Registry No. **2**, 76794-02-0; **3**, 37517-42-3; **4**, 76794-00-8; **5**, 76794-01-9; **6a**, 87782-60-3; **6b**, 81845-43-4; **6c**, 87782-61-4; **6d**, 87782-62-5; **6e**, 87782-63-6; **6f**, 87782-64-7; (*E*)-**7a**, 87782-65-8; (*Z*)-**7a**, 87858-32-0; (*E*)-**7b**, 81938-37-6; (*Z*)-**7b**, 81938-36-5; (*E*)-**7c**, 87782-66-9; (*Z*)-**7c**, 87858-33-1; (*E*)-**7d**, 87782-67-0; (*Z*)-**7d**, 87858-34-2; **8a**, 87782-68-1; **8a** tris($(CH_3)_3Si$) derivative, 87859-94-7; **8b**, 81845-44-5; **8b** tris($(CH_3)_3Si$) derivative, 87782-69-2; **8c**, 87782-70-5; **8c** tris($(CH_3)_3Si$) derivative, 87782-71-6; **8d**, 87782-72-7; **8d** tris($(CH_3)_3Si$) derivative, 87782-73-8; **9a**, 87858-19-3; **9a** tris($(CH_3)_3Si$) derivative, 87782-74-9; **9b**, 81872-04-0; **9b** tris($(CH_3)_3Si$) derivative, 87858-20-6; **9c**, 87858-21-7; **9c** tris($(CH_3)_3Si$) derivative, 87858-22-8; **9d**, 87858-23-9; **9d** tris($(CH_3)_3Si$) derivative, 87858-24-0; **10**, 81703-55-1; **11**, 77744-44-6; **12**, 87782-75-0; (*E*)-**14**, 87782-76-1; (*Z*)-**14**, 87858-25-1; **15**, 87782-77-2; **16**, 87858-26-2; **17**, 87782-78-3; **17** diTHP ether, 87782-83-0; **17** bis($(CH_3)_3Si$ ether, 87782-84-1; **18**, 87782-79-4; **18** diTHP ether, 87782-82-9; **18** tris($(CH_3)_3Si$) derivative, 87782-85-2; **19**, 87858-27-3; **19** methyl ester, 87858-31-9; **19** methyl ester, diTHP ether, 87858-30-8; **19** methyl ester, bis-($(CH_3)_3Si$) ether, 87858-35-3; **19** diTHP ether, 87858-29-5; **19** tris-($(CH_3)_3Si$) derivative, 87858-36-4; (*E*)-**20**, 87859-95-8; (*Z*)-**20**, 87782-80-7; **21**, 87782-81-8; **22**, 87858-28-4; $CH_3(CH_2)_2C{\equiv}CH$, 627-19-0; $CH_3C{\equiv}CSi(CH_3)_3$, 6224-91-5; $(CH_3)_3SiC{\equiv}CSi(CH_3)_3$, 14630-40-1; $(C_6H_5)_3P^+{-}CH_2(CH_2)_3CO_2H\ Br^-$, 17814-85-6; $HOCH_2(CH_2)CO_2Na$, 5299-61-6; ε-caprolactone, 502-44-3.

Thermal Electrocyclic Reactions of 2-Aza-1,3-butadiene Derivatives. A New N-Heterocyclic Annelation[1]

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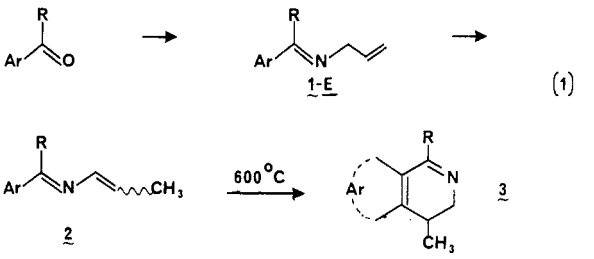
Received April 11, 1983

