Rearrangements of Azabiphenylenes. The Impact of Nitrogen Number and Position

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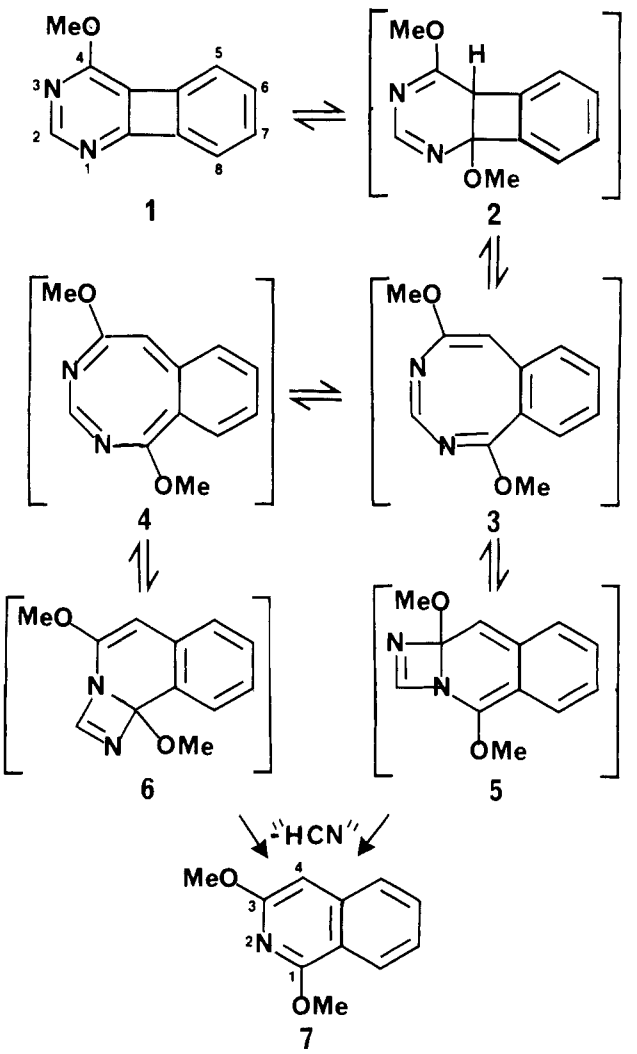
4-Methoxy-1-azabiphenylene and 1-methoxy-2-azabiphenylene have been synthesized from the appropriate precursor diethynylmethoxypyridines via cobalt-catalyzed cooligomerization with bis(trimethylsilyl)acetylene. When 4-methoxy-1,3-diazabiphenylene was transformed into 1,3-dimethoxyisoquinoline in methanolic sodium methoxide at reflux overnight, 1-methoxy-2-azabiphenylene required longer reflux time and 4-methoxy-1-azabiphenylene required forcing conditions for transformations to occur. The transformation product from the latter was shown to be 1,5-dimethoxy-2-benzazocine and that from the former was established by independent synthesis to be 3-methoxy-1-((*E*)-2-methoxyethenyl)isoquinoline. The impressive disparity in the products obtained from the methoxydiazabiphenylene and the two methoxyazabiphenylenes can be rationalized by consideration of the locus of methanol addition and sequential electrocyclic reactions.

During the course of designing dimensional probes of enzyme–coenzyme binding,[1a] we encountered some unusual rearrangements of 1,3-diazabiphenylenes.[1b,c] For example, 4-methoxy-1,3-diazabiphenylene (**1**) in methanol undergoes efficient transformation to 1,3-dimethoxyisoquinoline (**7**) in the presence of either trifluoroacetic acid or sodium methoxide. A mechanistic sequence was proposed that is consistent with the facts, with theoretical considerations, and with precedents.[2] The formal sequence elaborated in Scheme I is conceived to include minimally the following steps: (1) **1** ⇌ **2**, addition of methanol (H^+ or CH_3O^-); (2) **2** ⇌ **3**, disrotatory electrocyclic reaction, 6π electrons, thermally allowed;[3] (3) **3** ⇌ **4**, bond-shift isomerization; (4) **3** ⇌ **5**, disrotatory electrocyclic reaction, 6π electrons, thermally allowed; (5) **4** ⇌ **6**, disrotatory electrocyclic reaction, 6π electrons, thermally allowed; (6) **5** → **7** and **6** → **7**, irreversible loss of the elements of HCN, probably via an ionic process (CH_3OH with H^+ or CH_3O^-).

The intermediate **3** accommodates the "tub" form of the diazacyclooctatetraene better than does intermediate **4**, but no intermediates were isolated. We have not performed the requisite ^{15}N labeling to obtain a quantitative expression of preference. Nor should Scheme I be accorded any exclusivity. It does, however, suggest the desirability of testing both the ease and the course of possible transformations of the related azabiphenylenes **8** and **9** containing one nitrogen. For example, if 4-methoxy-1-azabiphenylene (**8**) were to undergo a sequence of steps similar to **2** ⇌ **3** ⇌ **5**, a final elimination, because it requires the loss of a two-carbon fragment (acetylene?), might not occur. If the sequence of steps were branched, similar to **2** ⇌ **3** ⇌ **4** ⇌ **6**, a final elimination of the elements of HCN might lead to 1,3-dimethoxynaphthalene. The course of the transformation of 1-methoxy-2-azabiphenylene (**9**) would be desirable for comparison. We have now prepared compounds **8** and **9** and have investigated their behavior in methanol with trifluoromethanesulfonic acid (triflic acid) and with sodium methoxide.

Scheme I



Synthesis of Methoxyazabiphenylenes. The isomeric methoxyazabiphenylenes were prepared by parallel syntheses as outlined in Scheme II. The starting material, 2,3,4-tribromopyridine (**10**), was prepared by the published

(1) (a) d'Alarcao, M.; Bakthavachalam, V.; Leonard, N. J. *J. Org. Chem.*, preceding paper in this issue. (b) d'Alarcao, M.; Leonard, N. J. *J. Am. Chem. Soc.* **1983**, *105*, 5958. (c) Bakthavachalam, V.: d'Alarcao, M.; Leonard, N. J. *J. Org. Chem.* **1984**, *49*, 289.

(2) For examplex of related transformations, see: (a) Kaminski, V. V.; Comber, R. N.; Wexler, A. J.; Swenton, J. S. *J. Org. Chem.* **1983**, *48*, 2337. (b) Kaminski, V. V.; Swenton, J. S.; Cottrell, C. E. *Tetrahedron Lett.* **1982**, *23*, 4207. (c) Comber, R. N.; Swenton, J. S.; Wexler, A. J. *J. Am. Chem. Soc.* **1979**, *101*, 5411. (d) Paquette, L. A.; Kakihana, T.; Hansen, J. F.; Philips, J. C. *J. Am. Chem. Soc.* **1971**, *93*, 152. (e) Paquette, L. A.; Kakihana, T.; Kelly, J. F. *J. Org. Chem.* **1971**, *36*, 435. (f) Snyder, J. P.; Lee, L.; Farnum, D. G. *J. Am. Chem. Soc.* **1971**, *93*, 3816. (g) Wentrup, C. *Tetrahedron* **1971**, *27*, 1027. (h) Barton, J. W.; Whitaker, K. E. *J. Chem. Soc. C* **1968**, 1663. (i) Trost, B. M.; Cory, R. M. *J. Am. Chem. Soc.* **1971**, *93*, 5573. (j) Trost, B. M.; Scudder, P. H.; Cory, R. M.; Turro, N. J.; Ramamurthy, V.; Katz, T. J. *J. Org. Chem.* **1979**, *44*, 1264. (k) Nair, V. J. *J. Heterocycl. Chem.* **1975**, *12*, 183. (l) Sindler-Kulyk, M.; Neckers, D. C. *J. Org. Chem.* **1983**, *48*, 1275.

(3) Woodward, R. B.; Hoffmann, R. "The Conservation of Orbital Symmetry"; Verlag Chemie, GmbH: Weinheim/Bergstrasse, 1970; pp 45, 51, 53.

