by delocalization of the developing negative charge in the transition state for nucleophilic addition.

For triazines **3a–c**, this site is C-3, which is not only electrophilic, but also produces a transition state in which the developing negative charge can be stabilized by delocalization into the C-6 ester substituent. Exclusive regioselectivity via route A led to excellent yields of γ-carbolines **6a** and **6b** in the reactions with **3a** and **3b** in close parallel to the regioselectivity observed in the reactions of tricarboalkoxy-1,2,4-triazines with enamines.[21] This exclusive regioselectivity contrasts with the mixture of regioisomers obtained in the cycloadditions of tricarboalkoxy-1,2,4-triazines with substituted acetylenes[16,22] and ketene acetal derivatives.[23]

The observation that 3-acetoxyindole gave a lower yield of cycloadducts with **3a** and at a slower rate than indole also supports a stepwise or highly nonsynchronous mechanism. The oxygen substitution at C-3 of the indole nucleus should lower the nucleophilicity of the C-3 position by simple resonance arguments but raise the HOMO energy. This electron-donating substitution would thus be expected to enhance a cycloaddition but retard a stepwise mechanism initiated by the nucleophilicity of the indole C-3 position.[24] In contrast, 5-methoxyindole and 1-methylindole would be expected to react at least as readily as indole with **3a** by the stepwise pathway, as was observed.[4i] Further evidence for a stepwise pathway is seen in the production of noncyclized adduct **23** in the reaction with the (dimethylamino)triazine **3h**.

When stabilization of the developing negative charge in the transition state onto the C-6 substituent is impossible, initial bond formation may occur at C-6 (triazines **3d** and **3e**) or C-5 (triazines **3f** and **3g**).[25] In the former cases, transition-state resonance to the triazine C-3 substituents stabilize initial C-6 attack leading to β-carbolines, while in the latter cases, electron-donating groups at C-3 or C-6 of the triazine divert the initial indole approach to the triazine C-5 site. Triazine **3d** also reacted to produce small amounts of rearranged product, **8d**, via the C-3/C-6 cycloaddition route, Scheme II, as well as 2-phenylquinoline, **20**. Quinoline **20** is presumably also formed via the C-3/C-6 cycloaddition pathway through the ring-opened diimine **24** (Scheme X). Hydrolysis of **24** either during workup or by water produced from the dehydrogenation of dihydro intemediate **10d** with subsequent ring closure would give **20**.

With this rationale of regioselectivity in mind, it was anticipated that triazines **3e**, **3f**, and **3j** would lead directly to β-carbolines via the C-6/C-3 cyclocondensation route. Indeed, **3j** has been reported to undergo cycloadditions with enamines in the correct regiochemical fashion to anticipate a β-carboline in its reaction with indole.[13a] Triazine **3e** has also been shown to participate in inverse electron demand Diels–Alder reactions with ketene acetals and related derivatives, but with a regioselectivity that is more variable.[23,26]

The low yields of β-carbolines in the reaction with **3e** (15%), and the absence of β-carbolines in the reactions with **3f** and **3j**, were therefore disappointing. The production of noncyclized diadduct **21** in the reaction with **3e** could proceed with initial addition of indole to either C-6 or C-5. The absence of noncyclized monoadducts with the addition occurring at C-5 (as in the reaction with **3f** and **3g**), as well as the production (albeit in poor yield) of β-carboline **11e** via the C-6/C-3 pathway, suggested that addition of indole to the C-6 site may occur first. If this is correct, then addition of a second molecule of indole to C-5 successfully competes with cyclization, limiting the yield of β-carboline. All attempts to vary the reaction conditions to eliminate this shunt, including dilution and varying the **3e**/indole ratio, failed to improve the yield of **11e**. At lower temperatures, no reaction ensued; further increase in temperature above the optimal conditions led to a decomposition of **3e**.

A more plausible explanation would be that indole addition to C-6 proceeds entirely to **11e**, but nucleophilic addition to C-5 as the initial step competes with the C-6/C-3 cyclocondensation route, with this C-5 adduct proceeding immediately to diadduct **21**. Nucleophilic additions to 1,2,4-triazines are known to add to C-5, barring any prohibitive substituent effects,[7,27] in accord with the greater stability of the negatively charged σ-adduct.[28] Nucleophilic addition at C-6 has been argued to be the least favorable of the regiochemical pathways for nucleophilic addition to a 1,2,4-triazine nucleus.[27,28] While in these literature examples the C-5 monoadduct was isolable, the unsubstituted C-6 position of the monoadduct formed from **3e** may simply be more susceptible to nucleophilic addition. Nonetheless, the sequence of addition of the indole nucleophiles in the formation of **21** remains ambiguous.

For triazine **3f**, the more electrophilic C-5 site apparently dominates over C-6 attack even though this latter route

(21) (a) Boger, D. L.; Panek, J. S. *J. Org. Chem.* **1982**, *47*, 3763. (b) Boger, D. L.; Panek, J. S. *J. Am. Chem. Soc.* **1985**, *107*, 5745. (c) Boger, D. L.; Duff, S. B.; Panek, J. S.; Yasuda, M. *J. Org. Chem.* **1985**, *50*, 5782.

(22) (a) Reim, H.; Steigel, A.; Sauer, J. *Tetrahedron Lett.* **1975**, 2901. Control of regioselectivity in the reaction of acetylenes with 1,2,4-triazines has been achieved by tethering the dienophile to the triazine ring. For example, see ref 2d,f–h, 12a, and 15.

(23) (a) Burg, B.; Dittmar, W.; Reim, H.; Steigel, A.; Sauer, J. *Tetrahedron Lett.* **1975**, 2897. (b) Muller, K.; Sauer, J. *Tetrahedron Lett.* **1984**, *25*, 2541.

(24) Similarly, the reaction of 3-acetoxyindole with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate is dramatically slower than the reaction of unsubstituted indole and giving markedly lower yields of cycloadducts: Benson, S. C.; Snyder, J. K. Unpublished results.

(25) For related examples, see ref 23, also: (a) Neunhoeffer, H.; Fruhauf, H. W. *Justus Liebigs Ann. Chem.* **1972**, *758*, 120. (b) Neunhoeffer, H.; Bachmann, M. *Justus Liebigs Ann. Chem.* **1985**, 1263.

(26) Gruseck, U.; Heuschmann, M. *Tetrahedron Lett.* **1987**, *28*, 6027.

(27) For some recent examples since reviews in ref 7: (a) Neunhoeffer, H.; Bachmann, M. *Justus Liebigs Ann. Chem.* **1985**, 1263. (b) Konno, S.; Ohba, S.; Sagi, M.; Yamanaka, H. *Chem. Pharm. Bull.* **1987**, *35*, 1378. (c) Konno, S.; Sagi, M.; Yoshida, N.; Yamanaka, H. *Heterocycles* **1987**, *26*, 3111. (d) Rykowski, A.; Makosza, M. *Justus Liebigs Ann. Chem.* **1988**, 627. (e) Konno, S.; Sagi, M.; Takahara, E.; Fujimura, S.; Hagashi, K.; Yamanaka, H. *Chem. Pharm. Bull.* **1988**, *36*, 1721.

(28) (a) Shepherd, R. G.; Fedrick, J. L. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic: New York, 1965; Vol. 4, pp 145–423. (b) Piskala, A.; Gut, J.; Sorm, F. *Collect. Czech. Chem. Commun.* **1975**, *40*, 2680. (c) Piskala, A.; Sorm, F. *Collect. Czech. Chem. Commun.* **1976**, *41*, 465.

would provide resonance stabilization to the C-3 carbomethoxy substituent. The methyl substituent at C-6 may block attack at this position. In a similar manner, the C-5 methyl group of the regioisomer **3c** blocked nucleophilic addition to C-5, yielding products only by the C-6/C-3 cycloaddition route.

Formation of the noncyclized adducts **9** via pathway B from the reactions with triazines **3f** and **3g** can be viewed as initial steps of a stepwise route across the N-2,C-5 azadiene system that failed to cyclize. Such N-2/C-5 cycloadditions, which have been reported for ynamines with 1,2,4-triazines,[23a,29] are thought to proceed by a stepwise mechanism.[2g,3c]

In order to deflect indole away from C-5 and hopefully back to the C-6/C-3 cycloaddition route, the dimethyltriazine **3i** was prepared. Unfortunately **3i** did not react with indole under any conditions.[31] The second electron-donating methyl group (compared to **3c** and **3f**) presumably prevents indole attack at C-5 and C-6. These sites are not as electrophlic as in the other triazines examined, and the methyl groups may also exert some steric hindrance to the approach of indole. Furthermore, the methyl group at C-6 also inhibits attack at C-3 since the cycloaddition transition state is no longer stabilized by a C-6 substituent.