A general, three-step annelation sequence, which ultimately gives 3,4-dihydro-2-quinolines and related derivatives (**3**), is described. The cyclization step is accomplished by pyrolysis of a 1-arenyl-2-aza-1,3-butadiene analogue (**2**) that apparently undergoes successive six-π-electron electrocyclization and 1,5-hydrogen migration reactions to yield the product. The conjugated azadienes, **2**, are prepared by the base-catalyzed isomerization of the unconjugated isomers, **1**. Compounds **1** are prepared by condensing arenyl ketones or aldehydes with 2-propenyl-1-amine. Steric effects of substituents on the azadiene chain and steric and electronic effects of the arenyl group on the cyclization step were studied. The following general conclusions were drawn: alkyl substituents R on the C=N terminus of **2** hinder a competing degradative process (commencing with a four-π-electron electrocyclization) and improve the yield of products **3**; electron-withdrawing substituents on Ar of **2** or electron-withdrawing Ar groups enhance the yield of cyclized products, but they impart little regioselectivity to the reaction; regioselectivity may be imparted by π bond fixation in Ar; electrocyclization also proceeds well with π-electron excessive Ar groups on **2**. The preferred conformation of the heterocyclic product **3** can be readily deduced by ^1H NMR spectroscopy.

Isoquinoline and dihydroisoquinoline ring systems have attracted much attention from chemists because of the spectrum of biological activity they possess.[2,3] Syntheses of the ring systems have relied very heavily on some type of intramolecular electrophilic substitution of a benzene or substituted benzene ring for ring closure. The classical Bischler–Napieralski reaction and the related Pictet–Gams, Pictet–Spengler, and Pomerantz–Fritsch reactions illustrate the approach.[4] This approach has not worked well when electron-withdrawing substituents are present on the benzene (or other aromatic) ring. Also, the approach has not been widely applied to annelations of heterocyclic aromatic rings, such as pyridine. Accordingly, new syntheses of the isoquinoline and di-and tetrahydroisoquinoline ring systems continue to be reported.[4c,5]

Herein we report an annelation based on the thermal electrocyclization of 1-aryl-2-aza-1,3-pentadiene derivatives, **2**, that yields, as initial products, 3,4-dihydroisoquinolines or analogous ring systems **3**. The three-step sequence of eq (1) has proved to be a general one, and works well when Ar is either electronegative or π-electron excessive relative to C_6H_5.



Related Electrocyclizations. About the time this work commenced Bergman and Wendling[6] reported that the thermal decomposition of 2*H*-azirines produced, in part, 2-azabutadienes which, at higher temperatures underwent cyclization to 3,4-dihydroisoquinolines (eq 2). Previously, Weber and co-workers[7] had reported the synthesis of 1,2-dihydronaphthalenes by the gas phase pyrolysis of substituted 1-phenyl-1,3-butadienes. The thermal electrocyclizations of eq (3)[8] and (4)[9] and other examples have been reported.

(1) Previous paper in this series: Worley, S. D.; Taylor, K. G.; Venugopalan, B.; Clark, Jr., M. S. *Tetrahedron* **1978**, *34*, 833–840.
(2) Dyke, S. F. In "Rodds Chemistry of Carbon Compounds"; S. Coffey, Ed.; Elsevier: New York, 1978; Vol. 4, Chapter 1.
(3) For examples see "Annual Reports in Medicinal Chemistry"; Academic Press, New York, 1965–1981; Vols. 1–16.
(4) (a) Whaley, W. M.; Govindachary, T. R. *Org. React.* **1951**, *5*, 74–190. (b) Gensler, W. J. *Ibid.* **1951**, *6*, 191–206. (c) Kametani, T.; Fukimoto, K. In "The Chemistry of Heterocyclic Compounds"; Grethe, G., Ed.; Wiley: New York, 1981; Chapter 2, Part 1.
(5) (a) Ellefson, C. R. *J. Org. Chem.* **1979**, *44*, 1533–1536. (b) Parham, W. E.; Bradsher, C. K.; Hunt, D. *Ibid.* **1978**, *43*, 1606–1607. (c) Poindexter, G. S. *Ibid.* **1982**, *47*, 3787–3788.
(6) Bergman, R. G.; Wendling, L. A. *J. Org. Chem.* **1976**, *41*, 831–836.
(7) Weber, W. P.; Brodie, T. D.; Castiello, A.; Conger, J. L.; Valkovich, P. B. *J. Am. Chem. Soc.* **1975**, *97*, 901–902.
(8) Kinstle, T. H.; Lawson, J.; Habash, P. "Abstracts of Papers", 173rd National Meeting of the American Chemical Society, New Orleans, LA., 1977; American Chemical Society: Washington, DC 1977; ORG 208.
(9) Rosen, B. I.; Weber, W. P. *J. Org. Chem.* **1977**, *42*, 47–50.

