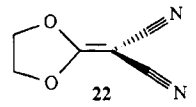
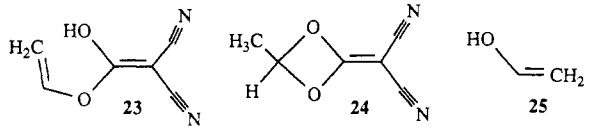
was raised. Quite clearly, no perpendicular alkene was formed, even in polar media, from this particular push–pull substituted alkene. Other possible species which might account for the 1601-cm^{-1} band are **23–25**.

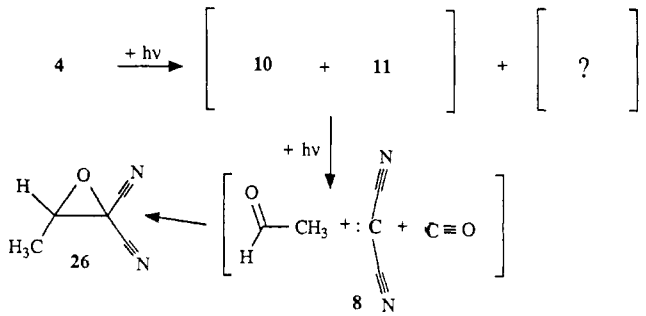


22



23 **24** **25**

Extended irradiation of **4** in argon demonstrated that secondary photoproducts were responsible for the IR bands at 2140, 1080, 970, and 890 cm^{-1} (Figure 1) along with additional bands, which eventually became visible, at 2250 (w), 2230 (m), 2200 (w), 1280 (w), 1200 (m), 1125 (w), 1115 (w), 1090 (m), 970 (m), and 890 (s) cm^{-1}. Chemical deduction suggested the final photostable products to be carbon monoxide and 2,2-dicyano-3-methyloxirane (**26**). Confirmation was made by comparison of the IR spectrum (argon) of an authentic sample, prepared by the epoxidation of the appropriate alkene, with the observed bands. In addition, the NMR bands for **26** were evident in the spectrum of a sample collected from the cesium iodide window after photolysis of **4**. These new products



were readily rationalized by the addition of carbene **8**,[11] formed photochemically from **10**, to the C=O bond of the acetaldehyde trapped adjacent to **8** in the matrix. This unique addition reaction suggested this route might be useful for further studies of the addition of carbenes to carbonyl compounds.

In conclusion, the data rule out a significant buildup of a perpendicular alkene during the low-temperature photolysis of **4**. As such, this argues against the existence of such intermediates in general. The first detailed photochemical study of a dipolar alkene in an apolar environment was shown to provide a novel fragmentation to dicyanoketene and acetaldehyde. In polar solution, no reaction occurred at room temperature. The photochemistry of caged dicyanoketene/acetaldehyde lead to a unique, direct insertion of dicyanocarbene into a C=O bond.

Experimental Section

Matrix isolation was performed on an Air Products CS-202 cryostat temperature controlled with the APD IC-2 controller. Perkin-Elmer 621 and Beckman Acta III spectrophotometers respectively were used to produce IR and UV spectra. Abraded potassium bromide or quartz disks in the reference beam compensated for light scattering. Matrix materials were argon (ultrahigh purity), heptane (concentrated H_2SO_4, distilled), acetonitrile (Spectral Grade), and water (triply distilled). Photochemical light sources were the unfiltered emission from Pen-Ray low-pressure mercury (254 nm) or Phillips low-pressure cadmium (229 nm) resonance lamps.

2-(Dicyanomethylene)-1,3-dioxacyclopentane (**4**) was prepared by a reported method.[9a] Vacuum (0.1 mm) sublimation of the crude, pink product proceeded readily at 5–10 °C below the melting point, giving colorless crystals of **4**: mp 119–120.5 °C; NMR ($CDCl_3$) δ 4.88 (s); ^{13}C NMR ($CDCl_3$, CD_3CN) 40.22, 71.45 (CH_2), 11.96 (CN), 178.36 (=$C(OR)_2$); IR ($CHCl_3$), 2225 (CN), 1613 (C=C), 1140 cm^{-1}; UV_{max} (CH_3CN) 239 nm (ε 24 000).

2,2-Dicyano-3-methyloxirane (26). 1,2-Dichloroethane (8.5 g), 1,1-dicyanopropene (0.10 g, 1.1 mmol), *m*-chloroperbenzoic acid (0.28 g, 1.6 mmol), and a little 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide were heated at (50–90 °C) for 26 h. The supernatant liquid was decanted after the volume was reduced (vacuum) to 4 mL and again after it was reduced to 1 mL. The resulting liquid was fractionated by GC (20% Apiezon L, 140 °C) to give 1,2-dichloroethane, a little 1,1-dicyanopropene, and predominantly, moderately stable **26**: NMR ($CDCl_3$) δ 1.66 (d, J = 5 Hz), 3.77 (q, J = 5 Hz); ^{13}C NMR ($CDCl_3$) δ 14.7, 39.3, 62.4, 110.7, 111.7; IR (CCl_4) 2250, 1430, 1400, 1275, 1195, 1130, 1105, 990, 880, 875 cm^{-1}.