Attempts were also undertaken to divert the reaction of triazine **3g** to the C-6/C-3 cycloaddition route by generating a sulfone substituent at C-3 which would stabilize the developing negative charge formed by initial attack of indole at C-6. Though numerous attempts were made to oxidize the thiomethyl group of **3g** to a sulfone moiety, all efforts failed due to the apparent dominance of ring oxidation.[30]

With the regiochemistry of the indole addition to triazines controlled by the triazine substituents, the remaining point of product partitioning that must be controlled is the dihydro intermediate on route A, Scheme II. The rearrangement to the benzonaphthyridines 8 is analogous to the reaction observed with the tetrazine adducts.[4a,6,17] The initially formed 1,2-dihydro adduct may tautomerize to the 1,4-dihydro form, Scheme II, with subsequent opening of the pyrrole ring followed by nucleophilic attack of the amide anion on the carboalkoxy group. The rearrangement may also proceed directly from the 1,2-dihydro form, as illustrated for the diazine adduct in Scheme IX. Comparison of the product ratios obtained in the reaction of indole with **3b** indicate that reaction conditions which facilitate dehydrogenation (excess **3b**) favor **6b** at the expense of **8b**.

Dihydro triazines **15a** and **15b** were the only hydrogenated triazines detected in this work. Either the other triazines are ineffective dehydrogenating agents, or their reduced, dihydro products are themselves rapidly dehydrogenated by other agents such as oxygen. It is also possible that the higher temperatures required to promote the reactions between indole and the other triazines leads to decomposition of the dihydrotriazines. In support of this latter explanation, the isolated yield of **15b** decreased with increasing temperature of the reaction, Table I. Furthermore, in a control experiment, **15b** slowly decomposed under the experimental conditions at 150 °C.

As expected, indole was much less reactive with 1,2-diazines in cycloadditions than with the 1,2,4-triazines. Inverse electron demand Diels–Alder reactions of 1,2-diazines are much less common and presumably are only successful with very electron rich dienophiles[32] or in an intramolecular mode.[33] Of the three diazines examined in this work, only **4b** underwent a cycloaddition with indole, and only at elevated temperatures to yield the rearranged product **12**. This same compound was reported by Acheson and co-workers in the reaction of indole with dimethyl acetylenedicarboxylate by a similar route.[17]

Summary

Indole undergoes cyclocondensation reactions with 1,2,4-triazines to produce γ-carbolines (**6**), pyridino-2-quinolones (**8**), β-carbolines (**11**), or noncyclized monoadducts (**9**). The formation of these products depends upon the dominance of one of three major routes of reactivity, Scheme II, as controlled by the substituents on the triazines. The diversion of the dihydro intermediate formed in route A, Scheme II, from the dehydrogenation to yield **6**, to rearrangement to give **8** can be minimized by using an excess of triazine.

With the understanding of the factors which control the regioselectivity of the reaction, entry into the γ-carboline or benzo[*f*][1,7]naphthyridine skeletons can be accomplished in good yield. Thus, γ-carboline **6b** was produced in 89% yield, and *N*-methyl **8b** in 49% yield in the reactions of **3b** with indole and *N*-methylindole, respectively. Indeed, this simple cycloaddition route to γ-carbolines, whose members include the potent hepatocarcinogens isolated from tryptophan pyrolysates, 1-methyl-3-amino-γ-carboline and 1,4-dimethyl-3-amino-γ-carboline,[34] compares very favorably with previously reported methods.[35] The best yield of the β-carboline skeleton obtained in this work was 50% in the reaction with **3d**. We are currently working to adapt this chemistry to the synthesis of the canthinone alkaloids.

Experimental Section

General Methods. ^1H and ^{13}C NMR spectra were recorded on a Varian XL-400 spectrometer (93.94 kG, 400 MHz for ^1H, 100 MHz for ^{13}C). The δ 7.25 resonance of residual $CHCl_3$, δ 2.49 for CHD_2SOCD_3, δ 2.04 for CHD_2COCD_3, and the δ 77.0 resonance of $^{13}CDCl_3$, δ 39.5 for $^{13}CD_3SOCD_3$, were used as internal references for ^1H and ^{13}C, respectively. Coupling constants of multiplets

(29) (a) Neunhoeffer, H.; Fruhauf, H. W. *Tetrahedron Lett.* **1970**, 3355. (b) Steigel, A.; Sauer, J. *Tetrahedron Lett.* **1970**, 3357. (c) Neunhoeffer, H.; Fruhauf, H. W. *J. Liebigs Ann. Chem.* **1972**, *758*, 125. (d) Neunhoeffer, H.; Lehmann, B. *Justus Liebigs Ann. Chem.* **1977**, 1413. Ynamines have also been reported to add on C-3/C-6 fashion with 3-substituted 1,2,4-triazines: (e) Neunhoeffer, H.; Fruhauf, H. W. *Tetrahedron Lett.* **1969**, 3151. Tethering an acetylene to the C-5 position of a 1,2,4-triazines can also force a C-5/N-2 cycloaddition: ref 2e.

(30) Difficulty in the oxidation of a sulfur tether directly attached to a 1,2,4-triazine ring have also been discussed by Taylor and co-workers who point out that displacement of the sulfoxide after oxidation may also interfere, ref 2j.

(31) 5-Methyl-1,2,4-triazines are prone to deprotonation, ref **2b**, also: (a) Neunhoeffer, H.; Frey, G. *Justus Liebigs Ann. Chem.* **1973**, 1963. (b) Oeser, E. *Justus Liebigs Ann. Chem.* **1973**, 1970. Triazine **3i** proved to be stable in the presence of indole even at 150 °C, so it is unlikely that the lack of reaction products is due to deprotonation.

(32) Neunhoeffer, H.; Werner, G. *Justus Liebigs Ann. Chem.* **1973**, 1955.

(33) See ref 2a and 3k, also: Boger, D. L.; Coleman, R. S. *J. Org. Chem.* **1986**, *51*, 3250.

(34) Hashimoto, Y.; Shudo, K.; Okamoto, T. *Chem. Pharm. Bull.* **1979**, *27*, 1058. (b) Hashimoto, Y.; Shudo, K.; Okamoto, T. *Biochem. Biophys. Res. Commun.* **1980**, *96*, 355. (c) Watanabe, J.; Kawajiri, K.; Yonekawa, H.; Nagao, M.; Tagashira, Y. *Biochem. Biophys. Res. Commun.* **1982**, *104*, 193.

(35) (a) Robinson, R.; Thornley, S. *J. Chem. Soc.* **1924**, *125*, 2169. (b) Smith, P. A. S.; Boyer, J. H. *J. Am. Chem. Soc.* **1951**, *73*, 2626. (c) Mann, F. G.; Prior, A. F.; Willcox, T. J. *J. Chem. Soc.* **1953**, 3830. (d) Dalton, L. K.; Demerac, S.; Teitei, T. *Aust. J. Chem.* **1969**, *22*, 185. (e) Ducrocq, C.; Civier, A.; Andre-Luoisfort, J.; Bisagni, E. *J. Heterocycl. Chem.* **1975**, *12*, 963. (f) Takeda, K.; Shudo, K.; Okamoto, T.; Kosage, T. *Chem. Pharm. Bull.* **1981**, *29*, 1280. (g) Lee, C. H.; Ohta, T.; Shuda, K.; Okamoto, T. *Heterocycles* **1981**, *16*, 1081. (h) Nguyen, C. H.; Bisagni, E. *Tetrahedron* **1987**, *43*, 527.

were assigned by extensive decoupling experiments. All pulse sequences were run using standard Varian software, version 6.1C. Selective INEPT spectra were recorded with the excitation and refocusing delays optimized for different coupling constants according to the formula $\Delta_1 = {}^1/_2J$ and $\Delta_2 = {}^1/_3J$, respectively,[36] with initial experiments optimized for ${}^3J_{^{13}C,^1H} = 7$ Hz. Infrared spectra were recorded on a Perkin-Elmer 1800 FTIR or a Perkin-Elmer 1300 spectrophotometer; mass spectra were recorded on a Finnigan MAT-90 (70 eV for EI). Centrifugal TLC was run on a Chromatotron (Harrison Research). Indole, 5-methoxyindole, phenyl glyoxal monohydrate, trimeric glyoxal dihydrate, 2,3-butanedione, and 3,6-dichloro-1,2-diazine (**4a**) were used as received (Aldrich). Dimethyl dioxosuccinate,[37] ethyl 2-oxoacetoacetonate,[38] *S*-methyl isothiosemicarbazide,[39] *N*-methylindole,[40] dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (**1**),[41] triethyl 1,2,4-triazine-3,5,6-tricarboxylate (**3a**)[10] and 3-carbethoxy-5,6-dicarbomethoxy-1,2,4-triazine (**3b**)[16] were prepared according to literature procedures. Other reagents were commercially available. All compounds were shown to be >95% pure by ^{1}H NMR spectroscopy.

Ethyl Oxalamidrazonate (14a).[10] The literature procedure was followed with the slight modification of stirring the anhydrous hydrazine with the ethyl thioamidooxalate for only 1 h (rather than 3 h) and maintaining an argon atmosphere above **14a** immediately after removal of the solvent. Under these conditions, **14a** was obtained as a white solid in quantitative yield and was used directly without further purification.

General Procedure A. Triazine Preparation via Condensation of Ethyl Oxalamidrazonate with Diones. The general procedure followed was that used by Boger et al. in the preparation of **3a**.[10] Ethyl oxalamidrazonate was suspended in anhydrous ethanol (50 mL/7.5 mmol) under argon with gentle heating. This suspension was then added dropwise with stirring to a solution of the dione (1 equiv unless otherwise noted) in anhydrous ethanol (50 mL/7.5 mmol) also under argon at room temperature. After completion of the addition, stirring was continued at room temperature for 16 h, and the mixture was subsequently refluxed for 1 h. The solvent was removed in vacuo, and the crude product was purified by flash chromatography on silica gel.