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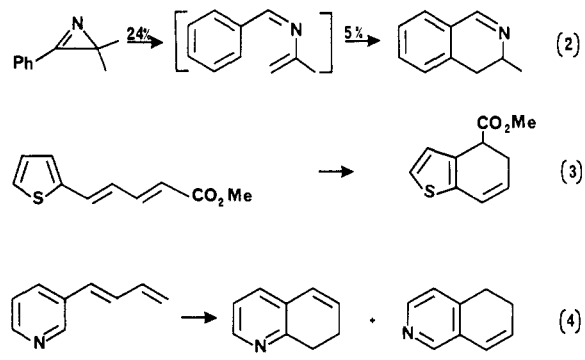
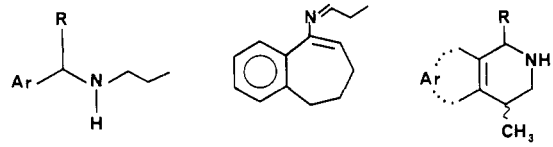


Unconjugated Azadienes, 1. These imines were prepared from ketones and allylamine by the methods of Roelofsen and Van Bekkum[10] or White and Weingarten[11] and were characterized by ^1H and ^{13}C NMR spectroscopy. Chemical characterization was accomplished either by $NaBH_4$ reduction, which yielded amines of general structure, 4,[12] or by isomerization to 2. NMR spectroscopy



4 5 6

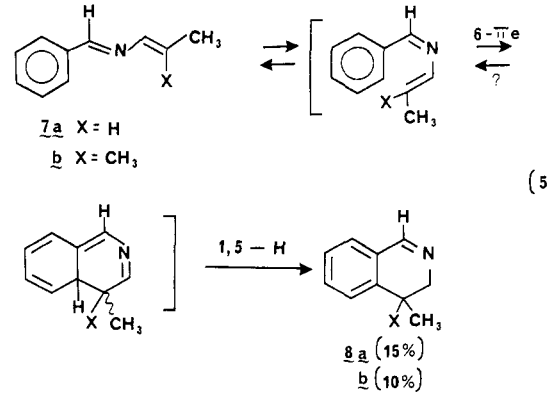
indicated that for imines 1 (R = H, CH_3, C_2H_5) the *E* configuration (as shown) was preferred. The proportion of the *Z* isomer became significant when the bulk of group R was increased to C_2H_5, or when group Ar possessed ortho substituents. Yields of 1 ranged from 60% to 100%.

Conjugated Azadienes, 2. Treatment of imines 1 in benzene with powdered KOH in the presence of 18-crown-6 ether usually effected complete isomerization to 2 after 20 h at room temperature. This procedure was superior to those using *t*-BuOK in Me_2SO[1] or in tetrahydrofuran.[13] For example, 1-(4-pyridyl)-2-aza-1,4-pentadiene was smoothly isomerized by KOH/18-crown-6 ether/benzene, while the *t*-BuOK-based reagents yielded mainly dark, intractable products. When R was CH_3 and the Ar group of 1 possessed an ortho substituent, appreciable amounts of 1-(*Z*) were present, and refluxing of the reaction mixture was necessary to complete the isomerization of the *Z* isomer.[14] The C=N configurations of 2 generally reflected those of the particular starting materials, 1, and isomerization usually produced *E,Z* C=C isomer mixtures as indicated by NMR spectroscopy. Thus, in the present work we encountered azadienes (eg., **33**), which were mixtures of the four possible isomers. Crystalline examples of 2 were invariably of the *E,E* configuration. Chemical shift assignments could be made in accordance with previous work[1] and these are summarized as chemical shift ranges in the Experimental Section. Azadiene isomer mixtures or their reduction products, amines 4, were characterizatized by elemental analysis.

The base-catalyzed isomerization method for preparing 2 described herein was generally useful but there were exceptions which should be noted. The imine 1 derived from pyrrole-2-carbaldehyde failed to undergo isomerization under a variety of conditions, and that from 9-fluorenone yielded an intractable product upon attempted isomerization. Also, isomerization of the imine from 2,3-benzocycloheptenone yielded 5 as the major component of a mixture of isomers as characterized by ^1H NMR spectroscopy and elemental analysis.