Acknowledgment. Partial financial support was provided by The Research Corporation and The University of Toledo Faculty Research Award and Fellowship program. Technical assistance was provided by G. Buenning, M. Johnson, J. Wrestler, D. Shoup, and W. Opdyke. In addition, the CNDO/S calculations were performed by H. Jaffe.

Registry No. **4**, 5694-65-5; **8**, 1884-65-7; **9**, 109960-67-0; **10**, 4361-47-1; **11**, 75-07-0; **26**, 109960-66-9; 1,1-dicyanopropene, 1508-07-2.

Indole as a Dienophile in Inverse Electron Demand Diels–Alder Reactions. 5*H*-Pyridazino[4,5-*b*]indoles as Cycloadducts with 3,6-Dicarbomethoxy-1,2,4,5-tetrazine

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The indole skeleton is a fundamental structural unit of numerous biologically active alkaloids. As such, the chemistry of indole has been widely investigated[1] and the indole-based alkaloids have been the target of countless synthetic efforts. Indole could prove to be an appropriate starting material for further alkaloid syntheses if suitable chemistry can be coaxed from this parent skeleton. The recent applications by Boger[2] and others[3] of the inverse electron demand Diels–Alder cycloaddition[4] in organic synthesis has turned our interest to the possibility of using indole as a dienophile for constructing higher alkaloids.

(1) Reviews: (a) Sundberg, R. J. *The Chemistry of Indoles*; Academic Press: New York, 1970. (b) Remers, W. A. In *The Chemistry of Heterocyclic Compounds*; Houlihan, W. J., Ed.; Wiley-Interscience: New York, 1973; Vol. 25, Part I, Chapter 1.

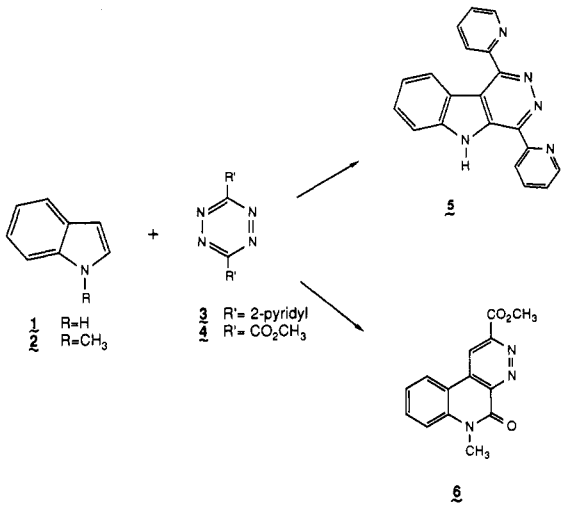
(2) (a) Boger, D. L.; Mullican, M. D. *Tetrahedron Lett.* **1982**, *23*, 4555. (b) Boger, D. L.; Mullican, M. D. *J. Org. Chem.* **1984**, *49*, 4033. (c) Boger, D. L.; Brotherton, C. E. *J. Org. Chem.* **1984**, *49*, 4050. (d) Boger, D. L.; Duff, S. B.; Panek, J. S.; Yasuda, M. *J. Org. Chem.* **1985**, *50*, 5782. (e) Boger, D. L.; Duff, S. R.; Panek, J. S.; Yasuda, M. *J. Org. Chem.* **1985**, *50*, 5790. (f) Boger, D. L.; Panek, J. S. *J. Am. Chem. Soc.* **1985**, *107*, 5745. (g) Boger, D. L.; Coleman, R. S. *J. Org. Chem.* **1986**, *51*, 3250.

(3) For some recent examples: (a) Posner, G. H.; Wettlaufer, D. G. *Tetrahedron Lett.* **1986**, *27*, 667. (b) Posner, G. H.; Wettlaufer, D. G. *J. Am. Chem. Soc.* **1986**, *108*, 7373. (c) Maggiora, L.; Mertes, M. P. *J. Org. Chem.* **1986**, *51*, 950.

(4) (a) Sauer, J. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 16. (b) Sauer, J.; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 779. (c) Boger, D. L. *Tetrahedron* **1983**, *39*, 2869.

0022-3263/87/1952-4610$01.50/0

Scheme I



Indeed, enamine moieties are known to be dienophilic in inverse electron demand Diels–Alder reactions.[5] Since the enamine functionality of indole dominates its reactivity, we felt successful cycloadditions with the 2,3-double bond were possible.

The use of indole (1) as a dienophile was reported previously utilizing the electron-deficient diene, 3,6-di-2-pyridyl-1,2,4,5-tetrazine (3) to obtain a 35% yield of what is formally a [4 + 2]-cycloadduct, 5.[6] *N*-Methylindole (2), however, was reported to yield a pyridazino quinolone, 6, upon reaction with the 3,6-dicarbomethoxy-1,2,4,5-tetrazine (4).[7] These earlier reports are summarized in Scheme I. The formation of 6 was suggested to result from a rearrangement of the initially formed cycloadduct prior to aromatization. A [4 + 2]-cycloadduct of indole was also obtained with tetrachlorothiophene 1,1-dioxide.[8] Other related reports of indole's participation in cycloaddition chemistry include [2 + 2 + 2]-condensations with alkynes mediated by cobalt;[9] 1,3-dipolar additions to the 2,3-bond of indole are also well-documented.[10] We report here our results concerning the dienophilicity of indole and *N*-acylindoles in inverse electron demand Diels–Alder reactions.