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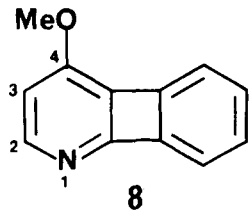

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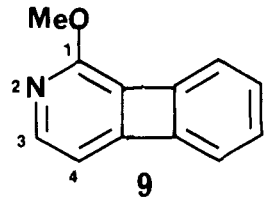

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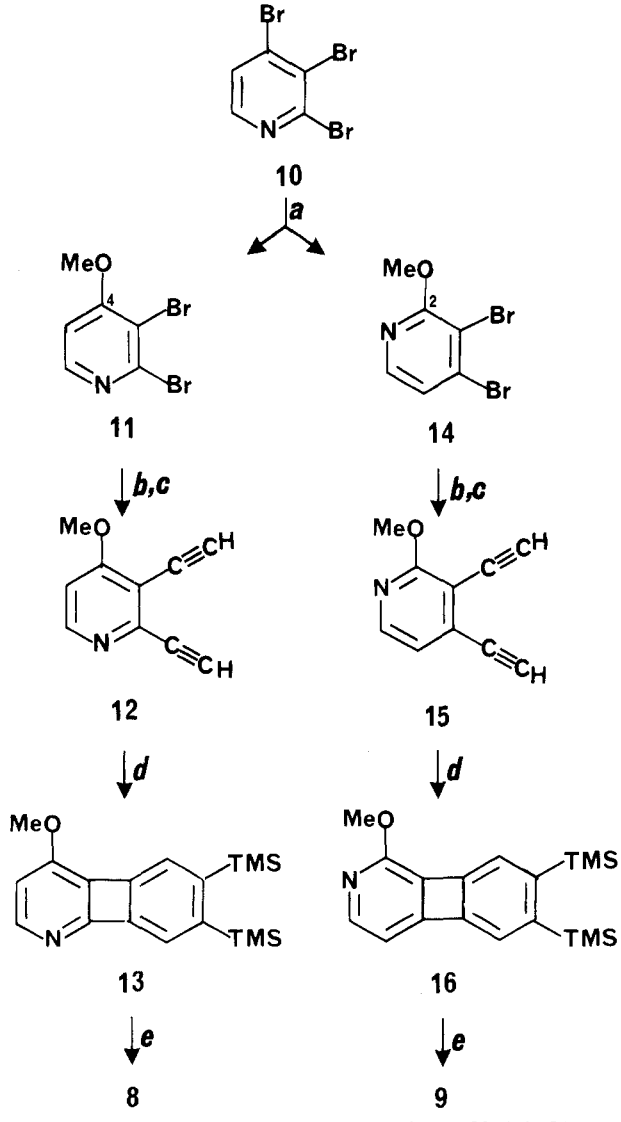
route[4] with a simplified workup. Conversion of **10** to a mixture of the dibromomethoxypyridines **11** and **14** by reaction with 1 equiv of sodium methoxide gave predominantly 2,3-dibromo-4-methoxypyridine (**11**) for the sequence **12** → **13** → **8**, but the 12–16% maximal yields of compound **11** was debrominated to afford the known 4-methoxypyridine (**19**).[6]

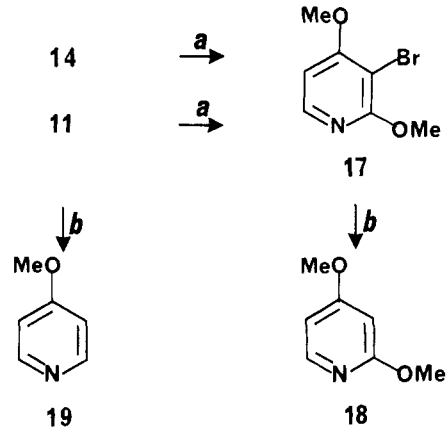
Scheme II[a]



[a] (a) 1 equiv NaOMe/MeOH; (b) $Me_3SiC{\equiv}CH$, $(Ph_3P)_2PdCl_2$, CuI, Et_3N, DMF; (c) 0.5 N NaOH/MeOH; (d) $CpCo(CO)_2$, bis(trimethylsilyl)acetylene; (e) CF_3SO_3H/cyclohexane.

3,4-dibromo-2-methoxypyridine (**14**) were made to suffice for the synthetic sequence **15** → **16** → **9** originating with this isomer. The proof of the structures of **11** and **14** is outlined in Scheme III. Both were converted to the same bromodimethoxypyridine **17**, which was debrominated to the known 2,4-dimethoxypyridine (**18**).[5] In addition,

Scheme III[a]

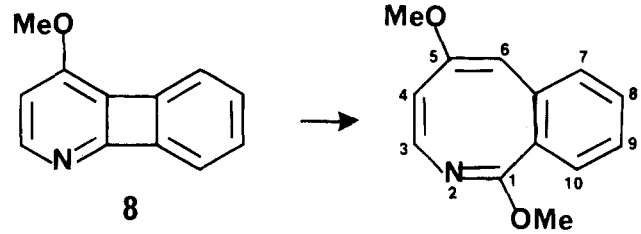


[a] (a) Excess NaOMe/MeOH; (b) H_2, Pd/C.

The corresponding diethynylmethoxypyridines (**12** and **15**) were obtained separately from **11** and **14** by the general approach of Takahashi et al.,[7] namely $(Ph_3P)_2PdCl_2$/CuI-mediated coupling of the bromine-bearing positions to (trimethylsilyl)acetylene, followed by removal of the trimethylsilyl groups. Each diethynylpyridine was then elaborated into an azabiphenylene (**13** and **16**) by cobalt-catalyzed cooligomerization with bis(trimethylsilyl)-acetylene. This reaction, developed by Vollhardt,[8] was also used in the synthesis of 1,3-diazabiphenylene (**1**).[1] The UV spectra of **13** and **16** showed 3-band patterns between 300 and 400 nm, and their ^1H NMR spectra showed ring proton resonances upfield of the normal aromatic region; these traits are typical of biphenylene-like 6-4-6 ring systems.[9] Protodesilylation of **13** and of **16** with triflic acid in cyclohexane then afforded the desired methoxyazabiphenylenes **8** and **9**.

Transformation of the Methoxyazabiphenylenes. Although 4-methoxy-1,3-diazabiphenylene (**1**) rearranged completely to 1,3-dimethoxyisoquinoline (**7**) within 1 h at room temperature in methanol containing 1% trifluoroacetic acid, both methoxyazabiphenylenes **8** and **9** were much less reactive with methanolic acid. Each was recovered essentially intact after 22 h at 140 °C in methanol containing 20% triflic acid; nevertheless, TLC after these incubations revealed traces of other compounds together with a small amount of immobile material at the origin.

The transformation of **1** into **7** also occurred in metha-



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(4) den Hertog, H. J. *Recl. Trav. Chim. Pays-Bas* **1945**, *64*, 85.
(5) Talik, Z. *Bull. Acad. Polon. Sci. Ser. Chim.* **1961**, 9, 561.
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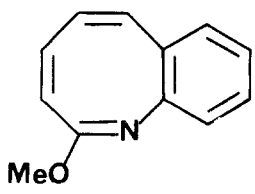
(7) Takahashi, S.; Kuroyama, Y.; Sonogashira, K., Hagihara, N. *Synthesis* **1980**, 627.
(8) (a) Vollhardt, K. P. C. *Acc. Chem. Res.* **1977**, *10*, 1. (b) Berris, B.; Lai, Y.-H.; Vollhardt, K. P. C. *J. Chem. Soc., Chem. Commum.* **1982**, 953.
(9) For other examples of the spectroscopic properties of biphenylenes, see: Barton, J. W.; Walker, R. B. *Tetrahedron Lett.* **1975**, *8*, 569. McBride, J. A. H. *J. Chem. Soc., Chem. Commun.* **1974**, 359. Boulton, A. J.; Chadwick, J. B.; Harrison, C. R.; McOmie, J. F. W. *J. Chem. Soc. C* **1968**, 328.