Thermolysis Results. Azadienes 2 were heated in vacuo at 600 °C as described in the Experimental Section. An inert atmosphere was maintained because, in its absence, oxidation of products 3 occurred to varying extents, thereby complicating the purification of products. The cyclized products were characterized directly or reduced to the amines 6 for elemental analysis. The yields of 3 as shown in parenthesis near the respective structure are unoptimized, isolated yields. In the ^1H NMR spectra of the pyrolysis products 3 the signal for the CH_3–CH group, at δ 1.2 ± 0.3 ($^3J_{HH}$ = 7.0 Hz), was characteristic and could be used to monitor the extent of cyclization in pyrolysis product mixtures. The CH_3–CN signal of 3, near δ 2.3, was downfield from the corresponding signal in 2 (R = CH_3), and it was used as a check on the assignment of the signal at δ 1.2. ^1H NMR spectroscopy revealed the preferred conformations of the dihydroazacyclic ring of 3. The two limiting conformations, with CH_3–CN quasi-equatorial or quasi-axial, are examplified in compounds **17c** and **12**, respectively, and the diagnostic signals were those of the diastereotopic protons of the CH_2N group. In the spectrum of **17c** the quasi-axial proton H_A resonated at δ 3.32 ($^2J_{HH}$ = 15 Hz, $^3J_{HH}$ = 11.5 Hz, and $^5J_{HH}$ = 1.8 Hz). In contrast, H_B resonated downfield at δ 3.85 ($^3J_{HH}$ = 6.7 Hz and $^5J_{HH}$ = 1.2 Hz). H_A, therefore, has a quasiaxial vicinal neighbor placing the CH_3 group in a quasi-equatorial conformation. Consistent with the conformational assignment for H_A is its larger ^5J value due to coupling with group CH–CN.[19] This conformation was preferred in compounds **8a**, **11**, **14**, **17a–c**, **18**, **20**, **22**, **23**, **25**, **26**, and **28**. In the spectrum of **12** H_B resonated at δ 3.50 ($^2J_{HH}$ = 16.4 Hz, $^3J_{HH}$ = 6.1 Hz, and $^4J_{HH}$ = 3.4 Hz); H_A resonated at δ 4.16 ($^2J_{HH}$ = 16.4 Hz and $^3J_{HH} \sim {}^4J_{HH} \sim$ 1.2 Hz). A quasiaxial conformation for H_B is also consistent with the observed larger ^4J value. The conformation with CH_3–CH axial was also preferred in compounds **19**. In compound **31** the signals for H_A and H_B were almost merged indicating comparable concentrations for both (interconverting) conformations.

Cyclization Pathway. When azadiene **7a**[1] was pyrolyzed dihydroisoquinoline derivative **8a** could be isolated in 15% yield. (*Z*)- and (*E*)-1-phenylpropene and some

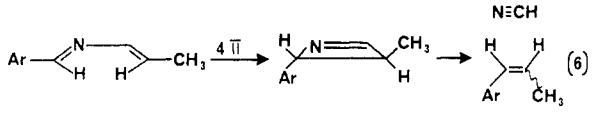


(5)

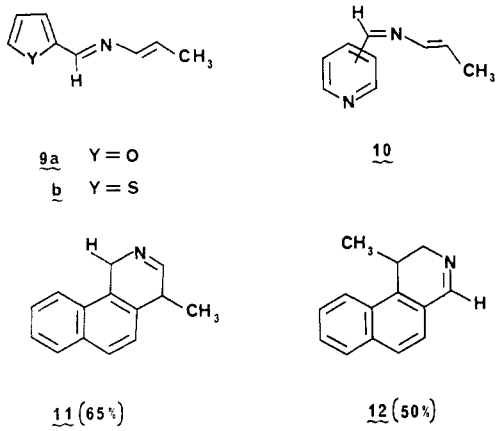
higher molecular weight substances were also produced. The formation of **8a** likely proceeds by way of eq 5. In **7a**, a mixture of *E* and *Z* C=C configurational isomers, the C=N configuration was *E*.[1] The required C=N *Z* con-

(10) Roelofsen, D. P.; Van Bekkum, H. *Recl. Trav. Chim. Pays-Bas* **1972**, *91*, 605–610.
(11) (a) White, W. A.; Weingarten, H. *J. Org. Chem.* **1967**, *32*, 213–214. (b) Ripoll, J. L.; Lebran, H.; Thuillier, A. *Tetrahedron Lett.* **1978**, 463–464.
(12) Presumably the reduction conditions were sufficiently basic and vigorous to isomerize any C=C to C=N, which then was reduced.
(13) Wender, P. A.; Schaus, J. M. *J. Org. Chem.* **1978**, *43*, 782–784.
(14) Molecular models suggest that proton abstraction from the *Z* isomer is more sterically hindered.