Results and Discussion

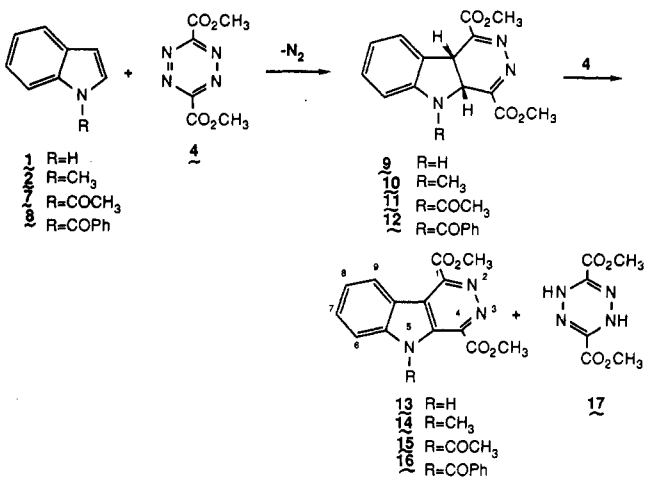
Numerous cycloadditions were attempted with indole and various electron-poor dienes previously reported to undergo inverse electron demand Diels–Alder reactions. Though an exhaustive number of reaction conditions were tested, no cycloadducts were detected with the exception of the reaction using 4. The most notable failures as potential dienes were 3,5,6-tricarbomethoxy-1,2,4-triazine and 5-carbomethoxy-2-pyrone, which would have given access to the carboline and carbazole skeletons, respectively,

Table I. Reaction of Indole and Acylindoles with 3,6-Dicarbomethoxy-1,2,4,5-tetrazine (4)

	conditions[a]	adduct (% yield)[b]	other products[c]
R = H, 1	A	13 (30)	18 (56)
R = H, 1	B	13 (68)	18 (9)[d]
R = CH_3, 2	C	14 (53)	6 (35)
R = CH_3CO, 7	C	15 (72)[e]	13 (17)
R = C_6H_5CO, 8	C	16 (80)	13 (<5)

[a] Conditions are detailed in Experimental Section. [b] All yields are isolated yields for purified products following chromatography and recrystallization. [c] All reactions were accompanied by a quantitative yield (1 equiv) of 17. [d] The yield of 18 was determined by integration of the NMR signals from the spectrum of the crude reaction mixture in comparison with those of 13. [e] By TLC, only a trace amount of 13 was detected. Deacylation to produce 13 occurred during the chromatography. No deacylation occurred during the chromatography of 16.

Scheme II



directly from indole.[11] Addition of a Lewis acid catalyst, in an effort to promote the cycloaddition, invariably led to indole dimer and trimer production along with intractable tars.

In an effort to reduce the nucleophilic reaction pathways of indole to allow a possibly "latent" dienophilicity to be manifested, *N*-acetylindole was also examined in parallel reactions with indole. Again, no cycloadducts were observed except with the tetrazine. In all other reactions, the *N*-acetylindole was invariably recovered unreacted. We decided at this stage to examine the scope of the tetrazine reactions.

With 1.9 equiv of 4, indole, *N*-methylindole, *N*-acetylindole, and *N*-benzoylindole[12] (1, 2, 7, and 8), respectively, all underwent [4 + 2]-cycloadditions with immediate release of diatomic nitrogen to produce the corresponding 5*H*-pyridazino[4,5-*b*]indoles, 13–16, Table I.[13] The dihydrotetrazine 17, the penultimate intermediate in the synthesis of the tetrazine, was also produced presumably

(5) See ref 4c, also: (a) Charushin, V. N.; van der Plas, H. C. *Tetrahedron Lett.* **1982**, *23*, 3965. (b) Marcelis, A. T. M.; van der Plas, H. C. *Heterocycles* **1985**, *23*, 683. (c) Komatsu, M.; Takamatsu, S.; Uesaka, M.; Yamamoto, S.; Ohshiro, Y.; Agawa, T. *J. Org. Chem.* **1984**, *49*, 2691. Boger has also made frequent use of enamines as dienophiles in the inverse electron demand Diels–Alder reaction, ref 2d and 2f.

(6) Takahashi, M.; Ishida, H.; Kohmoto, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1725.

(7) Seitz, G.; Kampchen, T. *Arch. Pharm. (Weinheim, Ger.)* **1976**, *309*, 679.

(8) Raasch, M. S. *J. Org. Chem.* **1980**, *45*, 856.

(9) Grotjahn, D. B.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1986**, *108*, 2091.