General Procedure B. Reaction of Indole with 1,2,4-Triazines and 1,2-Diazines. Indole (50 mg, 0.43 mmol), triazine or diazine, and the anhydrous solvent in the appropriate amounts were placed in a reaction vessel consisting of a Pyrex glass tube (5 mm i.d. × 150 mm) sealed at one end. The vessel was capped with a septum and purged with argon. A balloon filled with argon on a syringe needle was inserted through the septum to maintain an argon atmosphere without allowing pressure build up during the reaction. The vessel was then placed in a sand bath preequilibrated to the desired temperature. For exact conditions of time, temperature, solvent, atmosphere, and equivalents of triazine or diazine, refer to Tables I–III. After the reaction, the mixture was directly subjected to flash chromatography on silica gel, with final purification of the products by centrifugal TLC. For isolated yields, refer to Tables I–III; products are given in order of elution.

Diethyl 5-Methyl-1,2,4-triazine-3,6-dicarboxylate (3c) and Diethyl 6-Methyl-1,2,4-triazine-3,5-dicarboxylate (3f). Prepared from ethyl 2-oxoacetoacetonate (1.08 g, 7.5 mmol) according to general procedure A to give a mixture of **3c** and **3f** (46% combined yield, 10.5:1, **3c**:**3f**) which were separated by flash chromatography (CH_2Cl_2). **Diethyl 5-methyl-1,2,4-triazine-3,6-dicarboxylate (3c)**:[42] yellow solid (0.76 g, 42% yield); mp 91–93 °C; IR 3015, 2950, 1750, 1725, 1500, 1420, 1350, 1275, 1220, 1185, 1050 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.61 (q, J = 7.2 Hz, 2 H), 4.57 (q, J = 7.2 Hz, 2 H), 2.91 (s, 3 H), 1.50 (t, J = 7.2 Hz, 3 H), 1.49 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.2, 162.0, 160.9, 156.2, 151.5, 63.5, 63.2, 22.7, 14.1 (2 C); LRMS (EI, 70 eV) m/z 240 ([M + 1]$^+$, 18), 239 (M$^+$, 23), 221 (17), 195 (20), 194 (33), 167 (23), 110 (100); HRMS (EI, 70 eV) m/z 239.0889 (M$^+$, calcd for $C_{10}H_{13}N_3O_4$, 239.0906). **Diethyl 6-methyl-1,2,4-triazine-3,5-dicarboxylate (3f)** (0.072 g, 4% yield): yellow oil; IR (NaCl) 2975, 1740, 1375, 1255, 1122, 1015 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.59 (q, J = 7.2 Hz, 2 H), 4.51 (q, J = 7.2 Hz, 2 H), 3.02 (s, 3 H), 1.48 (t, J = 7.2 Hz, 3 H), 1.45 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.4, 162.0, 158.3, 155.5, 147.6, 63.5, 63.4, 20.5, 14.2, 14.1; LRMS (EI, 70 eV) m/z 239 (M$^+$, 6), 167 (12), 67 (30), 61 (100), 43 (70); HRMS (EI, 70 eV) m/z 239.0891 (M$^+$, calcd for $C_{10}H_{13}N_3O_4$, 239.0906).

Ethyl 5-Phenyl-1,2,4-triazine-3-carboxylate (3d) and Ethyl 6-Phenyl-1,2,4-triazine-3-carboxylate (3k).[43] Prepared from phenyl glyoxal monohydrate (1.14 g, 7.5 mmol) according to general procedure A to give a mixture of **3d** and **3k** (87% combined yield, 34:1, **3d**:**3k** from ^{1}H NMR) which were separated by flash chromatography (CH_2Cl_2–ethyl acetate, 9:1). **Ethyl 5-phenyl-1,2,4-triazine-3-carboxylate (3d)**: yellow solid (1.44 g, 84% yield): mp 83–84 °C; IR (KBr) 3060, 2980, 1735, 1535, 1500, 1310, 1220, 1155, 1050 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.78 (s, 1 H), 8.26 (d, J = 7.2 Hz, 2 H), 7.64–7.55 (m, 3 H), 4.59 (q, J = 7.2 Hz, 2 H), 1.49 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.6, 156.7, 156.0, 146.8, 133.1, 132.2, 129.4 (2C), 127.9 (2C), 63.0, 14.1; LRMS (EI, 70 eV) m/z 230 ([M + 1]$^+$, 4), 229 (21), 157 (23), 102 (100); HRMS (EI, 70 eV) m/z 229.0859 (M$^+$, calcd for $C_{12}H_{11}N_3O_2$, 229.0851). **Ethyl 6-phenyl-1,2,4-triazine-3-carboxylate (3k)**: yellow solid (0.034 g, 2% yield); mp 133–134 °C; IR (KBr) 2990, 1738, 1445, 1365, 1305, 1170, 1055, 1030 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.15 (s, 1 H), 8.17 (bd, J = 7.6 Hz, 2 H), 7.60–7.57 (m, 3 H), 4.60 (q, J = 7.2 Hz, 2 H), 1.50 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.3, 157.7, 155.3, 146.6, 132.1, 132.0, 129.6 (2 C), 127.4 (2 C), 63.2, 14.2; LRMS (EI, 70 eV) m/z 230 ([M + 1]$^+$, 13), 229 (M$^+$, 100), 184 (20), 103 (50), 102 (36); HRMS (EI, 70 eV) m/z 229.0855 (M$^+$, calcd for $C_{12}H_{11}N_3O_2$, 229.0851).

Ethyl 1,2,4-Triazine-3-carboxylate (3e).[44] Prepared from trimeric glyoxal dihydrate (3.15, 15 mmol, 2 equiv of trimer) according to general procedure A to give **3e**, which was purified by flash chromatography (CH_2Cl_2–ethyl acetate, 9:1): yellow solid (0.62 g, 54% yield); mp 72–73 °C (lit.[44] mp 72.5–73.8 °C); IR 2992, 1737, 1326, 1198, 1109 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.42 (d, J = 2.4 Hz, 1 H), 8.83 (d, J = 2.4 Hz, 1 H), 4.60 (q, J = 7.2 Hz, 2 H), 1.50 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.2, 157.2, 150.6, 149.3, 63.4, 14.2; LRMS (EI, 70 eV) m/z 154 ([M + 1]$^+$, 5), 153 (M$^+$, 6), 108 (82), 53 (100); HRMS (EI, 70 eV) m/z 153.0542 (M$^+$, calcd for $C_6H_7N_3O_2$, 153.0538).

Dimethyl 3-(Methylthio)-1,2,4-triazine-5,6-dicarboxylate (3g).[12] Prepared from dimethyl 2,3-dioxosuccinate (1.0 g, 5.75 mmol, in 20 mL anhydrous ethanol) according to general procedure A, substituting *S*-methylisothiosemicarbazide hydrogen iodide[39] (1.34 g, 5.75 mmol in 20 mL anhydrous ethanol) for ethyl oxalamidrazonate. The solid isothiosemicarbazide was added directly to the reaction mixture in one portion; heating was not necessary to affect dissolution. After stirring for 16 h at room temperature, the reaction was quenched by the addition of solid $NaHCO_3$ (0.3 g) and solid $Na_2S_2O_3$ (0.3 g). Stirring was continued for 30 min, and the reaction mixture was filtered, concentrated in vacuo, and purified by flash chromatography (CH_2Cl_2–ethyl acetate, 9:1) to give **3g** (0.97 g, 98% yield): yellow solid; mp 93–95 °C; IR 3010, 2957, 1748, 1510, 1437, 1339, 1221, 1089, 1046 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.07 (s, 3 H), 4.04 (s, 3 H), 2.75 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.3, 163.2, 162.8, 149.2, 142.9, 53.7, 53.5, 14.0; LRMS (EI, 70 eV) m/z 244 ([M + 1]$^+$, 7), 243 (M$^+$, 29), 185 (81), 170 (42), 157 (100), 142 (52); HRMS (EI, 70 eV) m/z 243.0314 (M$^+$, calcd for $C_8H_9N_3O_4S$, 243.0314).

Dimethyl 5-(Dimethylamino)-1,2,4-triazine-3,6-dicarboxylate (3h).[14] Dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate

(36) Bax, A. *J. Magn. Reson.* **1984**, *57*, 314.
(37) Fox, H. H. *J. Org. Chem.* **1947**, *12*, 535.
(38) (a) Denis, W. *Am. Chem. J.* **1907**, *38*, 587. (b) Muller, R. *Chem. Ber.* **1933**, *66*, 1669.
(39) Cattelain, E. *Bull. Soc. Chim. Fr.* **1944**, *11*, 249.
(40) Potts, K. T.; Saxton, J. E. In *Organic Syntheses*; Baumgarten, H. E., Ed.; John Wiley and Sons: New York, 1973; Collect. Vol. V, pp 769–761.
(41) Boger, D. L.; Coleman, R. S.; Panek, J. S.; Huber, F. X.; Sauer, J. *J. Org. Chem.* **1985**, *50*, 5377.
(42) For the dimethyl ester: Roffey, P.; Verge, J. P. *J. Heterocycl. Chem.* **1969**, *6*, 497.
(43) While both **3d** and **3k** have appeared in the literature (see ref 22a, 23a, and 29b), no details of the preparations or characterizations were given.
(44) Krass, D.; Paudler, W. W. *Synthesis* **1974**, *6*, 351.