figuration must be formed by isomerization at the high reaction temperature. While this isomerization was never directly observed, C=C isomerization, which has a higher activation energy, was observed by NMR spectroscopy of recovered **2**. This was clearly evident when the starting azadiene was configurationally pure. Electrocyclic ring closure of a 6π electron system is thermally allowed by the disrotatory mode. It is not known if this closure is reversible, but suprafacial 1,5-H migration, expected to be facile, would restore aromaticity and be irreversible, thus yielding the cyclized product **8a**. A reaction which competes with the formation of **8a** leads to (*Z*)- and (*E*)-1-propenylbenzene. This olefin is formed, we believe, by fragmentation of an intermediate 1-azetine derivative, the product of a 4π electron electrocyclization[5] (see eq 6).

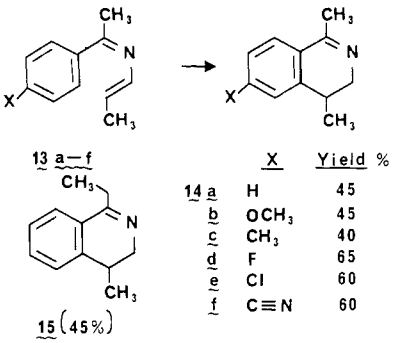


While 1-azetine itself gives 2-aza-1,3-butadiene and does not yield HCN upon pyrolysis,[15] C–N cleavage in the present case would give a reactive intermediate or transition state, stabilized by benzylic conjugation. The previously cited work of Bergman and Wendling[6] supports this pathway for 1-propenyl arene formation. In the cases of conjugated azedienes **9** and **10** derived from aldehydes, low yields of annelation product and high yields of 1-propenyl arenes were obtained. For example, **9a** gave (*Z*)- and (*E*)-2-(1-propenyl)furan in 80% yield. In these cases

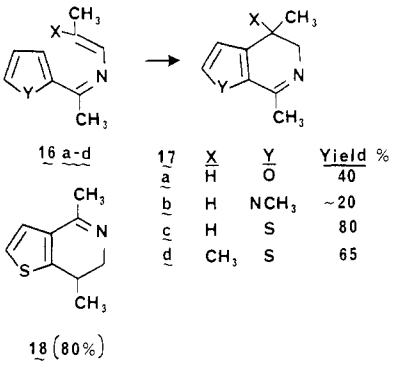


sufficient characterization of a distilled product mixture could be obtained by ^{1}H NMR spectroscopy, and if cyclization was a minor end result the reaction was usually not pursued further. The conjugated azadienes derived from naphthalene-1- and -2-carbaldehyde did undergo cyclization in reasonable yield, however, giving **11** (65%) and **12** (50%), respectively. Examination of the crude reaction mixtures of **12** gave no evidence of the presence of the other possible tricyclic isomer. Thus this cyclization was regioselective. The familiar partial fixation of the π bond between positions 1 and 2 of naphthalene may account for the observed regioselectivity.

Carbon Substitution at the C=N Terminus. Increasing the steric bulk of substituents at the termini of a 1,3-diene should sterically hinder formation of the transition state of a 4π-electron electrocyclization. Accordingly, substitution of CH_3 for H as group R in **2** would be expected to suppress 1-propenyl arene formation and, perhaps, permit the 6π electron electrocyclization to compete favorably. Indeed, **13a** was pyrolyzed to **14a** in 45%



yield. In the conjugated azadiene derived from 1-phenylpropanone (propiophenone) the proportion of C=N *Z* isomer was increased from about 5% to about 25%[16] but pyrolysis showed no yield improvement, and 1-ethyl-4-methyl-3,4-dihydroisoquinoline (**15**) was isolated also in 45% yield. Thus, the magnitude of the *K*eq for $E \rightleftharpoons Z$ isomerization about the C=N bond has little bearing on the yield of cyclization. With azadiene **16a**, cyclization to



17a in 40% yield was a dramatic improvement over the example of **9a**. When the yield of **17b** dropped to 20% and azadiene **16b** could be recovered after pyrolysis, this compound was not pursued further. We believe the reduced reactivity of **16b** and the low yield of **17b** results from the unfavorable N–CH_3:C–CH_3 syn–peri interaction that develops in the transition state leading to **17b**. The thiophene analogues **16c** and **16d** cyclized readily. Also, the azadiene from 3-acetylthiophene cyclized in good yield to **18**.