nolic sodium methoxide upon heating at reflux overnight. We therefore exposed each of the azabiphenylenes **8** and **9** to similar conditions and found that under forcing conditions (0.4 M CH_3ONa in CH_3OH, 140 °C), compound **8** was slowly (12% recovery of **8** after 24 h) converted in high yield to a product, mp 121–122 °C, identified by exact mass measurement as $C_{12}H_9NO$ (as in **8**) plus CH_3OH. The spectroscopic properties of this $C_{13}H_{13}NO_2$ product strongly suggested the 1,5-dimethoxy-2-benzazocine structure **20**. The comparatively featureless UV spectrum (EtOH, 277 nm, sh, ϵ 2140, and 244 nm, sh, ϵ 8500) is strikingly similar to that reported by Paquette et al.[10] for 2-methoxy-1-benzazocine (**21**) (280 nm, ϵ 1200, and 243 nm, sh, ϵ 7200). The IR spectrum shows absorption maxima at 1680, 1630, and 1590 cm^{-1}; 2-methoxyazocine (**23**) absorbs at 1675, 1640, and 1620 cm^{-1}.[11] The similarities between the ^1H NMR spectra of the methoxybenzazocines **21** and **22**,[10] of 2-methoxyazocine (**23**), and of azocine itself (**24**)[12] and the ^1H NMR spectrum of **20** further support the structural assignment. Specifically, a pair of doublets (J = 9 Hz) with chemical shifts of 6.59 and 5.10 ppm were observed for the 3- and 4-protons, and the 6-proton appeared as a singlet at 5.63 ppm. Although other bond-shift and valence isomers are presumably available, 1,5-dimethoxy-2-benzazocine exists predominantly as shown in **20**, since the azocine ring is fused to a benzene ring and is only lightly substituted.[13,14]



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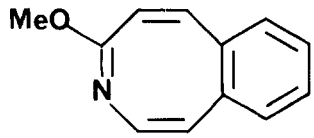

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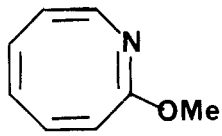

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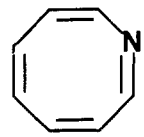

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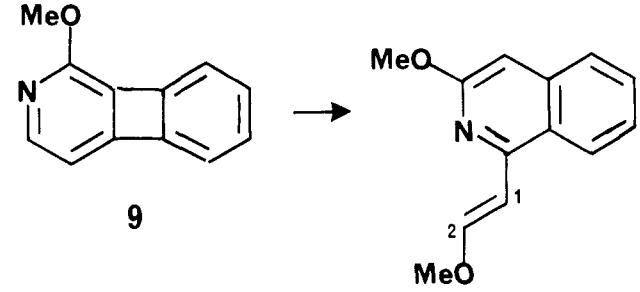
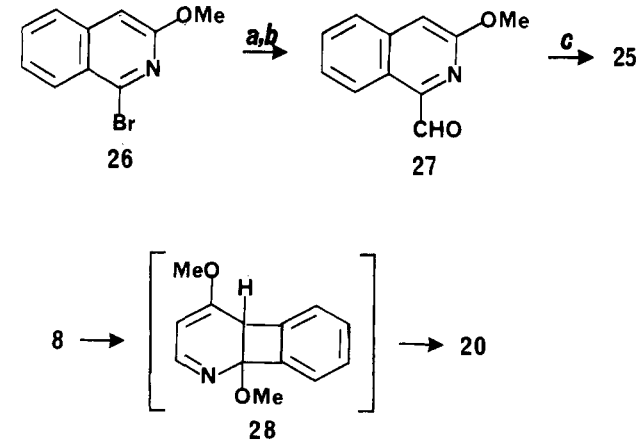
1-Methoxy-2-azabiphenylene (**9**) is considerably more reactive in methanolic sodium methoxide than its isomer **8**. Refluxing in 0.4 M CH_3ONa solution for 24 h was sufficient to convert **9** to a new fluorescent product in 71% yield; 48 h furnished a 94% yield. This product was also shown by exact mass measurement to have resulted from the addition of CH_3OH to the $C_{12}H_9NO$ starting material. The fluorescence was immediately suggestive of a substituted isoquinoline moiety, as in 1 → **7**, and the ultraviolet spectrum was consistent with a substituted quinoline or isoquinoline structure.[15] Two CH_3O groups (δ 3.85 and 4.00 ppm) were indicated in the ^1H NMR spectrum, while the surprising functionality CH=CHOCH$_3$ was indicated by the proton signals at δ 6.60 and 7.96, with doublets of J = 12.5 Hz requiring E geometry in the vinylic ether. We were fortunate to be able to compare the NMR and IR spectroscopic properties of the $C_{13}H_{13}NO_2$ product with those reported for three E–Z pairs of substituted (2-methoxyethenyl)naphthalenes.[16] Our tentative assignment of the structure of this transformation product of **9**



as 3-methoxy-1-((*E*)-2-methoxyethenyl)isoquinoline (**25**) was confirmed by its unequivocal synthesis (Scheme IV). No substituted isoquinoline of this type has apparently been reported previously. 1-Bromo-3-methoxyisoquinoline (**26**), easily prepared by the procedure of Simchen and Häfner,[17] underwent facile halogen–metal exchange upon treatment with n-butyllithium at −78 °C. The lithio derivative was formylated with DMF to afford 3-methoxyisoquinoline-1-carboxaldehyde (**27**) in 70% yield. The aldehyde in turn was caused to react with the triphenylphosphonium salt derived from Ph_3P and chloromethyl methyl ether in the presence of phenyllithium or ethoxide[18] to give the enol ether **25**, albeit in low yield. The identity of the fluorescent compounds from the two sources was established by high-field ^1H NMR, UV, and IR spectroscopy.

Comparisons of the Transformations of 1, 8, and 9. The reluctance of the methoxy-substituted monoazabiphenylenes **8** and **9** to undergo transformation in acidic methanol in contrast to the facile rearrangement of 4-methoxy-1,3-diazabiphenylene (**1**) has not been thoroughly investigated. It may be that **8** and **9** are simply protonated

Scheme IV[a]



[a] (a) n-Butyllithium; (b) DMF; (c) $(Ph_3PCH_2OCH_3)^+Cl^-$.

(10) Paquette, L. A.; Anderson, L. B.; Hansen, J. F.; Lang, S. A., Jr.; Berk, H. *J. Am. Chem. Soc.* **1972**, *94*, 4907.
(11) Paquette, L. A.; Kakihana, T. *J. Am. Chem. Soc.* **1968**, *90*, 3897.
(12) McNeil, D. W.; Kent, M. E.; Hedaya, E.; D'Angelo, P. F.; Schissel, P. O. *J. Am. Chem. Soc.* **1971**, *93*, 3817.
(13) For the X-ray structure of benzocyclooctene, see: Li, W.-K.; Chiu, S. W.; Mak, T. C. W.; Huang, N. Z. *THEOCHEM* **1983**, *11*, 285.
(14) For review, see: Paquette, L. A. *Tetrahedron* **1975**, *31*, 2855.
(15) Friedel, R. A.; Orchin, M. "Ultraviolet Spectra of Aromatic Compounds"; John Wiley and Sons: New York, 1951.
(16) Narasimhan, N. S.; Mali, R. S. *Tetrahedron* **1975**, *31*, 1005. This paper reports the NMR and IR spectra of three *Z*–*E* pairs of substituted (2-methoxyethenyl)naphthalenes. The correspondence of the values for the vinylic coupling constants and of the enol ether C=C vibrational frequencies with those of the product from **9** allows confident assignment of the *E* configuration in the present case.
(17) Simchen, G.; Häfner, M. *Liebigs Ann. Chem.* **1974**, 1802.
(18) Wittig, G.; Schlosser, M. *Chem. Ber.* **1961**, 1373.

on nitrogen in the pyridine moiety whereas **1**, which is about four powers of ten less basic, may be protonated instead on carbon 4a to form a stabilized oxonium–carbonium ion and initiate the reaction. It is also possible that initially carbon 8b in **1** reacts with methanol as the base present, since it is more susceptible to base attack than carbon 8b in **8** or the equivalent carbon 4a in **9**. A combination of events is not ruled out.