(1, 1.0 g, 5.05 mmol) and dimethylcyanamide (0.4 mL, 0.347 g, 5 mmol) were dissolved in anhydrous *o*-xylene (10 mL) under argon and refluxed for 12 h. After cooling to room temperature, the crude reaction mixture was subjected to flash chromatography on silica gel, eluting initially with CH_2Cl_2 to remove the *o*-xylene, and subsequently with CH_2Cl_2–ethyl acetate (1:1) to give pure **3h** (0.71 g, 59% yield): yellow solid; mp 129–130 °C (lit. 130 °C); IR (KBr) 2950, 1735, 1578, 1385, 1200, 1155, 1075 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.01 (s, 6 H), 3.18 (bs, 6 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.0, 163.1, 153.5, 152.0, 139.3, 53.4, 53.3, 38.9 (b, 2 C); LRMS (EI, 70 eV) *m/z* 241 ([M + 1]$^+$, 12), 240 (M$^+$, 84), 185 (34), 170 (63), 157 (100), 142 (55), 111 (92); HRMS (EI, 70 eV) *m/z* 240.0858 (M$^+$, calcd for $C_9H_{12}N_4O_4$, 240.0859).

Ethyl 5,6-Dimethyl-1,2,4-triazine-3-carboxylate (3i).[45] Prepared from 2,3-butanedione (650 mg, 7.5 mmol) according to general procedure A. Flash chromatography (CH_2Cl_2–ethyl acetate, 4:1) gave **3i** (0.94 g, 69% yield): yellow oil; IR (KBr) 1737, 1525, 1386, 1274, 1206, 1180, 1016 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.54 (q, J = 7.2 Hz, 2 H), 2.76 (s, 3 H), 2.64 (s, 3 H), 1.45 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.8, 159.8, 159.5, 155.2, 62.9, 21.7, 19.8, 14.1; LRMS (EI, 70 eV) *m/z* 182 ([M + 1]$^+$, 14), 181 (M$^+$, 100), 136 (52), 109 (36); HRMS (EI, 70 eV) *m/z* 181.0851 (M$^+$, calcd for $C_8H_{11}N_3O_2$, 181.0851).

3-(Methylsulfonyl)-1,2,4-triazine (3j). Prepared from trimeric glyoxal hydrate (2.42 g, 11.5 mmol, 2 equiv of trimer in 10 mL of ethanol + 2 mL of H_2O) according to general procedure A, substituting *S*-methylisothiosemicarbazide hydrogen iodide[39] (1.0 g, 5.75 mmol in 10 mL ethanol) for ethyl oxalamidrazonate. The solid isothiosemicarbazide was added directly to the reaction mixture in one portion; heating was not necessary to affect dissolution. After stirring for 16 h at room temperature, the reaction was complete (refluxing as described in general procedure A was not necessary). The reaction was quenched by adding solid $NaHCO_3$ (0.3 g) and $Na_2S_2O_3$ (0.3 g) and stirring for 30 min. The reaction mixture was filtered, and the solvent removed in vacuo. Flash chromatography (CH_2Cl_2–ethyl acetate, 9:1) gave 3-(methylthio)-1,2,4-triazine (0.73 g, 99+% yield): white solid; mp 28–30 °C (lit.[12b] mp 31–33 °C); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.90 (d, J = 2.4 Hz, 1 H), 8.35 (d, J = 2.4 Hz, 1 H), 2.62 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.4, 148.0, 145.1, 13.6; HRMS (EI, 70 eV) *m/z* 127.0207 (M$^+$, calcd for $C_4H_5N_3S$, 127.0204). 3-(Methylthio)-1,2,4-triazine (200 mg, 1.57 mmol) was dissolved in rigorously anhydrous CH_2Cl_2[30] (5 mL) and cooled to −40 °C. To this solution was added a suspension of *m*-chloroperbenzoic acid (MCPBA, 541 mg, 3.14 mmol) in anhydrous CH_2Cl_2 (5 mL) in dropwise fashion with stirring. Stirring was continued at −40 °C for 6 h. The solvent was removed in vacuo, and the residue was purified by flash chromatography on silica gel (*anhydrous* THF) to give **3j** (152 mg, 61%): off-white solid; mp 110–113 °C; IR (KBr) 3080, 2990, 2900, 1670, 1630, 1332, 1290, 1065, 960 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 9.59 (d, J = 2.4 Hz, 1 H), 9.06 (d, J = 2.5 Hz, 1 H), 2.99 (s, 3 H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 174.1, 151.97, 151.2, 39.6 (overlapped by DMSO, revealed at APT); HRMS (EI, 70 eV) *m/z* 159.0103 (M$^+$ calcd for $C_4H_5N_3O_2S$, 159.0103).

Tetramethyl 1,2-Diazine-3,4,5,6-tetracarboxylate (4b).[15a] Dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (1, 1.0 g, 5.05 mmol) and dimethyl acetylenedicarboxylate (0.92 mL, 1.07 g, 7.5 mmol) were dissolved in anhydrous *o*-xylene (3 mL) under argon and refluxed for 24 h. After cooling to room temperature, the crude reaction mixture was subjected to flash chromatography on silica gel eluting initially with CH_2Cl_2 to remove the *o*-xylene and subsequently with CH_2Cl_2–ethyl acetate (19:1) to give pure **4b** (0.945 g, 60% yield): yellow solid; mp 143–144 °C (lit.[15a] mp 143–144 °C), IR (KBr) 3010, 2960, 1752, 1440, 1385, 1310, 1230, 1010, cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.07 (s, 6 H), 3.97 (s, 6 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.13 (2 C), 163.06 (2 C), 150.6 (2 C), 130.2 (2 C), 54.0 (2 C), 53.9 (2 C); LRMS (EI, 70 eV) *m/z* 313 ([M + 1]$^+$, 4), 312 (M$^+$, 14), 282 (100), 281 (73); HRMS (EI, 70 eV) *m/z* 312.0582 (M$^+$, calcd for $C_{12}H_{12}N_2O_8$, 312.0594).

Dimethyl 2,3-Diazanaphthalene-1,4-dicarboxylate (4c). To a 3-necked flask fitted with two dropping funnels and a reflux condenser was added a solution of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (1, 1.5 g, 7.6 mmol). One dropping funnel was charged with anthranilic acid (1 g, 10.2 mmol) solution in anhydrous dioxane (10 mL) and the second dropping funnel with an isoamyl nitrite (1.38 mL, 1.2 g, 10.2 mmol) solution in anhydrous dioxane (10 mL). The contents of the two dropping funnels were slowly added over 1 h with gentle heating to maintain reflux. After the addition was complete, reflux was continued for 2 h. After cooling, the solvent was removed in vacuo, and flash chromatography on silica gel (CH_2Cl_2–ethyl acetate, 4:1) gave **4c** (0.897 g, 48% yield): yellow solid; mp 176–177 °C; IR 2945, 1720, 1440, 1265, 1230, 1145, 1038, 822 cm^{-1}; UV λ_{max} (CH_3OH) 228 nm (ϵ 19 800), 292 (2900); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.63 (dd, J = 6.4, 3.2 Hz, 2 H), 8.02 (dd, J = 6.4, 3.2 Hz, 2 H), 4.14 (s, 6 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.7 (2 C), 151.3 (2 C), 133.8 (2 C), 125.4 (2 C), 124.9 (2 C), 53.5 (2 C); LRMS (EI, 70 eV) *m/z* 247 ([M + 1]$^+$, 8), 246 (M$^+$, 23), 216 (25), 188 (100); HRMS (EI, 70 eV) *m/z* 246.0619 (M$^+$, calcd for $C_{12}H_{10}N_2O_4$, 246.0641).