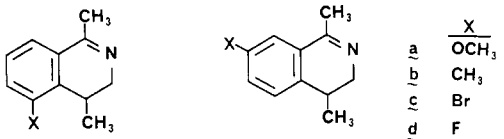
***Z* and *E* Methyl Substituents on the C=C Double Bond.** While a *Z* CH_3 substituent at the C=C terminus of **2** would be expected to suppress 4π electron electrocyclization, prediction of the effect of such substitution on the present 6π electron process was difficult. When azadiene starting material survived the pyrolysis tube it was enriched in the C=C *Z* isomer, but not dramatically so. We projected from that observation that cyclization of a given *Z* CH_3 isomer would proceed, but more slowly than an *E* CH_3 isomer. To test this azadienes **7b**[1] and **16d** were pyrolyzed under conditions similar to those for **7a**[1] and **16c**. Cyclized products **8b** and **17d** were obtained in 10% and 65% yields, respectively.

Electronic Effects of Group Ar. We tested a number of para- and meta-substituted phenyl groups, as group Ar on **2**, for their effect on the yield and regioselectivity of the cyclization. With azadienes **13**, synthesized from para-substituted acetophenones, electronegative substitu-

(15) Guillemin, J. C.; Denis, J. M.; Lablach-Combier, A. *J. Am. Chem. Soc.* **1981**, *103*, 468–469.

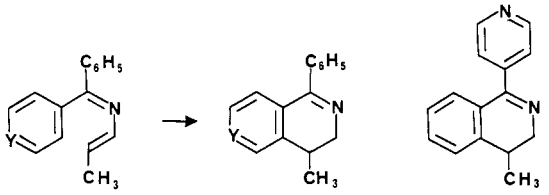
(16) This is consistent with previous observations on *N*-(1-phenylalkylidene)methaneamines. Bjoergo, J.; Body, D. R.; Watson, C. G.; Jennings, W. B. *J. Chem. Soc. Perkin Trans. 2* **1974**, 757–762.

ents enhanced the amount of conversion and reduced the amount of polymer in both the distilling and the pyrolysate receiver flasks. Thus, yields were reproducibly higher in these cases. With azadienes prepared from meta-substituted acetophenones the yields of cyclization gave **19** and **20**, in 40–65% yield, with little regioselectivity. The ratio

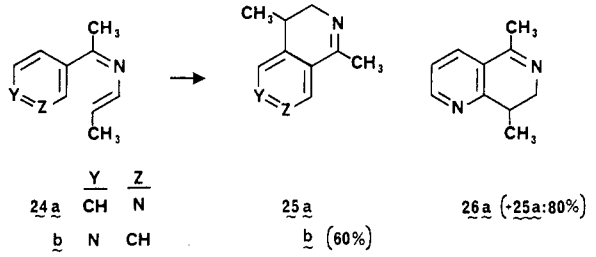


of **19a,c,d** to **20a,c,d** was 1.3:1, and that of **19b** to **20b** was 1:1.3.[17] The mixtures were characterized by NMR spectroscopy only and the components were not separated.

Azadiene **21a**, one of the few solids in this work, gave **22a** in 70% yield. Compound **21b** offered an interesting

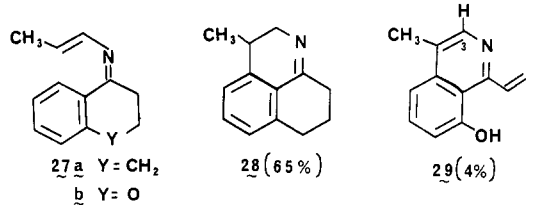


intramolecular competition for the cyclization. Again, little regioselectivity was observed; the ratio **22b:23** was 1.3:1. Isomer **22b** crystallized from ether, and silica gel chromatography effected a clean separation of the mothor liquors. Pyrolysis of **24** effected cyclizations into an aro-



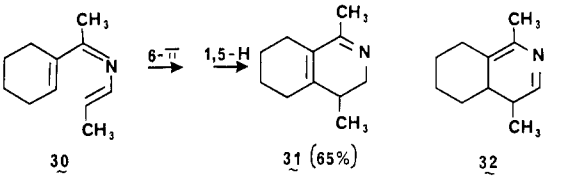
matic ring well-known for its resistance to electrophilic attack. The ratio of isomers **25a:26a** was 28:72, exactly that reported for the corresponding isomers of eq 4. Distillation effected separation of the lower boiling **26a** permitting its further characterization.