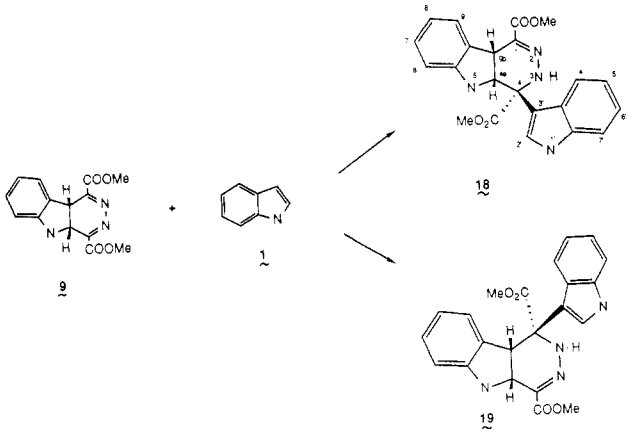
(10) (a) Ruccia, M.; Vivona, N.; Cusmano, G.; Marino, M. L.; Piozzi, F. *Tetrahedron* **1973**, *29*, 3159. (b) Laude, B.; Soufiaoui, M.; Arriau, J. *J. Heterocycl. Chem.* **1977**, *14*, 1183. (c) Fisera, L.; Mesko, P.; Lesko, J.; Dandarova, M.; Kovac, J.; Goljer, I. *Collect. Czech. Chem. Commun.* **1983**, *48*, 1845. (d) Bruche, L.; Zecchi, G. *J. Org. Chem.* **1983**, *48*, 2772.

(11) The triazine did not react with indole after 7 days in dioxane in a sealed tube at 150 °C. The pyrones underwent nucleophilic addition in refluxing toluene to produce 3-position adducts. Other dienes that failed to yield cycloadducts were hexachlorocyclopentadiene and tetraphenylcyclopentadienone.

(12) *N*-(Trifluoroacetyl)indole rearranged to the 3-(trifluoroacetyl)-indole under the reaction conditions, leading to a severe mixture of products.

(13) The use of 1 equiv of the tetrazine instead of 1.9 equiv halved the yields of 13–16. With increasing equivalents of tetrazine, increasing amounts of pigment byproducts formed during the chromatographic workup of the reaction. These byproducts, which rendered purification of the desired cycloadducts very difficult, are due to decomposition of the tetrazine during chromatography. See ref 23.

Scheme III



by the dehydrogenation of the intermediates, **9–12**, by tetrazine **4**, Scheme II.[14] The N-acyl adducts **15** and **16** could be quantitatively deacylated under mild conditions (anhydrous MeOH, SiO_2) to produce **13**. The observed cycloadditions, with immediate loss of nitrogen and subsequent aromatization, are in accord with previously reported cycloadditions of tetrazines with olefins, enol ethers, enol esters, and enamines.[15]

When the reaction between indole and the tetrazine was run at room temperature, the main product, **18**, was formed in 56% yield (based on indole). Comparable reactivity was not observed with the *N*-acylindoles, nor with *N*-methylindole. Furthermore, indole did not further react with **13** or **17** under the reaction conditions. Consequently, **18** most likely results from the interception of intermediate **9** by a second molecule of indole, Scheme III.

The structure of **18** was initially suggested by the observation of the molecular ion (EIMS) of *m/e* 404. The ^{1}H NMR spectra including the 2D-COSY spectrum clearly showed two separate ortho-disubstituted benzene systems, one typical of a 3-substituted indole (δ 7.79 d, 6.96 t, 7.09 t, 7.35 d) and one typical of an *o*-alkylaniline system (δ 7.11 d, 6.98 t, 6.50 t, 6.56 d). In addition, signals for the 2- and 3-protons of a dihydroindole (4.38 d, J = 10 Hz, H-9b; and 5.37 br dd, J = 10, 4 Hz, H-4a, respectively), the 2-proton of a 3-substituted indole (7.53 s, H-2′), and three exchangeable protons (5.89 d, J = 4 Hz, H-3; 8.98 br s, H-5, and 11.24 br s, H-1′) were also present. The observations of benzylic coupling between H-9 and H-9b and W-coupling between 5-NH and H-9b in the long range COSY spectrum (Δ = 0.4 s) confirmed the assignment of the δ 4.38 doublet as the benzylic proton. The identity of **18** rather than the regiochemical alternative **19** was subsequently established by the observation of W-coupling between the 3-NH of the tetrahydropyridazine ring and 4a-H of the dihydroindole ring. In **19**, analogous W-coupling would be observed to 9b-H.[16]

The relative stereochemistry of the 4-position (addition of indole to the exo face rather than the endo face) was assigned on the basis of NOE's, Figure 1, which also confirmed the regiochemistry of the indole addition (**18** rather than **19**). Specifically, NOE's between H-2′ of the indole nucleus to the H-4a and H-9b protons of the dihydro-

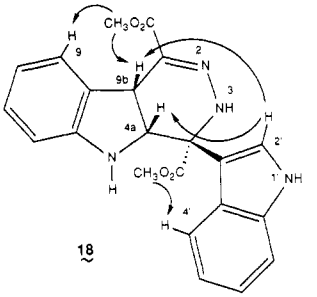


Figure 1. Observed NOE's for the determination of the structure of **18**.

pyridazinoindole moiety require the indicated stereochemistry. The nucleophilic addition of indole to the 4-position of intermediate **9** thus occurs from the convex face as expected.