Reaction of Indole with 3b. 1-Carbethoxy-3,4-dicarbomethoxy-γ-carboline (6b) was eluted and purified with CH_2Cl_2–ethyl acetate (9:1); yellow solid; mp 144–145 °C; IR (KBr) 3400, 2940, 1710, 1590, 1420, 1290, 1200, 1040 cm^{-1}; UV λ_{max} (CH_3OH) 200 nm (sh), 210 (ϵ 28 600), 269 (24 000), 321 (5400); ^1H NMR ($CDCl_3$, 400 MHz) δ 10.28 (bs, 1 H), 8.68 (d, J = 8.4 Hz, 1 H), 7.61–7.55 (m, 2 H), 7.38 (ddd, J = 8.4, 6.4, 1.6 Hz, 1 H), 4.61 (q, J = 7.2 Hz, 2 H), 4.02 (s, 3 H), 3.99 (s, 3 H), 1.49 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.3, 165.7, 165.3, 147.0, 145.2, 144.2, 141.0, 129.1, 125.5, 122.0, 120.9, 119.3, 111.5, 107.6, 62.5, 53.0 (2 C), 14.1; LRMS (EI, 70 eV) *m/z* 358 ([M + 2]$^+$, 6), 357 ([M + 1]$^+$, 32), 356 (M$^+$, 100); HRMS (EI, 70 eV) *m/z* 356.1041 (M$^+$, calcd for $C_{18}H_{16}N_2O_6$, 356.1008). **1-Carbethoxy-3,4-dicarbomethoxy-1-(3-indolyl)-2*H*-γ-carboline (16b).** Mixture of tautomers eluted with CH_2Cl_2–ethyl acetate (9:1): HRMS (EI, 70 eV) *m/z* 475.1748 (M$^+$, calcd for $C_{26}H_{25}N_3O_6$, 475.1743). **3-Carbethoxy-5,6-dicarbomethoxy-2,5-dihydro-1,2,4-triazine (15b)** was eluted and purified with CH_2Cl_2–ethyl acetate (4:1): colorless oil; IR (NaCl) 3300, 2950, 1720, 1645, 1440, 1320, 1185, 1130, 1010 cm^{-1}; UV λ_{max} (CH_3OH) 215 nm (ϵ 12 000), 270 (23 600), 320 (5500); ^1H NMR ($CDCl_3$, 400 MHz) δ 9.69 (bs, 1 H), 5.62 (s, 1 H), 4.43 (dq, J_{AB} = 10.4, J = 7.2 Hz, 1 H), 4.38 (dq, J_{AB} = 10.4, J = 7.2 Hz, 1 H), 3.89 (s, 3 H), 3.73 (s, 3 H), 1.39 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.3, 162.4, 159.7, 144.1, 131.6, 63.9, 55.0, 53.2, 53.1, 14.0; LRMS (EI, 70 eV) *m/z* 273 ([M + 2]$^+$, 13), 272 ([M + 1]$^+$, 100), 271 (M$^+$, 5), 212 (27); HRMS (EI, 70 eV) *m/z* 271.0800 (M$^+$, calcd for $C_{10}H_{13}N_3O_6$, 271.0804). **3-Carbethoxy-5,6-dicarbomethoxy-3-(3-indolyl)-2,3,4,5-tetrahydro-1,2,4-triazine (19b)** was eluted and purified with CH_2Cl_2–ethyl acetate (4:1): white solid; mp 217–218 °C; IR 3330, 3320, 2950, 2910, 1725, 1705, 1622, 1430, 1310, 1250, 1110 cm^{-1}; UV λ_{max} (CH_3OH) 217 nm (ϵ 13 000), 242 (sh), 277 (7 800), 286 (sh), 302 (sh); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.33 (bs, 1H), 7.68 (d, J = 8.4 Hz, 1 H), 7.39 (d, J = 8.4 Hz, 1 H), 7.21 (dd, J = 8.4, 6.8 Hz, 1 H), 7.18 (d, J = 2.4 Hz, 1 H), 7.12 (dd, J = 8.4, 6.8 Hz, 1 H), 6.19 (bs, 1 H), 6.15 (bs, 1 H), 4.71 (d, J = 2.4 Hz, 1 H), 4.34 (dq, J_{AB} = 11.2, J = 7.2 Hz, 1 H), 4.32 (dq, J_{AB} = 11.2, J = 7.2 Hz, 1 H), 3.76 (s, 3 H), 3.60 (s, 3 H), 1.36 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.5, 169.0, 161.1, 136.5, 134.9, 124.8, 124.0, 122.6, 120.3, 119.8, 112.2, 111.6, 62.3, 59.6, 58.6, 53.0, 52.6, 14.2; LRMS (EI, 70 eV) *m/z* 389 ([M + 1]$^+$, 33), 388 (M$^+$, 90), 329 (100), 228 (25), 200 (23), 143 (45); HRMS (EI, 70 eV) *m/z* 389.1411 ([M + 1]$^+$, calcd for $C_{18}H_{20}N_4O_6$, 388.1383). **Dimethyl 5-oxobenzo[*f*][1,7]naphthyridine-2,3-dicarboxylate (8b)** was eluted and purified with CH_2Cl_2–MeOH (19:1): white solid; mp 234–235 °C; IR 3432, 3050, 2970, 1726, 1684, 1436, 1318, 1280, 1145 cm^{-1}; UV λ_{max} (CH_3OH) 203 nm (ϵ 24 600), 226 (31 200), 243 (sh), 275 (12 700), 334; ^1H NMR (DMSO-d_6, 400 MHz) δ 12.17 (bs, 1 H), 9.35 (s, 1 H), 8.52 (d, J = 8.0 Hz, 1 H), 7.61 (dd, J = 8.0, 6.8 Hz, 1 H), 7.40 (d, J = 8.0 Hz, 1 H), 7.33 (dd, J = 8.0, 6.8 Hz, 1 H), 3.95 (s, 3 H), 3.94 (s, 3 H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 166.0, 165.4, 158.5, 148.7, 142.4, 137.3, 133.8, 132.1, 131.8, 128.7, 124.7, 123.1, 116.4, 115.6, 53.5, 53.3; LRMS (EI, 70 eV) *m/z* 313 ([M + 1]$^+$, 20), 312 (M$^+$, 100), 186 (15); HRMS (EI, 70 eV) *m/z* 312.0762 (M$^+$, calcd for $C_{16}H_{12}N_2O_5$, 312.0746).

Aromatization of 16b. 3,4-Dicarbomethoxy-1-(3-indolyl)-γ-carboline (17b). Diadduct **16b** (50 mg, 6.11 mmol) and 10% Pd/C (56 mg) were added to methanol (10 mL), and

(45) While **3i** has appeared in the literature no details of the preparation or characterization were given: Dittmar, W.; Sauer, J.; Steigel, A. *Tetrahedron Lett.* **1969**, 5171.

the reaction mixture was refluxed for 24 h while slowly bubbling O_2 through the mixture. After cooling, the reaction mixture was filtered, and the Pd/C was washed with with methanol. The solvent was removed in vacuo, and the residue was purified by flash chromatography on silica gel (CH_2Cl_2–ethyl acetate, 4:1) to give **17b** (25 mg, 60% yield): tan solid; mp 140–142 °C; IR (KBr) 3406, 2951, 1725, 1562, 1434, 1385, 1285, 1211, 1181 cm^{-1}; UV λ_{max} (CH_3OH) 211 nm (ϵ 39 000), 271 (22 600), 320 (sh), 357 (sh); ^1H NMR ($CDCl_3$, 400 MHz) δ 10.20 (bs, 1 H), 8.95 (bs, 1 H), 7.76 (d, J = 8.0 Hz, 1 H), 7.72 (d, J = 2.4 Hz, 1 H), 7.68 (d, J = 7.6 Hz, 1 H), 7.55 (d, J = 8.0 Hz, 1 H), 7.46 (dd, J = 8.0, 6.8 Hz, 1 H), 7.41 (d, J = 8.4 Hz, 1 H), 7.27 (dd, J = 8.4 Hz, 7.2 Hz, 1 H), 7.12 (dd, J = 7.6, 6.8 Hz, 1 H), 7.09 (dd, J = 8.0, 7.2 Hz, 1 H), 4.04 (s, 3 H), 4.01 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) 168.6, 166.1, 152.3, 148.6, 144.8, 140.0, 136.3, 127.3, 126.4, 125.9, 123.2, 122.7, 121.3, 121.0 (2 C), 120.8, 118.5, 115.7, 111.5, 111.2, 103.2, 52.9, 52.7; LRMS (EI, 70 eV) m/z 400 ([M + 1]$^+$, 24), 399 (M$^+$, 78), 398 (57), 311 (73), 310 (100), 280 (33); HRMS (EI, 70 eV) m/z 399.1212 (M$^+$, calcd for $C_{23}H_{17}N_3O_4$, 399.1219).

Formation of 19b from Indole and 15b. Dihydrotriazine **15b** (28 mg, 0.10 mmol) and indole (18 mg, 0.15 mmol) in dioxane (27 μL) were heated to 100 °C for 16 h according to general procedure B. Flash chromatography as described above yielded unreacted **15b** (14.6 mg, 0.53 mmol) and **19b** (16 mg, 91% yield based on reacted **15b**).

Reaction of 5-Methoxyindole with 3b. 1-Carbethoxy-3,4-dicarbomethoxy-8-methoxy-γ-carboline was eluted and purified with CH_2Cl_2–ethyl acetate (9:1): yellow solid; mp 191–192 °C; IR (KBr) 3260, 2940, 1725, 1458, 1285, 1200, 1154 cm^{-1}; UV λ_{max} (CH_3OH) 202 nm (sh), 212 (ϵ 36 000), 237 (sh), 284 (23 600), 322 (sh), 386 (1200); ^1H NMR ($CDCl_3$, 400 MHz) δ 10.22 (bs, 1 H), 8.18 (d, J = 2.8 Hz, 1 H), 7.42 (d, J = 8.8 Hz, 1 H), 7.18 (dd, J = 8.8, 2.8 Hz, 1 H), 4.58 (q, J = 7.2 Hz, 2 H), 3.97 (s, 3 H), 3.96 (s, 3 H), 3.90 (s, 3 H), 1.47 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.4, 165.7, 165.2, 155.2, 146.7, 145.2, 144.1, 135.7, 120.9, 119.8, 118.7, 112.1, 107.6 (2 C), 62.4, 55.7, 52.9 (2C), 14.2; LRMS (EI, 70 eV) m/z 387 ([M + 1]$^+$, 3), 386 (13), 229 (100); HRMS (EI, 70 eV) m/z 386.1110 (M$^+$, calcd for $C_{19}H_{18}N_2O_7$, 386.1114). **Dimethyl 9-methoxy-5-oxobenzo[*f*][1,7]-naphthyridine-2,3-dicarboxylate** was eluted and purified with CH_2Cl_2–ethyl acetate (9:1): yellow solid; mp 251–252 °C; IR (KBr) 3400, 3160, 3020, 2950, 1728, 1658, 1500, 1302, 1280, 1265, 1142, 1070 cm^{-1}; UV λ_{max} (CH_3OH) 202 nm (ϵ 36 900), 231 (33 600), 251 (sh), 277 (9900), 365 (3700); ^1H NMR (DMSO-d_6, 400 MHz) δ 12.07 (bs, 1 H), 9.43 (s, 1 H), 7.97 (d, J = 2.0 Hz, 1 H), 7.34 (d, J = 8.8 Hz, 1 H), 7.25 (dd, J = 8.8, 2.0 Hz, 1 H), 3.95 (s, 3 H), 3.93 (s, 3 H), 3.89 (s, 3 H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 165.6, 165.5, 157.8, 155.2, 147.9, 142.4, 133.9, 131.9, 131.4, 128.9, 120.6, 117.6, 116.2, 106.9, 56.0, 53.3, 53.1; LRMS (EI, 70 eV) m/z 343 ([M + 1]$^+$, 20), 342 (M$^+$, 100), 298 (21), 226 (48); HRMS (EI, 70 eV) m/z 342.0852 (M$^+$, calcd for $C_{17}H_{14}N_2O_6$, 342.0855).