Bridging Two Rings. In a general sense the annelation sequence of eq 1 can be viewed as a method for aromatic alkylation ortho to an electron-withdrawing (meta-directing) group. As such the process should be useful for bridging two rings and the synthesis of two heterocyclic tetrahydrophenalene analogues were attempted. In contrast with the isomerization of the imine derived from 2,3-benzocycloheptenone, which gave azadiene **5**, the isomerization of the imines from benzocyclohexenone and benzopyranone was controlled and gave **27** in good yield.



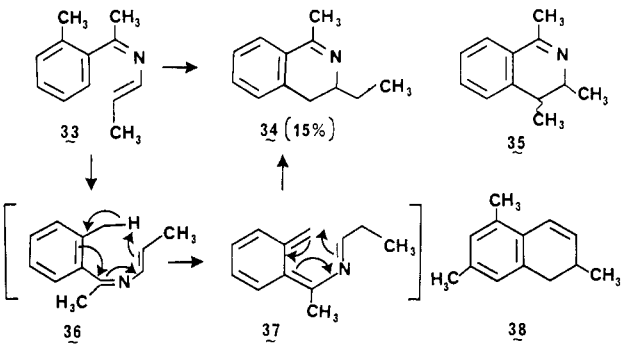
Azadiene **27a** underwent a smooth cyclization to **28**. In the case of **27b** pyrolysis produced a brown gum from which a low yield of **29** could be crystallized. ^{1}H NMR spectroscopy revealed the following structural features for **29**: CH_3-C (δ 2.30, s), CH_2= (δ 6.95, 7.05, AB of ABM), —HC= (δ 7.25, M of ABM, $^3J_{HH}$ = 9 and 7 Hz, $^5J_{H,H3}$ = 1.5 Hz), H3 aromatic (δ 7.7, br m), HC=N (δ 8.25, br s), HO (δ 14.3, br s). ^{13}C NMR gated decoupling experiments revealed one alkyl carbon, two vinyl carbons, and nine aromatic carbons of which five were quaternary carbons. The formation of **29** appears to involve an electrocyclization and a β elimination which opens the chroman ring (not necessarily in that order) followed by an oxidation which aromatizes the ring system.

A Nonaromatic Case. With azadiene **30** we had hoped the propensity for 1,5-hydrogen migration after cyclization would be reduced sufficiently to permit the detection or isolation of the initial electrocyclization product (**32**).



However, the thermolysis went smoothly at 500 °C to yield **31**, the product of electrocyclization and 1,5-hydrogen shift. Azadiene **30** was converted incompletely to **31** at 350 °C. Careful examination of reaction mixtures (VPC, NMR spectroscopy) provided no evidence for the presence of the initial cyclization product **32** (a less substituted diene system).

Effect of an Ortho Substituent in Ar. The low conversion of **16b** to **17b** was attributed to the development of a syn–peri interaction in the transition state of cyclization. We explored this facet further with the pyrolyses of azadiene **33**. It seemed possible that a strong syn–peri



repulsion might prevent cyclization meta to the CH_3 substituent and, in fact, lead to an ipso cyclization. If this were followed by a 1,5 migration of CH_3, the product produced would be that of a regioselective cyclization. Pyrolysis of **33** at 600 °C led to a substantial recovery of the starting material and an estimated 30% conversion to **34** (isolated yield, 15%). No evidence for the formation of **35**, the product which would result from ipso cyclization and CH_3 migration, was seen. ^{1}H NMR spectroscopy revealed the following structural features of **34**: CH_3CH_2 (δ

(17) When a substituent perturbs the π electrons of a benzene ring, the π orbital coefficients ortho to the substituent are larger than that of the para position. (See: Kobayashi, T.; Nagakura, S. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 2563–2572. Therefore, electrocyclization to give **19** might enjoy better orbital overlap in the transition state. Methyl, having the largest steric substituent constant (E_s)[18] may affect the **19/20** ratio in that fashion.