N-Methylindole yielded **14** in the cycloaddition, though a significant amount of **6** was also isolated, Table I. Seitz and Kampchen previously isolated **6** in 45% yield as the only reported product in the cycloaddition of **2** and **4** (refluxing CH_2Cl_2), but with only 1 equiv of the tetrazine.[7] With the additional equivalent of **4** we employed in our reaction conditions, we rationalized that dehydrogenation of intermediate **10** occurred before rearrangement to **6**. However, when we repeated the reaction in refluxing CH_2Cl_2 (24 h) using only 1 equiv of **4**, a 45% yield of **14** was obtained with no **6** detected by NMR (<2%), though a trace was observed on TLC. These results stand in contrast to those reported earlier,[7] for reasons that are as yet unclear.

As has been suggested for other cycloadditions utilizing a tetrazine as the diene, there may be highly polar character to the reaction of **4** with indole. The production of **18** in this reaction most likely results from the interception of intermediate **9** by a second molecule of indole. This nucleophilic addition is significant in that it may represent the first step of a cyclocondensation reaction between nucleophilic indole and the electrophilic dihydropyridazine **9**, perhaps modeling the pathway for the reaction between indole and **4**, but without the final ring closure.

Nucleophilic addition of indole to **9** therefore competes with aromatization. Performing the reaction under conditions that maintain a high concentration of **4**, which functions as both diene and dehydrogenating agent, relative to indole should thus favor the production of **13** relative to **18**. Indeed, dropwise addition of a solution of indole to a solution of **4** in refluxing methylene chloride led to 68% isolated yield of **13**, with only 9% of **18**.[17]

The failure to secure cycloadducts with dienes other than **4** could result from a rapid retrocycloaddition of the initially formed adducts that proceeds at a significantly faster rate than dehydrogenation. This seems an unlikely explanation in view of the rapid reaction between indole and **4**. While the loss of the 10 π-electron aromaticity of indole may contribute to the inability to observe cycloadducts, cycloadditions do occur between naphthalene and hexachlorocyclopentadiene, a diene that did not react with indole in our experiments.[18] Cycloadditions involving the 2,3-double bond of indole with dienes less electron deficient than **4** are probably just energetically unfavorable.

Regardless of the mechanism, however, the cycloadditions with **4** reported here provide easy access to 5*H*-

(14) We cannot empirically rule out dehydrogenation occurring prior to the loss of nitrogen, but a priori consider a tetraazabarrelene intermediate unlikely.

(15) (a) Sauer, J.; Mielert, A.; Lang, D.; Peter, D. *Chem. Ber.* **1965**, *98*, 1435. (b) Molz, T.; Konig, P.; Goes, R.; Gauglitz, G.; Meier, H. *Chem. Ber.* **1984**, *117*, 833.

(16) The 4a-H and 9b-H are distinguished by their chemical shifts, 4a-H being at lower field, confirmed by the observed coupling between 5-NH and 4a-H.

(17) We are grateful to a referee for suggesting these reaction conditions.

(18) Danish, A. A.; Silverman, M.; Tajima, Y. A. *J. Am. Chem. Soc.* **1954**, *76*, 6144.

pyridazino[4,5-*b*]indole derivatives, compounds of interest due to their antihypertensive properties.[19,20]

Experimental Section

General Procedures. All melting points are uncorrected. The ^1H NMR and ^{13}C NMR spectra were recorded on a Varian XL-400 (93.93 kg) or JEOL FX90-Q (21.13 kg) spectrometers, in $CDCl_3$ unless otherwise noted; chemical shifts are reported in ppm downfield from Me_4Si, internal standard. Chemical shift assignments in the ^1H and ^{13}C NMR spectra of **18** were made with the aid of COSY and HETCOR experiments; multiplicities in ^{13}C NMR spectrum of **18** were made by using the APT experiment. The assignment of all N-H protons (**13** and **18**) were confirmed by D_2O exchange. Infrared spectra were recorded on a Perkin-Elmer 1800 FT-IR spectrophotometer. Mass spectra were recorded on a Finnigan MAT 8200 instrument. All solvents were dried and distilled prior to use. Freshly opened indole, purchased from Aldrich Chemical Company, was used without additional purification, previously opened indole was recrystallized from benzene/petroleum ether (bp 30–60 °C) prior to use. *N*-Methylindole,[21] *N*-acetylindole,[22] *N*-benzoylindole,[22] 3,6-dicarbomethoxy-1,2,4,5-tetrazine,[23] 3,5,6-tricarbomethoxy-1,2,4-triazine,[24] and 5-carbomethoxy-2-pyrone[25] were prepared according to literature procedures.

Procedure for Cycloaddition Reactions between Indole Derivatives and 3,6-Dicarbomethoxy-1,2,4,5-tetrazine. All reactions were conveniently monitored by the color change as the bright red **4** is consumed to produce the adducts and the orange **17**. Use of an inert atmosphere did not affect the yields. Nearly quantitative yields of **17** were obtained for each reaction. All reported yields are on isolated, recrystallized product.

Method A. To a solution of indole (**1**, 0.100 g, 0.85 mmol) in anhydrous methylene chloride (5 mL) was added solid **4** (0.318 g, 1.61 mmol) at room temperature. The evolution of nitrogen ensued immediately, and when it subsided (5 min), the reaction mixture was refluxed for 10 min to ensure completion. Filtration of the resultant precipitate and recrystallization from EtOAc gave pure **18** (0.097 g, 56% based on indole). The filtrate was evaporated under reduced pressure and the residual oil chromatographed [flash silica gel; 1:2 methylene chloride/ethyl acetate] to yield crude **13**. Recrystallization from ethyl acetate/petroleum ether (bp 30–60 °C) gave pure **13** (0.0725 g, 30% yield).