Reaction of 1-Methylindole with 3b: 1-Carbethoxy-3,4-dicarbomethoxy-5-methyl-γ-carboline was eluted and purified with CH_2Cl_2–ethyl acetate (9:1): yellow solid; mp 160–161 °C; IR 2956, 1718, 1447, 1327, 1252, 1203, 1146, 1094 cm^{-1}; UV λ_{max} (CH_3OH) 205 nm (sh), 214 (ϵ 22 000), 270 (27 200), 302 (sh), 355 (sh); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.73 (d, J = 8.0 Hz, 1 H), 7.64 (t, J = 8.0 Hz, 1 H), 7.48 (d, J = 8.0 Hz, 1 H), 7.39 (t, J = 8.0 Hz, 1 H), 4.63 (q, J = 7.2 Hz, 2 H), 4.10 (s, 3 H), 4.03 (s, 3 H), 3.88 (s, 3 H), 1.53 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.6, 165.9, 165.4, 143.1, 142.8, 142.3, 138.7, 129.4, 125.6, 121.9, 121.5, 118.8, 117.1, 109.1, 62.6, 53.4, 53.3, 30.4, 14.2; LRMS (EI, 70 eV) m/z 371 ([M + 1]$^+$, 3), 370 (M$^+$, 11), 298 (25), 216 (28), 188 (100); HRMS (EI, 70 eV) m/z 370.1155 (M$^+$, calcd for $C_{19}H_{18}N_2O_6$, 370.1165). **Dimethyl 6-methyl-5-oxobenzo[*f*][1,7]-naphthyridine-2,3-dicarboxylate** was eluted and purified with CH_2Cl_2–ethyl acetate (1:1): white solid; mp 218–219 °C; IR (KBr) 2950, 1726, 1670, 1440, 1423, 1295, 1152, 1080 cm^{-1}; UV λ_{max} (CH_3OH) 202 nm (ϵ 33 200), 227 (36 400), 244 (sh), 276 (14 600), 307 (sh), 330 (sh); ^1H NMR ($CDCl_3$, 400 MHz) δ 9.03 (s, 1 H), 8.23 (dd, J = 8.0, 1.2 Hz, 1 H), 7.65 (ddd, J = 8.0, 7.2, 1.2 Hz, 1 H), 7.44 (bd, J = 8.0 Hz, 1 H), 7.37 (ddd, J = 8.0, 7.2, 0.8 Hz, 1 H), 4.01 (s, 3 H), 4.00 (s, 3 H), 3.83 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.8, 165.1, 158.8, 150.1, 141.7, 138.4, 132.8, 131.8, 130.4, 128.5, 124.0, 123.2, 116.1, 115.4, 53.3, 53.1, 30.6; LRMS (EI, 70 eV) m/z 327 ([M + 1]$^+$, 15), 326 (M$^+$, 76), 210 (100); HRMS (EI, 70 eV) m/z 326.0915 (M$^+$, calcd for $C_{17}H_{14}N_2O_5$, 326.0903).

Reaction of Indole with 3c. Diethyl 3-methyl-γ-carboline-1,4-dicarboxylate (6c) was eluted and purified with CH_2Cl_2–ethyl acetate (9:1): yellow solid; mp 193–195 °C; IR (NaCl) 3400, 2980, 2920, 1720, 1685, 1590, 1412, 1278, 1252, 1220, 1185 cm^{-1}; UV λ_{max} (CH_3OH) 214 nm (ϵ 25 500), 252 (sh), 269 (15 000), 314 (4100); ^1H NMR ($CDCl_3$, 400 MHz) δ 10.38 (bs, 1 H), 8.63 (d, J = 8.0 Hz, 1 H), 7.55–7.50 (m, 2 H), 7.34 (ddd, J = 8.0, 6.0, 1.6 Hz, 1 H), 4.65 (q, J = 7.2 Hz, 2 H), 4.54 (q, J = 7.2 Hz, 2 H), 3.03 (s, 3 H), 1.53 (t, J = 7.2 Hz, 3 H), 1.51 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.7, 166.4, 155.7, 147.6, 143.8, 140.4, 128.2, 125.2, 121.6, 120.0, 118.9, 111.1, 108.9, 62.4, 61.8, 26.5, 14.4, 14.3; LRMS (EI, 70 eV) m/z 326 (M$^+$, 14), 255 (16), 254 (100), 208 (21), 179 (13), 165 (19); HRMS (EI, 70 eV) m/z 326.1252 (M$^+$, calcd for $C_{18}H_{18}N_2O_4$, 326.1267). **Ethyl 2-methyl-5-oxobenzo[*f*][1,7]naphthyridine-2-carboxylate (8c)** was eluted and purified with CH_2Cl_2–MeOH (19:1): white solid; mp 269–270 °C; IR (KBr) 3430, 3179, 2978, 1729, 1682, 145, 1255, 1224, 1077 cm^{-1}; UV λ_{max} (CH_3OH) 206 nm (sh), 226 (ϵ 26 200), 266 (11 800), 303 (6100); ^1H NMR (DMSO-d_6, 400 MHz) δ 12.00 (bs, 1 H), 9.13 (s, 1 H), 8.37 (d, J = 7.6 Mz, 1 H), 7.53 (t, J = 7.6 Hz, 1 H), 7.36 (d, J = 7.6 Hz, 1 H), 7.28 (t, J = 7.6 Hz, 1 H), 4.41 (q, J = 7.2 Hz, 2 H), 2.81 (s, 3 H), 1.40 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 165.9, 158.7, 157.4, 142.1, 136.4, 133.2, 130.3, 128.9, 128.4, 123.7, 122.5, 115.9 (2C), 61.7, 24.2, 14.0; LRMS (EI, 70 eV) m/z 283 ([M + 1]$^+$, 23), 282 (M$^+$, 100), 254 (20), 226 (30), 209 (12), 207 (25); HRMS (EI, 70 eV) m/z 282.1002 (M$^+$, calcd for $C_{16}H_{14}N_2O_3$, 282.1004).