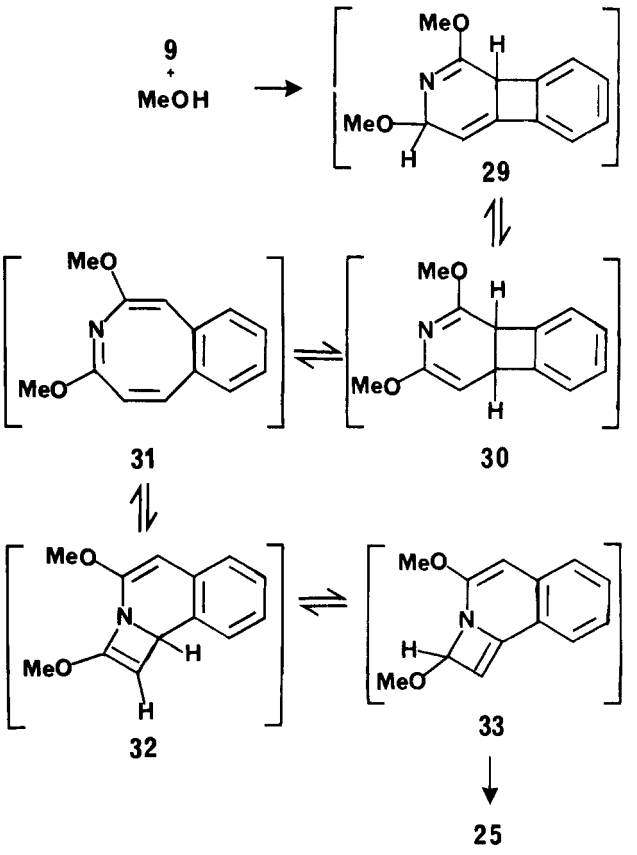
The difference in the behavior of **1** (→ **7**), **8** (→ **20**), and **9** (→ **25**) on treatment with methanolic sodium methoxide is impressive. First, there is a gradation in reactivity, in decreasing order: **1** > **9** > **8**. Second, when two nitrogens are present, as in 4-methoxy-1,3-diazabiphenylene (**1**), methanol addition occurs and an HCN equivalent is lost. When only one nitrogen is present, as in **8** and **9**, only the addition of a CH_3OH equivalent occurs. Third and most obvious, the transformation products from **1**, **8**, and **9** are quite different.

There is analogy between the intermediate **3** (from **1**) postulated in Scheme I and the benzazocine **20** that was formed from **8**. We propose that the benzazocine **20** arises via nucleophilic attack by CH_3O^- at the 8b position of 4-methoxy-1-azabiphenylene (**8**), which would be expected to be the most acidic position. The partial double bond fixation in the 6-4-6 ring system[19] gives the N–C8b bond some imine character. Protonation of C4a, either directly if the anion formed by initial attack were sufficiently delocalized, or as a result of stepwise double bond migration via anionic intermediates, would afford the adduct **28**. This intermediate could then undergo a thermally allowed 6π electrocyclic reaction to afford the observed product that evidently does not react further even under the forcing conditions employed and that does not have final recourse to elimination of the elements of HCN as does the analogous intermediate **3** (through **5**) in Scheme I. These findings are internally consistent, and the postulate of the intermediacy of **3** in the transformation of **1** to **7** is supported.

A rationalization for the transformation in methanolic sodium methoxide of 1-methoxy-2-azabiphenylene (**9**) into 3-methoxy-1-((*E*)-2-methoxyethenyl)isoquinoline (**25**) is presented in Scheme V. By the use of the argument developed in the preceding paragraph, C3 would be expected to be the position in **9** most susceptible to CH_3O^- attack. Attack at this position would afford a delocalized anion, which could be trapped at C8b to afford **29**. An allylic rearrangement, i.e., loss of the proton at C3 to afford an anion trappable at C4a, would give **30**. This intermediate could then undergo a thermally allowed 6π disrotatory electrocyclic reaction to afford the benzazocine **31**. Another 6π electrocyclic reaction could lead to **32**. From there, **25** could be formed via another allylic rearrangement (→ **33**) and a final 4π electrocyclic reaction. In the ultimate step, a conrotatory electrocyclic conversion is thermally allowed, and the observed product would result from the cyclic racemate in which the methoxyl group and the n electrons on nitrogen are cis. Even in the diastereomeric pair having the H on the sp^3 carbon and the n electrons on nitrogen cis, facile inversion at the nitrogen atom[3] would make possible the formation of the (*E*)-enol ether **25**. Without the inversion at nitrogen, the product would be 3-methoxy-1-((*Z*)-2-methoxyethenyl)isoquinoline. It is satisfying that the unexpected rearrangement of 1-methoxy-2-azabiphenylene (**9**) can be interpreted in terms, certainly nonexclusive, similar to those which account plausibly for the transformations of its relatives. Taken together, the data here enhance our understanding of the rich and varied chemistry of the azabiphenylenes.

(19) See, for example: Barton, J. W. In "Non-Benzenoid Aromatics"; Snyder, J. P., Ed.; Academic Press: New York, 1969; pp 45–49.

Scheme V



Experimental Section

Melting points were determined on a Büchi capillary melting point apparatus and are uncorrected. ^1H NMR spectra were obtained on a Varian EM-390 (90 MHz) or a Varian XL-200 (200 MHz) spectrometer; ^{13}C NMR spectra were obtained on a Varian XL-200 (50 MHz) or a Nicolet NTC-360 (90 MHz) spectrometer. IR spectra were obtained on a Perkin-Elmer 337 instrument; UV spectra were obtained on a Beckman Acta MVI spectrophotometer. Mass spectra were obtained on a Varian MAT CH-5 (low resolution) or a Varian MAT-731 (high resolution) spectrometer, coupled to a 620i computer and a STATOS recorder. Analyses were conducted by Josef Nemeth and his staff at the University of Illinois.

Methanol was dried by distillation from $Mg(OMe)_2$. Petroleum ether had a boiling range of 30–60 °C. Thin-layer chromatography was carried out on Brinkmann 0.25-mm layer silica gel plates (with fluorescent indicator). When the fluorescence of products is noted, this refers to the color of the fluorescence as seen on these plates under long-wavelength light (365 nm). Brinkman 0.2–0.5-mm silica gel was used for column chromatography.

2,3-Dibromo-4-methoxypyridine (11) and 3,4-Dibromo-2-methoxypyridine (14). 2,3,4-Tribromopyridine (**10**) was prepared from 2,4-dihydroxypyridine by a modification of the method of den Hertog[4] in which the neutralized aqueous quench of the $POBr_3$ reaction was extracted with $CHCl_3$, which was then evaporated to dryness. Ethanol (95%, about 10 mL/g of starting material used in the reaction) was added. The solution was warmed for a few min on a stream bath and decanted from particulates and/or oily residue. The product crystallized from the supernatant in 55–70% yield upon addition of water and cooling. Reaction of **10** with 1 equiv of NaOMe was carried out under different conditions, depending on whether a maximal yield of **11** or **14** was desired. *Method A (maximal 11)*: To a solution of **10** (1 g, 3.16 mmol) in dry MeOH (60 mL) was added a solution of Na (73 mg, 3.16 mmol) in dry MeOH (7.3 mL). The mixture was heated at reflux overnight (15 h, 8 h sufficed in other cases) and worked up as described below. *Method B (maximal 14)*: **10**

(10 g, 31.6 mmol) was placed in a pressure vessel with dry MeOH (100 mL). A solution of Na (0.73 g, 31.6 mmol) in dry MeOH (30 mL) was added, and the vessel was sealed. It was placed in an oil bath at 140 °C for 1.25 h.