Method B. To a solution of **4** (0.318 g, 1.61 mmol) in anhydrous methylene chloride (15 mL) was added a solution of indole (**1**, 0.100 g, 0.85 mmol) in anhydrous methylene chloride (50 mL) dropwise over 4 h with stirring at mild reflux. Following the addition, stirring was continued for 4 h. Workup proceeded as in method A for the isolation of **13**.

Method C. To a solution of **2**, **7**, or **8** (0.6–0.8 mmol) in anhydrous toluene (5 mL) was added solid **4** at room temperature with stirring. The reaction solution was refluxed (16 h) under anhydrous conditions. The reaction mixture was subsequently evaporated to dryness, the residue chromatographed [flash silica gel; 3:2 methylene chloride/ethyl acetate], and the product recrystallized from ethyl acetate.

1,4-Dicarbomethoxy-5*H*-pyridazino[4,5-*b*]indole (13): method A, yield 0.0725 g (0.26 mmol), 30%; method B, yield 0.163 g (0.59 mmol), 68%; mp 195–197 °C; IR (KBr) 3360 (s), 1731 (s), 1686 (s), 1299 (s), 1217 (s) cm^{-1}; UV λ_{max} (CH_3CN) 218 nm (ϵ 15 400), 268 (20 100), 310 (4900), 352 (1700); ^1H NMR δ 10.6 (br s, ex, NH-5), 8.89 (br d, J = 8 Hz, H-9), 7.73 (ddd, J = 8, 8, 1 Hz, H-7), 7.68 (br d, J = 8 Hz, H-6), 7.48 (ddd, J = 8, 8, 1 Hz, H-8), 4.21 (s, 3 H, OCH_3), 4.18 (s, 3 H, OCH_3); ^{13}C NMR δ 165.85 (2 C), 146.18, 140.98, 137.41, 136.70, 131.07, 126.68, 122.78, 121.32, 118.17, 112.27, 53.33 (2 C); HRMS, calcd for $C_{14}H_{11}N_3O_4$ 285.0750, found (m/z) 285.0749.

1,4-Dicarbomethoxy-5-methyl-5*H*-pyridazino[4,5-*b*]indole (14): method C, beginning with 0.1000 g (0.76 mmol) of **2**, 0.2845 (1.44 mmol) of **4**; yield 1.2043 g (0.40 mmol) 53%; mp 154–156 °C; IR (KBr) 2960 (w), 1730 (s), 1217 (s) cm^{-1}; UV λ_{max} (CH_3CN) 220 nm (ϵ 13 500), 268 (19 700), 348 (1800); ^1H NMR δ 8.83 (br d, J = 8 Hz, H-9), 7.76 (ddd, J = 8, 8, 1 Hz, H-7), 7.60 (br d, J = 8 Hz, H-6), 7.48 (ddd, J = 8, 8, 1 Hz, H-8), 4.19 (s, 3 H, OCH_3), 4.17 (s, 3 H, OCH_3), 4.01 (s, 3 H, NCH_3); ^{13}C NMR δ 165.79, 165.65, 145.90, 142.62, 140.23, 135.26, 130.68, 126.32, 122.60, 120.63, 117.96, 109.98, 53.68, 53.47, 32.56; HRMS, calcd for $C_{15}H_{13}N_3O_4$ 299.0905, found (m/z) 299.0906.

1,4-Dicarbomethoxy-5-acetyl-5*H*-pyridazino[4,5-*b*]indole (15): method C, beginning with 0.1000 g (0.63 mmol) of **7**, 0.2358 g (1.20 mmol) of **4**, yield 0.141 g (0.43 mmol), 72%; mp 173–175 °C; IR (KBr) 3091 (w), 3033 (w), 2960 (w), 1730 (s), 1716 (s), 1490 (s), 1311 (s), 1269 (s), 1207 (s) cm^{-1}; UV λ_{max} (CH_3CN) 220 nm (ϵ 20 500), 278 (10 200), 325 (sh); ^1H NMR δ 8.78 (br d, J = 8 Hz, H-9), 7.92 (br d, J = 8 Hz, H-6), 7.75 (ddd, J = 8, 8, 1 Hz, H-7), 7.54 (ddd, J = 8, 8, 1 Hz, H-8), 4.20 (s, 3 H, OCH_3), 4.12 (s, 3 H, OCH_3), 2.84 (s, 3 H, $COCH_3$); ^{13}C NMR δ 167.69, 165.36, 164.87, 143.84, 139.30, 133.99, 131.72, 126.73, 124.89, 123.64, 120.50 (2 C), 113.68, 53.54, 53.43, 27.00; HRMS, calcd for $C_{16}H_{13}N_3O_5$ 327.0852, found (m/z) 327.0855.