Reaction of Indole with 3d. 2-Phenylquinoline[46] was eluted and purified with petroleum ether–CH_2Cl_2 (1:4): white solid; mp 82–83 °C (lit.[46a] mp 83–84 °C); UV λ_{max} (CH_3OH) 204 nm (ϵ 29 100), 252 (27 900), 279 (sh), 314 (sh); ^1H NMR (acetone-d_6, 400 MHz) δ 8.37 (d, J = 8.8 Hz, 1 H), 8.31 (bd, J = 7.2 Hz, 2 H), 8.11 (d, J = 8.4 Hz, 1 H), 8.08 (d, J = 8.4 Hz, 1 H), 7.94 (d, J = 8.4 Hz, 1 H), 7.76 (ddd, J = 8.4, 7.2, 1.6 Hz, 1 H), 7.59–7.46 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.4, 148.3, 139.7, 136.8, 129.7, 129.6, 129.3, 128.8 (2 C), 127.6 (2 C), 127.4, 127.2, 126.3, 119.0; LRMS[46b] (EI, 70 eV) m/z 206 ([M + 1]$^+$, 14), 205 (M$^+$, 100), 204 (62); HRMS (EI, 70 eV) m/z 205.0889 (M$^+$, calcd for $C_{15}H_{11}N$, 205.0891). **Ethyl 2-phenyl-β-carboline-4-carboxylate (11d)** was eluted and purified with CH_2Cl_2: white solid; mp 186–188 °C; IR (NaCl plate) 3380, 3050, 2960, 1712, 1590, 1440, 1190, 750 cm^{-1}; UV λ_{max} (CH_3OH) 205 nm (ϵ 42 000), 217 (sh), 275 (41 500), 380 (5200); ^1H NMR ($CDCl_3$, 400 MHz) δ 9.92 (bs, 1 H), 8.58 (s, 1 H), 8.20 (d, J = 7.6 Hz, 1 H), 8.15 (bd, J = 7.2 Hz, 2 H), 7.62–7.56 (m, 2 H), 7.50 (t, J = 7.2 Hz, 2 H), 7.40 (bt, J = 7.2 Hz, 1 H), 7.34 (ddd, J = 7.6, 6.8, 1.6 Hz, 1 H), 4.62 (q, J = 7.2 Hz, 2 H), 1.56 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.1, 147.5, 141.1, 139.8, 136.5, 132.6, 129.3, 129.2, 128.7 (2 C), 128.1, 127.0 (2 C), 121.8, 121.2, 120.6, 115.4, 111.9, 61.9, 14.4; LRMS (EI, 70 eV) m/z 318 ([M + 2]$^+$, 24), 317 ([M + 1]$^+$, 100), 316 (M$^+$, 25); HRMS (EI, 70 eV) m/z 316.1214 (M$^+$, calcd for $C_{20}H_{16}N_2O_2$, 316.1212). **2-Phenyl-β-carboline (11m)** was eluted and purified with CH_2Cl_2–ethyl acetate (4:1): white solid; mp 253–254 °C; IR 3400, 3100, 1630, 1463, 1341, 1242, 749 cm^{-1}; UV λ_{max} (CH_3OH) 200 nm (ϵ 17 300), 220 (17 000), 233 (sh), 270 (24 600), 288 (sh), 336 (sh); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.99 (s, 1 H), 8.73 (bs, 1 H), 8.38 (s, 1 H), 8.18 (d, J = 8.0 Hz, 1 H), 8.08 (d, J = 7.2, 2 H), 7.55–7.45 (m, 4 H), 7.38 (t, J = 7.6 Hz, 1 H), 7.30 (bdd, J = 8.0, 6.8 Hz, 1 H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 145.5, 141.1, 140.1, 135.4, 133.5, 128.9, 128.6 (2C), 128.3, 127.5, 121.91 (2 C), 122.0, 121.0, 119.3, 112.1, 111.1; LRMS (EI, 70 eV) m/z 245 ([M + 1]$^+$, 33), 244 (M$^+$, 100), 243 (48), 242 (15), 122 (13); HRMS (EI, 70 eV) m/z 244.1000 (M$^+$, calcd for $C_{17}H_{12}N_2$, 244.1000). **3-Phenylbenzo[*f*][1,7]naphthyridin-5-one (8d)** was eluted and purified with CH_2Cl_2–ethyl acetate (1:1): white solid; mp 300–302 °C; IR 3432, 3040, 2919, 1674, 1592, 1465, 1427, 1350 cm^{-1}; UV λ_{max} (CH_3OH) 200 nm (sh), 213 (ϵ 31 600), 227 (sh), 282 (24 400), 317 (12 000); ^1H NMR (DMSO-d_6, 400 MHz) δ 11.98 (bs, 1 H), 9.03 (d, J = 8.4 Hz, 1 H), 8.44 (bd, J = 8.4, 8.0 Hz, 2 H), 8.29 (bd, J = 8.0 Hz, 2 H), 7.60–7.49 (m, 4 H), 7.38 (d, J = 8.0 Hz, 1 H), 7.29 (bt, J = 8.0, 6.8 Hz, 1 H); ^{13}C NMR (DMSO-d_6, 100 MHz)

(46) (a) Cromwell, N. H.; Mercer, G. D. *J. Am. Chem. Soc.* **1957**, *79*, 3815. (b) Koch, C. W.; Milberg, R. M.; Katt, R. J.; Markgraf, J. H.; Wege, P. M. *J. Heterocycl. Chem.* **1974**, *11*, 475.

δ 159.5, 155.9, 141.4, 137.8, 136.4, 132.7, 130.1, 129.8, 129.6, 128.9 (2 C), 127.0 (2 C), 123.8, 123.5, 122.4, 116.5, 115.9; LRMS (EI, 70 eV) m/z 273 ($[M + 1]^+$, 19), 272 (M^+, 100), 244 (82); HRMS (EI, 70 eV) m/z 272.0947 (M^+, calcd for $C_{18}H_{12}N_2O$, 272.0950).

Conversion of Ethyl 2-Phenyl-β-carboline-4-carboxylate (11d) to 2-Phenyl-β-carboline (11m). To a solution of KOH (22 mg, 0.4 mmol) in absolute ethanol (10 mL) was added **11d** (50 mg, 0.16 mmol), and the mixture was refluxed for 2 h. After cooling, the reaction mixture was neutralized with 5% HCl solution and filtered. The filtrate was evaporated in vacuo to give crude 2-phenyl-β-carboline-4-carboxylic acid, which was purified by flash chromatography on silica gel (CH_2Cl_2–MeOH, 2:1): 46 mg, 100% yield; ^1H NMR (acetone-d_6, 400 MHz) δ 11.14 (bs, 1 H), 9.04 (s, 1 H), 8.42 (d, J = 8.0 Hz, 1 H), 8.32 (d, J = 7.6 Hz, 2 H), 7.88 (d, J = 8.4 Hz, 1 H), 7.65 (dd, J = 8.4, 7.2 Hz, 1 H), 7.52 (t, J = 7.6 Hz, 2 H), 7.42 (t, J = 7.6 Hz, 1 H), 7.36 (dd, J = 8.0, 7.2 Hz, 1 H). This carboxylic acid was suspended in freshly distilled quinoline (20 mL), copper powder was added (50 mg, 0.8 mmol), and the reaction mixture was refluxed for 4 h. The reaction mixture was concentrated by removing the bulk of the quinoline by vacuum distillation, and **11m** was purified by flash chromatography on silica gel (CH_2Cl_2–ethyl acetate, 2:1): 15 mg, 38% yield. Spectral data is given above.

Reaction of Indole with 3e. Ethyl β-carboline-4-carboxylate (11e) was eluted and purified with CH_2Cl_2–ethyl acetate (9:1): white solid; mp 145–146 °C; IR (KBr) 3400, 2960, 2920, 1685, 1615, 1308, 1245, 1205, 1180 cm^{-1}; UV λ_{max} (CH_3OH) 205 nm (ε 27 500), 242 (8300), 253 (sh), 267 (sh), 297 (sh), 360 (1200); ^1H NMR (DMSO-d_6, 400 MHz) δ 11.65 (bs, 1 H), 8.46 (d, J = 4.8 Hz, 1 H), 8.39 (d, J = 4.8 Hz, 1 H), 8.28 (d, J = 8.0 Hz, 1 H), 7.78 (d, J = 8.4 Hz, 1 H), 7.59 (ddd, J = 8.4, 6.8, 1.2 Hz, 1 H), 7.28 (bdd, J = 8.0, 6.8 Hz, 1 H), 4.48 (q, J = 7.2 Hz, 2 H), 1.40 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 165.6, 141.5, 137.9, 136.1, 130.9, 129.9, 129.1, 121.9, 120.1 (2 C), 118.9, 112.9, 61.0, 14.4; LRMS (EI, 70 eV) m/z 240 (M^+, 49), 195 (53), 169 (27), 168 (100), 167 (35), 166 (69), 140 (31); HRMS (EI, 70 eV) m/z 240.0897 (M^+, calcd for $C_{14}H_{12}N_2O_2$, 240.0899). **Ethyl 5,6-*trans*-di(3-indolyl)-1,2,5,6-tetrahydro-1,2,4-triazine-3-carboxylate (21)** was eluted and purified with CH_2Cl_2–ethyl acetate (4:1): tan solid; mp 145–150 °C; IR (KBr) 3400, 3045, 2975, 1710, 1625, 1455, 1380, 1300, 1195, 1095, 740 cm^{-1}; UV λ_{max} (CH_3OH) 203 nm (sh), 215 (ε 62 100), 286 (sh), 277 (14 300), 286 (sh), 305 (sh); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.31 (bs, 1 H), 8.21 (bs, 1 H), 7.42 (d, J = 7.6 Hz, 1 H), 7.33 (d, J = 7.6 Hz, 1 H), 7.19 (d, J = 8.0 Hz, 1 H), 7.18 (d, J = 8.0 Hz, 1 H), 7.10 (bdd, J = 8.0, 6.8 Hz, 1 H), 7.06 (bdd, J = 8.0, 6.8 Hz, 1 H), 7.00 (ddd, J = 7.6, 6.8, 1.2 Hz, 1 H), 6.91 (t, J = 7.2 Hz, 1 H), 6.77 (d, J = 2.4 Hz, 1 H), 6.67 (d, J = 2.4 Hz, 1 H), 5.67 (bs, 1 H), 5.57 (bs, 1 H), 5.06 (d, J = 7.2 Hz, 1 H), 4.39 (d, J = 7.2 Hz, 1 H), 4.34 (q, J = 7.2 Hz, 2 H), 1.34 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.9, 137.0, 136.3, 136.0, 126.2, 125.2, 123.2, 123.1, 122.0, 121.9, 119.6, 119.5, 119.1, 119.0, 113.6, 112.6, 111.4, 111.2, 62.1, 55.6, 52.3, 14.1; LRMS (CI, isobutane) m/z 389 ($[M + 2]^+$, 68), 388 ($[M + 1]^+$, 100), 387 (M^+, 44), 386 (20), 356 (33), 272 (21), 271 (52), 269 (17), 244 (17), 243 (18), 145 (13), 117 (13); HRMS (EI, 70 eV) m/z 387.1692 (M^+, calcd for $C_{22}H_{21}N_5O_2$, 387.1695).