Workup: The reaction mixtures contained up to four components. In order of decreasing R_f (TLC, silica, $CHCl_3$) these were the 2-methoxy product **14** (0.77), the starting material **10** (0.69), the dimethoxy product **17** (0.5), and the 4-methoxy product **11** (0.43). The reaction mixture was evaporated onto a small amount of silica gel (just enough to give a free-running solid) and applied to a silica gel column (~40 g of silica gel/g of **10** used in the reaction) packed in 20% ether–petroleum ether, and developed in this solvent until any **10** present had been eluted. Resolution of **17** from **11** was completed in 50% ether–petroleum ether. Isolated yields in the examples given above: Method A, **11**, 74%, **14**, 8%; Method B, **11**, 73%, **14**, 16%. Comparable yields have been obtained in reactions ranging in scale from 0.1 g to 10 g of **10**.

Characterization of **11**: mp 128–129 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.96 (s, 3, OCH_3), 6.76 (d, J = 6 Hz, 1, 5-H), 8.18 (d, J = 6 Hz, 1, 6-H); ^{13}C NMR (50 MHz, $CDCl_3$, fully decoupled) δ 56.8 (OCH_3), 106.6 (C-5), 113.0 (C-3), 145.1 (C-2), 149.0 (C-6), 163.7 (C-4). Anal. Calcd for $C_6H_5Br_2NO$: C, 27.00; H, 1.89; Br, 59.87; N, 5.24. Found: C, 27.26; H, 1.88; Br, 59.57; N, 5.09. For structure proof, **11** (97 mg, 0.36 mmol) was dehalogenated hydrogenolytically (10 mg of 10% Pd/C, 50 mL of 95% EtOH containing 0.1 N NaOH, 2 h, 23 °C, 2.7 atm). The mixture was filtered, and the filtrate was evaporated. Water (a few mL) was added, and the result was extracted with $CHCl_3$ (30 mL). The extract was dried ($MgSO_4$) and evaporated to a yellow oil, the ^{1}H NMR spectrum of which was identical with that reported for 4-methoxypyridine (**19**).[6]

Characterization of **14**: mp 83–85 °C; ^{1}H NMR (90 MHz, $CDCl_3$) δ 4.00 (s, 3, OCH_3), 7.10 (d, J = 5 Hz, 1, 5-H), 7.82 (d, J = 5 Hz, 1, 6-H); ^{13}C NMR (50 MHz, $CDCl_3$, fully decoupled) δ 55.1 (OCH_3), 110.5 (C-3), 121.9 (C-5), 136.6 (C-4), 145.1 (C-6), 161.5 (C-2). Anal. Calcd for $C_6H_5Br_2NO$: C, 27.00; H, 1.89; Br, 59.87; N, 5.24. Found: C, 27.01; H, 1.86; Br, 59.70; N, 5.12.

3-Bromo-2,4-dimethoxypyridine (17). Method A, from 2,3-Dibromo-4-methoxypyridine (11). A solution of **11** (0.6 g, 2.2 mmol) was made in 30 mL of MeOH in a pressure vessel. NaOMe (4 equiv, made from 200 mg of Na dissolved in 20 mL of MeOH) was added, and the vessel was sealed and placed in an oil bath at 130 °C overnight (13 h). The sample was evaporated to dryness, suspended in saturated NH_4Cl (20 mL), and extracted with ether (5 × 50 mL). The ether layers were dried ($MgSO_4$) and evaporated onto 5 g of silica gel, which was applied to a 40-g column of silica gel packed in 33% ether–petroleum ether. The column was eluted in the same solvent, and the major product was collected. A yellow oily residue was removed from the white crystals with pentane (3 × 1 mL) to afford an analytical sample (300 mg, 61%): mp 84–86 °C; ^{1}H NMR (90 MHz, $CDCl_3$) δ 3.97 (s, 3, 4-OCH_3), 4.04 (s, 3, 2-OCH_3),[20] 6.52 (d, J = 6 Hz, 1, 5-H), 8.07 (d, J = 6 Hz, 1, 6-H); ^{13}C NMR (50 MHz, $CDCl_3$, fully decoupled) δ 54.6 and 56.5 (OCH_3's), 94.5 (C-3), 102.4 (C-5), 146.2 (C-6), 161.8 and 163.7 (C-2 and C-4); IR (mineral oil) 1600, 1400, 1275, 1122, 1114, 1040, 793 cm^{-1}. Anal. Calcd for $C_7H_8BrNO_2$: C, 38.55; H, 3.71; Br, 36.64; N, 6.43. Found: C, 38.50; H, 3.68; Br, 36.63; N, 6.42. For structure verification, a sample of **17** (300 mg, 1.38 mmol) was dehalogenated as for **11** to afford an oily yellowish product identified as (somewhat impure) 2,4-dimethoxypyridine (**18**): ^{1}H NMR (90 MHz, $CDCl_3$) δ 3.80 (s, 3, OCH_3), 3.92 (s, 3, OCH_3), 6.17 (d, J = 2 Hz, 1, 3-H), 6.43 (dd, $J_{3,5}$ = 2 Hz, $J_{5,6}$ = 6 Hz, 1, 5-H), 7.93 (d, J = 6 Hz, 1, 6-H); ^{13}C NMR (50 MHz, $CDCl_3$, fully decoupled) δ 53.6 and 55.1 (OCH_3's), 94.0 (C-3), 106.2 (C-5), 147.4 (C-6), 166.1 and 167.9 (C-2 and C-4). An ethanolic solution of the oil afforded a **picrate**, mp 159–161 °C (lit.[5] mp 159 °C).

Method B, from 3,4-Dibromo-2-methoxypyridine (14). The reaction was carried out by using **14** (40 mg, 0.15 mmol) and NaOMe (4 equiv) as in Method A. The sample was evaporated and extracted into $CHCl_3$ (2 mL). The solvent was evaporated, and the product was dissolved in 1 N HCl (~ 2 mL) and decanted from a yellowish residue. Dropwise addition of 10 N NaOH caused precipitation of the product; warming followed by cooling afforded crystals. The product was identical with that prepared by Method A (TLC, melting point, mixture melting point, IR, and ^{1}H NMR).

2,3-Diethynyl-4-methoxypyridine (12). Under a N_2 atmosphere, a 150-mL serum bottle[21] was charged with **11** (2 g, 3.7 mmol), $(Ph_3P)_2PdCl_2$ (0.26 g, 0.37 mmol), CuI (0.26 g, 1.4 mmol), Ph_3P (0.58 g, 2.2 mmol), DMF (25 mL, distilled from CaH_2 under reduced pressure), Et_3N (5 mL, distilled from Na benzophenone), (trimethylsilyl)acetylene (6.5 mL, 45 mmol), and a stirring bar. The bottle was sealed with a silicone rubber septum held in place with an aluminum crimp, and the mixture was stirred at 23 °C for 15 min. The mixture was then stirred behind a shield in an oil bath at 140 °C for 3.5 h. After cooling, the reaction mixture was added to 2 L of water and extracted with CH_2Cl_2 (5 × 50 mL). The CH_2Cl_2 extracts were dried ($MgSO_4$) and evaporated to a dark oil or tar, which was redissolved in CH_2Cl_2 (~5 mL). Rapid addition of petroleum ether (250 mL) caused precipitation of a black powdery residue, which was collected on a filter and washed with petroleum ether (2 × 100 mL). The combined petroleum ether fractions were evaporated to an oil. Methanol (60 mL) containing NaOH (1.2 g) was added, and the mixture was stirred at 23 °C for 20 min. A small amount of silica gel was added, and the mixture was evaporated to dryness. Since **5** is appreciably volatile, all evaporations were conducted at room temperature during as short a time as possible. The sample was applied to an 80-g column of silica gel, which was packed and developed in 75% ether–petroleum ether. Fractions containing a slightly fluorescent compound were evaporated to an oil, which upon coevaporation with CH_2Cl_2 (5 mL) and pentane (5 mL) afforded a dark solid suitable for the next reaction (0.61 g, 52%).[22] Compound **12** is thermally unstable and was stored at −20 °C. ^{1}H NMR (90 MHz, $CDCl_3$) δ 3.4 (s, 1, C≡CH), 3.6 (s, 1, C≡CH), 4.0 (s, 3, OCH_3), 6.8 (d, J = 6 Hz, 1, 5-H), 8.45 (d, J = 6 Hz, 1, 6-H); IR (mineral oil) 3260, 3150, 2100, 1560, 1300, 1175, 1065 cm^{-1}; MS (70 eV), m/e (relative intensity) 157 (80, M^+), 127 (100, $M^+ - CH_2O$), 100 (41), 74 (33), 63 (25); HREIMS found m/e 157.0533, $C_{10}H_7NO$ 157.0528.