1,4-Dicarbomethoxy-5-benzoyl-5*H*-pyridazino[4,5-*b*]indole (16): method C, beginning with 0.136 g (0.60 mmol) of **8**, 0.2247 g (1.14 mmol) of **4**, yield 0.187 g (0.48 mmol), 80%; mp 160–161 °C; IR (KBr) 2960 (w), 1745 (sh), 1733 (s), 1710 (s), 1455 (s), 1404 (s), 1211 (s), 1091 (s) cm^{-1}; UV λ_{max} (CH_3CN) 220 nm (ϵ 13 900), 250 (15 200), 280 (6400); ^1H NMR δ 8.83 (br d, J = 8 Hz, H-9), 7.81 (br d, J = 8 Hz, 2 H, H-2′, H-6′), 7.73 (br dd, J = 8, 8 Hz, H-7), 7.57 (ddd, J = 8, 8, 1 Hz, H-4′), 7.55 (br dd, J = 8, 8 Hz, 2 H, H-3′, H-5′), 7.50 (br dd, J = 8, 8 Hz, H-8), 7.28 (br d, J = 8 Hz, H-6), 4.23 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3); ^{13}C NMR δ 168.58, 165.45, 164.44, 146.95, 142.13, 141.00, 135.70, 134.85, 132.99, 131.30, 130.38 (2 C), 129.41 (2 C), 126.47, 124.42, 123.17, 119.31, 113.50, 53.58, 53.18; HRMS, calcd for $C_{21}H_{15}N_3O_5$ 389.1012, found (m/z) 389.1012.

1,4-Dicarbomethoxy-4-(3-indolyl)-3,4,4a,9b-tetrahydro-5*H*-pyridazino[4,5-*b*]indole (18): method A, beginning with 0.1000 g (0.85 mmol) of **1**, 0.3180 g (1.61 mmol) of **4**; yield 0.097 g (0.24 mmol) 56% (based on **1**): mp 265 °C dec; IR (KBr) 3409 (s), 3348 (s), 1729 (s), 1697 (s), 1601 (m), 1284 (s), 1117 (s) cm^{-1}; UV λ_{max} (CH_3CN) 218 nm (end absorption), 234 (ϵ 15 600), 276 (10 300), 286 (9700); ^1H NMR (DMSO-d_6) δ 11.24 (br s, exchangeable, NH-1′), 8.98 (br s, exchangeable, NH-3), 7.79 (br d, J = 8 Hz, H-4′), 7.53 (s, H-2′), 7.35 (br d, J = 8 Hz, H-7′), 7.11 (br d, J = 7 Hz, H-9), 7.08 (br t, J = 8 Hz, H-6′), 6.98 (br t, J = 8, *H*-5′), 6.96 (br t, J = 7 Hz, H-7), 6.56 (br d, J = 7 Hz, H-6), 6.50 (br t, J = 7 Hz, H-8), 5.89 (d, J = 4 Hz, exchangeable, NH-5), 5.34 (br m, after D_2O exchange, sharpens to d, J = 10 Hz, H-4a), 4.38 (d, J = 10 Hz, H-9b), 3.65 (s, 3 H, 4-CO_2CH_3), 3.56 (s, 3 H, 1-CO_2CH_3); ^{13}C NMR δ 169.9 (s), 164.7 (s), 151.9 (s), 136.5 (s), 135.3 (s), 128.3 (d, C-7), 128.3 (s), 125.7 (d, 2 C, C-2′, C-9), 124.4 (s), 121.6 (d, C-6′), 120.1 (d, C-4′), 119.3 (d, C-5′), 117.7 (d, C-8), 111.8 (d, C-7′), 110.2 (s), 109.9 (d, C-6), 62.8 (d, C-4a), 62.2 (s), 52.8 (q, 4-CO_2CH_3), 51.5 (q, 1-CO_2CH_3), 38.8 (d, C-9b); HRMS, calcd for $C_{22}H_{20}N_4O_4$ 404.1484, found (m/z) 404.1485.

Deacylation of 15 and 16. N-Acyl compounds, **15** or **16** (0.100 g), were suspended in anhydrous methanol (5 mL) with an equal weight of silica gel and refluxed with stirring for 5 h. The reaction

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(20) We were unable to affect a second cycloaddition of the 5*H*-pyridazino[4,5-*b*]indoles with 1,1-diethoxyethylene to afford carbazole derivatives using sealed tube reactions in toluene at 190 °C. See ref 3c. Examples of cycloadditions involving pyridazines, see ref 2g and 4c, also: Boger, D. L.; Coleman, R. S. *J. Org. Chem.* **1984**, *49*, 2240.

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(25) Prepared via diazomethane methylation of coumalic acid (Aldrich).

mixture was filtered and the methanol evaporated under reduced pressure. Workup proceeded as in method B, giving quantitative yields of 13.