Reaction of Indole with 3f. Diethyl 5-(3-indolyl)-6-methyl-2,5-dihyro-1,2,4-triazine-3,5-dicarboxylate (9f) was eluted and purified with CH_2Cl_2–ethyl acetate (4:1): white solid; mp 151–153 °C; IR (KBr) 3340, 3220, 2970, 1720, 1615, 1455, 1320, 1200, 1010 cm^{-1}; UV λ_{max} (CH_3OH) 216 nm (ε 16 000), 242 (sh), 273 (5000), 273 (sh), 305 (1500); ^1H NMR ($CDCl_3$, 400 MHz) δ 9.21 (bs, 1 H), 8.53 (bs, 1 H), 7.56 (d, J = 8.0 Hz, 1 H), 7.25 (d, J = 7.6 Hz, 1 H), 7.14 (bdd, J = 7.6, 6.8 Hz, 1 H), 7.06 (bdd, J = 8.0, 6.8 Hz, 1 H), 6.95 (d, J = 2.4 Hz, 1 H), 4.33 (q, J = 7.2 Hz, 2 H), 4.27 (dq, J_{AB} = 11.0, J = 7.2 Hz, 1 H), 4.26 (dq, J_{AB} = 11.0, J = 7.2 Hz, 1 H), 1.97 (s, 3 H), 1.24 (t, J = 7.2 Hz, 3 H), 1.23 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.7, 160.8, 144.4, 144.3, 136.8, 125.4, 123.6, 121.9, 119.9, 119.7, 112.9, 111.6, 64.2, 63.1, 62.1, 19.7, 14.1, 13.8; LRMS (EI, 70 eV) m/z (M^+ not observed), 284 (18), 283 (100), 211 (16), 143 (14); HRMS (EI, 70 eV) m/z 356.1480 (M^+, calcd for $C_{18}H_{20}N_4O_4$, 356.1485).

Reaction of Indole with 3g. Dimethyl 5-(3-indolyl)-3-(methylthio)-2,5-dihydro-1,2,4-triazine-5,6-dicarboxylate (9g) was eluted and purified with CH_2Cl_2–MeOH (99:1): white solid; mp 237–238 °C; IR (KBr) 3370, 3295, 2910, 1715, 1598, 1449, 1270, 1130 cm^{-1}; UV λ_{max} (CH_3OH) 202 (sh), 215 (ε 36 400), 259 (7800), 284 (sh), 302 (sh); ^1H NMR (DMSO-d_6, 400 MHz) δ 11.69 (bs, 1 H), 11.04 (bs, 1 H), 7.59 (d, J = 8.4 Hz, 1 H), 7.34 (d, J = 8.4 Hz, 1 H), 7.05 (dd, J = 8.4, 6.8 Hz, 1 H), 7.00 (d, J = 2.4 Hz, 1 H), 6.94 (dd, J = 8.4, 6.8 Hz, 1 H), 3.71 (s, 3 H), 3.64 (s, 3 H), 2.31 (s, 3 H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 170.3, 163.4, 151.3, 136.6, 133.5, 125.4, 123.6, 121.1, 121.0, 118.6, 112.9, 111.6, 61.4, 52.4 (2 C), 12.4; LRMS (EI, 70 eV) m/z 362 ($[M + 2]^+$, 16), 361 ($[M + 1]^+$, 27), 360 (M^+, 100), 243 (40); HRMS (EI, 70 eV) m/z 360.0890 (M^+, calcd for $C_{16}H_{16}N_4O_4S$, 360.0892).

Methylation of 9g. Dimethyl 5-(3-Indolyl)-2-methyl-3-(methylthio)-2,5-dihydro-1,2,4-triazine-5,6-dicarboxylate (22).[18] To an ice-cooled solution of **9g** (40 mg, 0.11 mmol) in DMF (1.2 mL) was added 50% oil-immersion NaH (5.4 mg, 0.11 mmol) with stirring. Stirring was continued for 30 min, and then methyl iodide (0.007 mL, 0.11 mmol) was added and the stirring was continued at 0 °C for 1 h. The DMF was removed in vacuo (1 mmHg), and the residue was dissolved in ethyl acetate (10 mL) and filtered. The ethyl acetate was removed in vacuo, and 22 (18 mg, 43%) was purified by flash chromatography on silica gel (CH_2Cl_2–ethyl acetate, 19:1): white solid; mp 219–220 °C; IR (KBr) 3350, 2950, 2930, 1747, 1722, 1605, 1435, 1100, 1050 cm^{-1}; UV λ_{max} (CH_3OH) 202 (sh), 215 (ε 36 000), 259 (7000), 284 (sh), 306 (3500); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.19 (bs, 1 H), 7.76 (d, J = 8.0 Hz, 1 H), 7.27 (d, J = 8.0 Hz, 1 H), 7.14 (dd, J = 8.0, 6.8 Hz, 1 H), 7.07 (dd, J = 8.0, 6.8 Hz, 1 H), 6.93 (d, J = 2.4 Hz, 1 H), 3.82 (s, 3 H), 3.79 (s, 3 H), 3.48 (s, 3 H), 2.40 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.2, 163.5, 153.4, 136.6, 132.6, 125.5, 122.8, 122.0, 121.7, 119.7, 114.3, 111.2, 61.9, 53.0, 52.9, 40.7, 14.3; ^{13}C NMR (DMSO-d_6, 100 MHz) δ 170.4, 163.1, 152.9, 136.7, 132.8, 125.3, 123.6, 121.21, 121.18, 118.8, 112.7, 111.7, 61.5, 52.6 (2 C), 40.4, 13.9; LRMS (EI, 70 eV) m/z 374 (M^+, 1), 316 (22), 315 (100); HRMS (EI, 70 eV) m/z 374.1048 (calcd for $C_{17}H_{18}N_4O_4S$, 374.1048).

Reaction of Indole with 3h. Dimethyl 3-(3-indolyl)-5-(*N*,*N*-dimethylamino)-3,6-dihydro-1,2,4-triazine-3,6-dicarboxylate (23) was eluted and purified with CH_2Cl_2–ethyl acetate (1:1): tan solid; mp 205–210 °C; IR (KBr) 3320, 2960, 2930, 1722, 1619, 1460, 1430, 1385, 1242, 1115 cm^{-1}; UV λ_{max} (CH_3OH) 202 nm (sh), 212 (ε 15 900), 237 (5800), 260 (sh), 283 (sh), 317 (2300); ^1H NMR (DMSO-d_6, 400 MHz) δ 11.15 (bs, 1 H), 7.79 (d, J = 8.0 Hz, 1 H), 7.36 (d, J = 8.0 Hz, 1 H), 7.09 (ddd, J = 8.0, 6.8, 1.2 Hz, 1 H), 7.03 (bdd, J = 8.0, 6.8 Hz, 1 H), 6.86 (d, J = 2.4 Hz, 1 H), 5.58 (s, 1 H), 3.68 (s, 3 H), 3.02 (bs, 3 H), 2.90 (s, 3 H), 2.85 (bs, 3 H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 163.6, 157.4, 140.7, 136.1, 126.8, 125.5, 121.5, 119.5, 118.8, 115.2, 111.7, 105.9, 51.4, 46.1, 41.5, 36.5 (2 C); LRMS (EI, 70 eV) m/z (M^+ not observed) 313 (100), 270 (37), 211 (37), 155 (46), 71 (33), 44 (33); HRMS (EI, 70 eV) m/z 357.1440 (M^+, calcd for $C_{17}H_{19}N_5O_4$, 357.1437).

Reaction of Indole with 4b. Trimethyl 6-oxo-5*H*-phenanthridine-2,3,4-tricarboxylate (12):[17] tan solid; mp 266–268 °C; IR 3440, 3040, 2960, 1730, 1670, 1440, 1290, 1263, 1248, 1010 cm^{-1}; UV λ_{max} (CH_3OH) 202 nm (ε 23 800), 226 (25 600), 236 (sh), 270 (9500), 326 (4300); ^1H NMR (DMSO-d_6, 400 MHz) δ 12.05 (bs, 1 H), 8.95 (s, 1 H), 8.49 (d, J = 7.6 Hz, 1 H), 7.59 (bdd, J = 8.0, 7.2 Hz, 1 H), 7.41 (d, J = 8.0 Hz, 1 H), 7.31 (bdd, J = 7.6, 7.2 Hz, 1 H), 3.92 (s, 3 H), 3.82 (s, 3 H), 3.81 (s, 3 H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 167.3, 166.0, 165.9, 158.6, 137.2, 136.9, 134.7, 133.7, 131.5, 129.2, 125.0, 124.4, 124.2, 123.0, 116.3, 116.0, 53.3, 53.2, 52.6; LRMS (EI, 70 eV) m/z 370 ($[M + 1]^+$, 15), 369 (M^+, 85), 338 (100); HRMS (EI, 70 eV) m/z 369.0853 (M^+, calcd for $C_{19}H_{15}NO_7$, 369.0848).

Acknowledgment. We gratefully thank the Research Corporation, the donors of the Petroleum Research Fund, administered by the American Chemical Society, the Camille and Henry Dreyfus Foundation, and the Boston University Seed Grant Committee for financial support. We also thank Jeanne DeCara for preparing **4b** and Heather Nimmons and Michael Creech of Boston University for running the mass spectra.