6,7-Bis(trimethylsilyl)-4-methoxy-1-azabiphenylene (13). A 50-mL three-necked flask was fitted with a condenser and one glass stopper. The other neck and the top of the condenser were fitted with serum caps, and the system was flushed with argon via needles inserted through the cap on the condenser. The flask was charged with xylenes (6 mL, distilled from Na benzophenone), bis(trimethylsilyl)acetylene (6 mL), and $CpCo(CO)_2$ (0.3 mL) and was brought to reflux with stirring. A syringe with a 1-ft needle was charged with a solution of **12** (300 mg, 1.9 mmol) in xylenes (6 mL); an identical second syringe contained bis(trimethylsilyl)acetylene (6 mL) and $CpCo(CO)_2$ (0.3 mL). The needles were inserted through the serum cap on the flask so that their tips were below the surface of the liquid. A 250-W floodlight was turned on 30 cm from the flask. The syringes were attached to a syringe drive and their contents were added to the flask over 0.5 h. When addition was complete, the reaction mixture was allowed to cool. It was evaporated onto a small amount of silica gel and applied to a 30-g column of silica gel in 20% ether–petroleum ether. The column was eluted in the same solvent and the product (R_f 0.52, TLC, silica, $CHCl_3$) was collected (250 mg, 38%). Recrystalliation from $EtOH/H_2O$ afforded analytically pure yellow needles: mp 127.5–128.5 °C; ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.42 (s, 18, Me_3Si),

(20) The methoxy signals in **17** were assigned from the ^{1}H NMR spectrum of the product of reaction (4 h at 60 °C) of **11** with excess CD_3ONa in CD_3OD. The product lacked the signal at δ 4.04, identifying this as the proton signal for the 2-OCH_3.

(21) These heavy-walled flat-bottomed glass bottles were used for historical reasons; a stainless steel pressure vessel would probably have served equally well. For acidic reactions at modest pressures, these bottles have the advantage over sealed tubes in that their contents can easily be stirred. Samples can also be withdrawn via syringe for monitoring the reactions without opening the bottle.

(22) It is advisable to obtain an NMR spectrum of each batch of **12** because the compound formed by reaction of only one bromine is not readily differentiable from **12** by TLC. The monsubstitution product was sometimes obtained when old bottles of catalyst were used. Its characteristics: ^{1}H NMR (90 MHz, $CDCl_3$) δ 3.40 (s, 1, C≡CH), 3.96 (s, 3, OCH_3), 6.77 (d, J = 6 Hz, 1, 5-H), 8.32 (d, J = 6 Hz, 1, 6-H); MS (10 eV), m/e (relative intensity) 213 (94, M^+, ^{81}Br), 211 (100, M^+, ^{79}Br), 183 (7.5), 181 (6.9), 102 (21).

3.94 (s, 3, OCH_3), 6.16 (d, J = 6 Hz, 1, 3-H), 6.98 (s, 1, benzene H), 7.20 (s, 1, benzene H), 7.56 (d, J = 6 Hz, 1, 2-H); ^{13}C NMR (90 MHz, $CDCl_3$, fully decoupled) δ 1.9, 57.0, 114.5, 122.5, 123.7, 129.6, 147.6, 149.2, 150.3, 151.2, 153.6, 173.4; UV (EtOH) λ_{max} (log ϵ) 349 (3.82), 330 (3.75), 315 (3.49), 300 (sh, 3.15), 263 nm (4.74); MS (10 eV), m/e (relative intensity) 327 (100, M^+), 312 (31, M^+-CH_3), 296 (13), 269 (10), 73 (9). Anal. Calcd for $C_{18}H_{25}NOSi_2$: C, 65.99; H, 7.77; N, 4.27. Found: C, 65.89; H, 7.53; N, 4.18.

4-Methoxy-1-azabiphenylene (8). Compound **13** (50 mg, 0.15 mmol) was dissolved in cyclohexane (~ 2 mL), and CF_3SO_3H (0.3 mL) was added. The vessel was stoppered and the two-phase mixture was stirred at 22 °C for 2 h. The reaction mixture was added to H_2O (30 mL) and neutralized with Et_3N. The mixture was extracted with CH_2Cl_2 (4 × 20 mL). The combined organic layers were evaporated onto a small amount of silica gel and chromatographed on a 15-g silica gel column in $CHCl_3$. Fractions containing product (R_f 0.22, TLC, silica, $CHCl_3$) were evaporated to a yellow oil (24 mg, 86%) which crystallized on standing for a few minutes at 20 °C. After recrystallization from $EtOH/H_2O$, which left the material slightly wet (1.5% H_2O), its properties were as follows: mp 67–68 °C; ^1H NMR (90 MHz, $CDCl_3$) δ 3.97 (s, 3, OCH_3), 6.17 (d, J = 6 Hz, 1, 3-H), 6.54–6.91 (br m, 4, benzene ring H's), 7.55 (d, J = 6 Hz, 1, 2-H); IR (mineral oil) 1650, 1580, 1310, 1280, 1200, 1040, 1010, 910, 810, 730 cm^{-1}; MS (10 eV), m/e (relative intensity) 183 (100, M^+), 153 (23), 140 (26); HREIMS found m/e 183.0680, $C_{12}H_9NO$ 183.0684.

3,4-Diethynyl-2-methoxypyridine (15). Under a N_2 atmosphere, a 30-mL serum bottle was charged with compound **14** (0.40 g, 1.5 mmol), $(Ph_3P)_2PdCl_2$ (100 mg, 0.15 mmol), CuI (100 mg, 0.53 mmol), Ph_3P (230 mg, 0.88 mmol), DMF (8 mL), Et_3N (1.6 mL), (trimethylsilyl)acetylene (1.3 mL, 9.0 mmol), and a stirring bar. The bottle was sealed as for **5**, and the mixture was stirred for 15 min at 23 °C before being placed in an oil bath at 100 °C for 18 h. The reaction mixture was worked up as described for **5**, except that one-third amounts of water and petroleum ether were used for DMF removal and catalyst precipitation, deprotection was carried out in 20 mL of methanolic NaOH, and chromatography was carried out on a 30-g column of silica gel in 5% ether–petroleum ether. Fractions containing a slightly fluorescent product (R_f 0.5, TLC, silica, $CHCl_3$) were evaporated to apparent dryness. The residue was coevaporated with CH_2Cl_2 (10 mL) to afford a yellow solid (147 mg, 62%) which was stored at −20 °C; ^1H NMR (90 MHz, $CDCl_3$) δ 3.49 (s, 1, C≡CH), 3.58 (s, 1, C≡CH), 4.04 (s, 3, OCH_3), 6.94 (d, J = 6 Hz, 1, 5-H), 8.05 (d, J = 6 Hz, 1, 6-H); IR (mineral oil) 3260, 3140, 2100, 1580, 1540, 1310, 1260, 1170, 1090, 1055, 830 cm^{-1}; MS (10 eV), m/e (relative intensity) 157 (100, M^+), 129 (80), 102 (66); HREIMS found m/e 157.0527, $C_{10}H_7NO$ 157.0528.