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Unexpected Regioselectivity in the Base-Promoted Cyclization of an ϵ-Epoxy Sulfone

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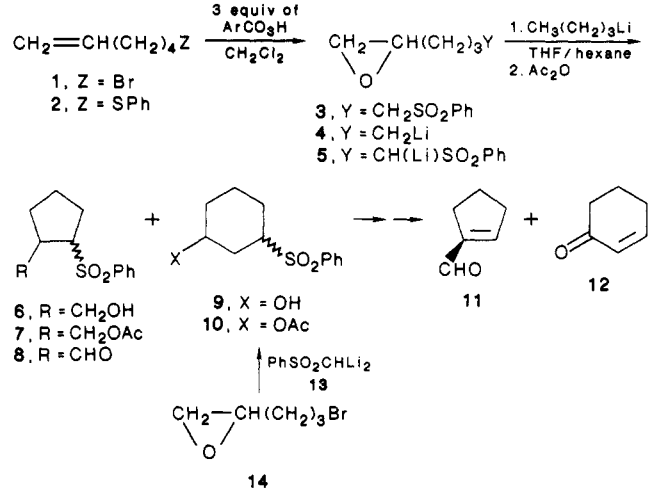
Recently, Eisch and co-workers published a communication[1] that described the use of [(phenylsulfonyl)methylene]dilithium (13) as a cyclizing reagent for electrophilic bifunctional organic substrates (e.g., α,ω-dihalides or halo epoxides). As an illustration of this methodology, they reported the conversion of 5-bromo-1,2-epoxypentane (14) to 3-(phenylsulfonyl)cyclohexanol (9) in 64% yield. Formation of the product of maximum ring size (i.e., 9 rather than 6), they claimed, argues for an initial attack of dilithio derivative 13 on the epoxide function, since the alternate pathway would have resulted in intermediate 5 and subsequent cyclization to afford the smaller cycloalkane (6), on the basis of previous studies[2] involving γ- and δ-epoxy sulfones. Indeed, further support for this argument (i.e., 5 → 6) can be found in a study of the regioselectivity in the base-promoted cyclization of epoxy nitriles by Stork and co-workers,[3] subsequently reinvestigated by Lallemand and Onanga,[4] as well as a recent report[5] that lithio epoxide 4 cyclized to afford predominantly cyclopentylmethanol.

In view of our interest[6,7] in intramolecular alkylations involving epoxides and the knowledge that, a priori, both modes of cyclization are feasible[8] for the lithio derivative 5 of epoxy sulfone 3, we decided to synthesize independently lithio derivative 5 and determine its cyclization products (i.e., 6 and/or 9).

ϵ-Epoxy sulfone 3 was obtained in 80% yield from the commerically available[9] 6-bromo-1-hexene (1) by reaction

Scheme I



of the latter with the anion derived from thiophenol, followed by subsequent oxidation of the corresponding thioether (2) with 3 equiv of 3-chloroperoxybenzoic acid (Scheme I). Contrary to expectations, treatment of sulfone 3 with 1 equiv of *n*-butyllithium afforded, in >85% yield, a cyclization product shown by ^{1}H NMR analysis to consist of both regioisomeric alcohols (6 and 9), the spectral properties of the major component being consistent with those reported[1] for 3-(phenylsulfonyl)cyclohexanol (9).

Since TLC analysis indicated that separation of this cyclization product (6 and 9, each an undetermined mixture of stereoisomers) would be problematical, further transformations were undertaken to confirm the structural identity and exact composition of its components. Oxidation of the cyclized product mixture with 4 molar equiv of pyridinium chlorochromate[10] was accompanied by substantial elimination of the phenylsulfonyl moiety to afford 2-cyclohexenone (12) as the major product, accompanied by minor amounts of aldehydic sulfone 8.[11] Subsequent treatment of this latter mixture of products in ether with 20% aqueous potassium hydroxide at 20 °C afforded 2-cyclohexenone (12) accompanied by a minor amount of 1-cyclopentenecarbaldehyde (11)[12] as the only volatile products, whose identities were further confirmed by ^{1}H NMR and VPC[13] analysis (co-injection with authentic samples).

Further evidence confirming the structure of the cyclization products derived from lithio derivative 5 was obtained after acetylation[14] of the mixture. Gratifyingly, ^{1}H NMR analysis[15] of the acetylated products (7 and 10)

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(11) Aldehyde 8 was characterized by a ^{1}H NMR absorption band at δ 9.64 (CHO). The sluggishness toward elimination of the phenylsulfonyl moiety exhibited by aldehyde 8 indicates that hydroxy sulfone 6 probably has the trans configuration.
(12) An authentic sample of aldehyde 11 was prepared as described in the literature. See: Brown, J. B.; Henbest, H. B.; Jones, E. R. H. *J. Chem. Soc.* **1950**, 3634.
(13) A 6 ft × $^1/_8$ in. column packed with 5% OV-17 on 100–120-mesh Gas Chrom Q (oven temperature 88 °C, flow 15 mL/min) was used for this analysis. Retention times: 2.05 min (aldehyde 11) and 3.29 min (ketone 12).
(14) A procedure described by Hassner and co-workers was used to ensure quantitative acetylation of the cyclized product. See: Hassner, A.; Krepski, L. R.; Alexanian, V. *Tetrahedron* **1978**, *34*, 2069.
(15) The ^{1}H NMR spectrum of cyclopentanoid 7 exhibited a doublet (J = 6 Hz, CH_2OAc) at δ 3.99 and a singlet (O=CCH_3) at δ 1.98. The corresponding absorptions for acetate 10 occurred at δ 5.00–4.39 (CHOAc, cis stereoisomer), 5.43–5.11 (CHOAc, trans stereoisomer), and 2.03 (s, O=CCH_3).

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