6,7-Bis(trimethylsilyl)-1-methoxy-2-azabiphenylene (16). This compound was prepared by the method used for compound **13**, with the following modifications. A 25-mL three-necked flask was charged initially with toluene (5 mL, distilled from Na benzophenone), bis(trimethylsilyl)acetylene (5 mL), and $CpCo(CO)_2$ (0.25 mL); one syringe contained **15** (80 mg, 0.51 mmol) in toluene (5 mL), and the other contained bis(trimethylsilyl)-acetylene (5 mL) and $CpCo(CO)_2$ (0.25 mL). The workup was as described for **13**, except that chromatography was conducted in 10% ether–petroleum ether. The product (R_f 0.4, TLC, silica, $CHCl_3$) was obtained in 62% yield; it was recrystallized from $EtOH/H_2O$ to give fine, yellow needles: mp 76–78 °C; ^1H NMR (90 MHz, $CDCl_3$) δ 0.48 (s, 18, Me_3Si), 3.99 (s, 3, OCH_3), 6.44 (d, J = 4 Hz, 1, 4-H), 6.94 (s, 1, benzene H), 7.01 (s, 1, benzene H), 7.90 (d, J = 4 Hz, 1, 3-H); ^{13}C NMR (50 MHz, $CDCl_3$, fully decoupled) δ 2.0, 54.6, 108.7, 122.6, 124.1, 128.0, 147.1, 150.1, 150.5, 151.4, 153.9, 164.3; UV (EtOH) λ_{max} (log ϵ) 351 (3.21), 334 (3.32), 318 (3.25), 286 (sh, 4.05), 265 nm (4.85); MS (10 eV), m/e (relative intensity) 237 (100, M^+), 312 (41, $M^+ - CH_3$), 296 (26), 73 (34). Anal. Calcd for $C_{18}H_{25}NOSi_2$: C, 65.99; H, 7.77; N, 4.27. Found: C, 65.82; H, 7.58; N, 4.12.

1-Methoxy-2-azabiphenylene (9). This compound was prepared in 89–96% yield from **16** by the method used for the desilylation of **13**. Fractions containing product (R_f 0.26, TLC, silica, $CHCl_3$) were evaporated to a fruity smelling, bright yellow oil which solidified on standing overnight at 4 °C: mp 40–41 °C; ^1H NMR (90 MHz, $CDCl_3$) δ 4.00 (s, 3, OCH_3), 6.42 (d, J = 5 Hz, 1, 4-H), 6.55–6.89 (br m, 4, benzene ring H's), 7.91 (d, J = 5 Hz, 1, 3-H); IR (neat) 1660, 1590, 1400, 1290, 1210, 1010, 825, 740 cm^{-1}; MS (10 eV), m/e (relative intensity) 183 (100, M^+), 182 (64), 154 (26), 153 (17); HREIMS found m/e 183.0682, $C_{12}H_9NO$, 183.0684.

Attempted Reaction of 8 and 9 with Methanol under Acidic Conditions. Small amounts (5 mg or less) of **8** or **9** were dissolved in MeOH (5–20 mL) under a N_2 atmosphere and CF_3SO_3H was added dropwise to a final concentration of 20% (v/v). The solutions, the yellow color of which became much more intense upon addition of acid, were placed in sealed tubes in an oil bath at 140 °C. Samples were taken after 3–5 h (the tubes were cooled before being opened under N_2) and after 22 h. The samples were neutralized either with aqueous $NaHCO_3$ followed by CH_2Cl_2 extraction, or by exposure of the TLC plates, to which the mixture had been applied directly, to the vapors above concentrated NH_4OH. TLC was carried out with $CHCl_3$ as the developing solvent.

Reaction of 8 with Methanolic NaOMe. Compound **8** (32 mg, 0.17 mmol) was dissolved in NaOMe (0.4 M) in MeOH (5 mL). The solution was placed in a sealed tube and heated at 140 °C for 24 h. The mixture was neutralized with solid NH_4Cl, evaporated to dryness, suspended in CH_2Cl_2, filtered to remove salt, and evaporated onto a small amount of silica gel, which was dry-loaded onto a 15-g silica gel column packed in 10% ether–petroleum ether. Elution with the same solvent afforded product (29 mg, 88% based on recovered **8**) as a crystalline, off-white solid, and starting material (4 mg, 12%). Vacuum drying overnight in a pistol containing petroleum ether afforded colorless crystals: mp 121–122 °C; R_f 0.5, TLC, silica gel, $CHCl_3$; ^1H NMR (90 MHz, $CDCl_3$) δ 3.66 (s, 3, OCH_3), 3.86 (s, 3, OCH_3), 5.10 (d, J = 9 Hz, 1, 4-H), 5.63 (s, 1, 6-H), 6.59 (d, J = 9 Hz, 1, 3-H), 6.89–7.36 (br m, 4, benzene ring H's); IR (mineral oil) 1680, 1630, 1590, 1300–1270, 1185, 1165, 1050–1030, 825, 765 cm^{-1}; UV (EtOH) λ_{max} (log ϵ) 277 (sh, 3.33), 244 nm (sh, 3.93); MS (10 eV), m/e (relative intensity) 215 (23, M^+), 200 (100, $M^+ - CH_3$), 185 (29), 169 (15). Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.53; H, 6.10; N, 6.51. Found: C, 72.29; H, 6.27; N, 6.41.

Reaction of 9 with Methanolic NaOMe. A solution of **9** (43 mg, 0.23 mmol) in methanolic NaOMe (0.4 M, 20 mL) was heated at reflux under a $CaSO_4$ drying tube for 48 h. At the end of this period a trace of starting material remained, but most of it had been converted to a faster running product with pale blue fluorescence (R_f 0.4, TLC, silica, $CHCl_3$). The mixture was brought to pH 7 with aqueous KH_2PO_4, extracted into CH_2Cl_2 (3 × 30 mL), dried ($MgSO_4$), and evaporated to an oil. This was chromatographed on a 20-g column of silica gel in 50% $CHCl_3$–petroleum ether. Fractions containing product were evaporated to a yellowish oil (48 mg, 94%). On another occasion, the product was isolated in 71% yield after 24 h at reflux; starting material also was present. The characteristics of this product: ^1H NMR (200 MHz, $CDCl_3$) δ 3.85 (s, 3, OCH_3), 4.00 (s, 3, OCH_3), 6.60 (d, J = 12.5 Hz, 1, C*H*=CHOMe), 6.78 (s, 1, 4-H), 7.31 (ddd, 1, 7-H), 7.50 (ddd, 1, 6-H), 7.62 (d, J = 9 Hz, 1, 5-H), 7.96 (d, J = 12.5 Hz, 1, CH=C*H*OMe), 8.02 (d, J = 9 Hz, 1, 8-H); IR (neat) 3050, 3000, 2920, 2840, 1630 (s), 1580 (s), 1540, 1450, 1320, 1210 (s), 1170, 1130 (s), 1070, 1030, 940, 860, 815, 780 cm^{-1}; UV (EtOH) λ_{max} (relative intensity)[23] 365 (1.0), 289 (0.76), 258 (1.10), 238 (4.8), minima at 315, 274, and 249 nm; MS (10 eV), m/e (relative intensity) 215 (61, M^+), 200 (32, $M^+ - CH_3$), 186 (32), 129 (13), 51 (29), 49 (100), the latter two peaks represent CH_2Cl^+, which came from CH_2Cl_2 used to transfer the sample; HREIMS found m/e 215.0942, $C_{13}H_{13}NO_2$ 215.0946.

Lithiation of 1-Bromo-3-methoxyisoquinoline (26). Compound **26** was prepared from *o*-nitrophenylacetic acid as described,[17] except that **26** was isolated by silica gel column chromatography with 5% ether–petroleum ether as the developing solvent: ^1H NMR of **26** (200 MHz, $CDCl_3$) δ 3.89 (s, 3, OCH_3), 6.79 (s, 1, 4-H), 7.22–7.32 (ddd, 1, 7-H), 7.36–7.54 (m, 2, 5- and 6-H), 7.98 (d, J = 8 Hz, 1, 8-H). A solution of **26** (48 mg, 0.2 mmol) in THF (5 mL, freshly distilled from Na benzophenone) under N_2 at −78 °C was treated with 1.1 equiv of *n*-butyllithium (2.2

(23) Although the positions of the maxima and minima were reproducible from one sample to another, we observed variation of up to 10% in the relative intensities of the peaks. It is possible that the UV spectrum of this compound reflects gradual changes in structure or that it is very sensitive to the presence of contaminants or decomposition products.

M solution in hexane, 0.1 mL). After 5 min, CH_3OD (0.1 mL) was added and the mixture was allowed to warm to room temperature. It was evaporated onto a small amount of silica gel and chromatographed on a 10-g silica gel column with 10% ether–petroleum ether as the eluting solvent. The major product (22 mg, 68%) was identified by its UV spectrum[17] as 3-methoxyisoquinoline; its NMR spectrum lacked a singlet at ca. 9 ppm, indicating that the 1-position was deuterated. A minor fraction with dark blue fluorescence was also recovered. This was tentatively identified as a mixture containing 1-butyl-3-methoxyisoquinoline and 3-methoxy-1-methylisoquinoline on the basis of mass spectrometry, including exact mass measurements on the peaks at m/e 215 and 173, and NMR, which showed no signals near 9 ppm, indicative of 1-substitution of the isoquinolines. We suspect that the 1-methyl compound, which gave the most intense peak in the mass spectrum, arose via methylation of the anion by starting material; for this reason, we tried to prepare the anion in dilute solution and to trap it promptly with an excess of the desired reagent. On another occasion, 3-methoxyisoquinoline was isolated from a failed reaction; it was identified by its UV spectrum and by ^1H NMR: (200 MHz, $CDCl_3$) δ 4.03 (s, 3, OCH_3), 7.00 (s, 1, 4-H), 7.33–7.40 (ddd, 1), 7.52–7.60 (ddd, 1), 7.68 (d, J = 8 Hz, 1, 5-H), 7.88 (d, J = 8 Hz, 1, 8-H), 8.95 (s, 1, 1-H).

3-Methoxyisoquinoline-1-carboxaldehyde (27). A solution of **26** (250 mg, 1.05 mmol) in THF (100 mL) was cooled under N_2 to −78 °C and 1.1 equiv of n-butyllithium was added. The solution immediately became yellow. DMF (1.62 mL, 21 mmol, distilled under reduced pressure from CaH_2 and stored over CaH_2) was added via syringe within 5 s; the solution at once became lighter in color. After warming to room temperature, the reaction mixture was added to saturated NH_4Cl solution (120 mL) and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL); the combined organic layers were dried ($MgSO_4$) and evaporated to an oil which was chromatographed on a 30-g silica gel column in 50% $CHCl_3$–petroleum ether. The central tube among the fractions containing product was evaporated separately from the rest, which contained traces of fluorescent impurities. The central fraction was dried overnight at 38 °C under high vacuum to afford an analytically pure yellow solid (16%); on TLC, the product had a pale blue fluorescence. The slightly impure material (71% overall yield) was adequate for further transformation: mp 86–87 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 4.07 (s, 3, OCH_3), 7.17 (s, 1, 4-H), 7.40–7.60 (m, 2), 7.66 (d, J = 8 Hz, 1, 5-H), 9.11 (d, J = 8 Hz, 1, 8-H), 10.25 (s, 1, CHO); IR (mineral oil) 1700 (s), 1590 (s), 1310 (s), 1240, 1185, 1052, 885, 875 cm^{-1}; UV (EtOH) λ_{max} (log ϵ) 380 (3.36), 346 (3.57), 289 (3.20), 277 (3.38), 257 nm (sh, 3.75); MS (10 eV), m/e (relative intensity) 187 (100, M^+), 186 (53), 158 (33), 143 (18), 130 (30), 116 (31), 102 (26), 89 (25); HREIMS found m/e 187.0632, $C_{11}H_9NO_2$ 187.0633. Anal. Calcd for $C_{11}H_9NO_2$: C, 70.57; H, 4.86; N, 7.48. Found: C, 70.53; H, 4.83; N, 7.44.

Wittig Reaction of 27. On a 20- to 50-mg scale, the aldehyde **27** was caused to react with $(Ph_3PCH_2OCH_3)^+Cl^-$ using either EtO^- or phenyllithium as the base, as described by Wittig and Schlosser[18,24] for reaction of this salt with benzaldehyde. A fluorescent product with the same R_f (TLC) as the product derived from 1-methoxy-2-azabiphenylene was isolated in 9–15% yield by silica gel chromatography in 50% $CHCl_3$–petroleum ether. The identity of this product with compound **25** was established by ^1H NMR, UV, and IR spectroscopy.[25]

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Registry No. **1**, 87954-15-2; **7**, 87954-17-4; **8**, 96246-03-6; **9**, 96246-06-9; **10**, 2402-91-7; **11**, 96245-98-6; **12**, 96246-01-4; **13**, 96246-02-5; **14**, 96245-99-7; **15**, 96246-04-7; **16**, 96246-05-8; **17**, 96246-00-3; **18**, 18677-43-5; **18**·picrate, 93087-25-3; **19**, 620-08-6; **20**, 96246-07-0; **25**, 96246-08-1; **26**, 55086-52-7; **27**, 96246-10-5; TMSC≡CH, 1066-54-2; TMSC≡CTMS, 14630-40-1; o-$O_2NC_6H_4CH_2CO_2H$, 3740-52-1; $(Ph_3PCH_2OCH_3)^+Cl^-$, 4009-98-7; 2,4-dihydroxypyridine, 84719-31-3; 3-bromo-2,4-dihydroxypyridine, 96245-97-5; 3-methoxyisoquinoline, 16535-84-5; 1-butyl-3-methoxyisoquinoline, 96246-09-2; 3-methoxy-1-methylisoquinoline, 23832-77-1.

(24) A valuable modification of this reaction has been reported: Earnshaw, C; Wallis, C. J.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1979**, 3099.

(25) The Z isomer was not isolated, although its presence was suggested by a pair of doublets (δ 5.96 and 6.48 ppm, J = 7 Hz) in the ^1H NMR (200 MHz, $CDCl_3$) spectrum of an impure, more polar fraction of the reaction mixture. These chemical shift and J values correspond well to those reported for several (2-methoxyethenyl)naphthalenes.[16] The isolation of the Z isomer by preparative TLC (silica, 5% EtOH–$CHCl_3$) was complicated by its slow ($t_{1/2}$ > 2 h) isomerization to the E isomer on silica gel in the solvent used. The slowness of this isomerization reassures us that the E configuration of the product from **9** did not result from an artifact of chromatography.

Annelation of Guanosine by Reaction with Methyl *N*-Cyanomethanimidate and Sodium Methoxide To Give a Tricyclic, Fluorescent Analogue of Adenosine

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A reagent consisting of methyl *N*-cyanomethanimidate and sodium methoxide in methanol converts guanosine to a fluorescent product, 8-amino-3,10-dihydro-10-oxo-3-β-D-ribofuranosyl-1,3,5-triazino[1,2-*a*]purine. The tricyclic *N*-ribonucleoside thus formed resembles adenosine in its periphery and is an inhibitor of adenosine deaminase. This annelation of guanosine is the first example of a potentially general transformation of a natural *N*-ribonucleoside into an entity whose structure more closely resembles, in the periphery, that of a different natural *N*-ribonucleoside. The product can also serve as a "protected" guanosine since it reverts readily to guanosine upon treatment with dilute aqueous alkali. The reagent itself can be used in parallel with chloroacetaldehyde as a spray for fluorescence detection of guanosine and adenosine and differentiation between these on chromatograms. Guanosine, 8-bromoguanosine, 9-benzylguanine, and 9-benzyl-3-bromoguanine were used as representative substrates for the annelation reaction.

The purpose of this enterprise was to find the means of converting a natural *N*-ribonucleoside into a structure that more closely resembles, in the periphery, that of a different natural *N*-ribonucleoside.[1] We have chosen to attach the

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