(18) Gordon, A. J.; Ford, R. A. "The Chemist's Companion"; Wiley: New York, 1972; pp 150–156.

Table I. Melting Points or Boiling Points of Azadienes, 2, or Their Reduction Products, 4[a]

compd or Ar/R of 2	mp or bp (mm), °C	hydrochloride of reduction products: formula	mp, °C
5	98 (0.2)	$C_{14}H_{22}ClN$	228-230
9a	38 (0.2)	$C_8H_{14}ClNO$	123-125
9b	51 (0.2)	$C_8H_{14}ClNS$	167-168
1-naphthyl/H	116 (0.2)	$C_{14}H_{18}ClN$	195-197
2-naphthyl/H	51		
13a	58 (0.3)		
13b	66-68		
13c	72 (0.3)	$C_{12}H_{20}ClN$	215-216
13d	65 (0.3)	$C_{11}H_{17}ClFN$	182
13e	80 (0.3)	$C_{11}H_{17}Cl_2N$	225-226
13f	68-69		
C_6H_5/C_2H_5	66 (0.3)		
16a	50 (0.3)	$C_9H_{16}ClNO$	123-125
16b	60 (0.2)		
16c	62 (0.2)	$C_9H_{16}ClNS$	130-131
16d	65 (0.2)		
3-$MeOC_6H_4/CH_3$	82 (0.25)	$C_{12}H_{20}ClNO$	158-160
3-MeC_6H_4/CH_3	71 (0.3)	$C_{12}H_{20}ClN$	190-191
3-BrC_6H_4/CH_3	92 (0.2)	$C_{11}H_{17}BrClN$	147-148
3-FC_6H_4/CH_3	63 (0.3)	$C_{11}H_{17}ClFN$	222-224
21a	115 (0.2)		
21b	125 (0.2)	$C_{15}H_{20}Cl_2N_2$	214-215
2-pyridyl/CH_3	62 (0.2)	$C_{10}H_{18}Cl_2N_2$	134-135
24a	62 (0.2)	$C_{10}H_{18}Cl_2N_2$	170-171
24b	61 (0.2)	$C_{10}H_{18}Cl_2N_2$	180-182
27a	90 (0.2)		
27b	49-50		
thiophen-3-yl/CH_3	63 (0.2)	$C_9H_{16}ClNS$	119-120
30	51 (0.2)	$C_{11}H_{22}ClN$	170-175
33	74 (0.3)	$C_{12}H_{20}ClN$	215-217

[a] Satisfactory elemental analyses (±0.4% for C, H, N) were obtained for all reduction product hydrochlorides listed in the table. Where no reduction product is listed, satisfactory elemental analyses (±0.4%, for C, H, N) were obtained for the azadienes, 2.

1.04, t, $^3J_{HH}$ = 7), CH_3CH_2 chiral carbon (δ 2.00, m), $ArCH_2$-chiral carbon (δ 2.30, AB of ABX), $CH_3C{=}N$ (δ 2.36, d, $^5J_{HH}$ = 2.9 Hz), HCN (δ 4.07, br m). Homonuclear decoupling experiments confirmed the following couplings: HCN with the CH_3 doublet at δ 2.36 and with both CH_2 groups; the CH_2 at δ 2.00 with the CH_3 at δ 1.04 and with H-CN. Gated decoupled ^{13}C NMR spectra confirmed the presence of the ethyl group, the $CH_3C{=}N$ group, another CH_2 group, and three quaternary carbon atoms, all with appropriate chemical shifts. A reaction pathway of **33** → **36** → **37** → **34** gives a plausible explanation for the formation of **34**. Conversion of **33** to **37** involves a 1,7-hydrogen shift. Inspection of molecular models suggested that the thermally allowed antarafacial mode of H transfer should be sterically facile, and a 6π electron electrocyclization should complete the conversion to **34**. This pathway, rather than the one involving CH_3 migration, appears to best explain the formation of **38** from the pyrolysis of (*E*)-1-mesityl-1,3-butadiene.[7]

Experimental Section

General Methods. IR spectra were recorded on a Perkin-Elmer 283 spectrometer. NMR spectra were recorded on a Bruker WH-90DS spectrometer. Chemical shifts were measured in $CDCl_3$ with Me_4Si and internal standard for ^1H and ^{13}C NMR spectra. UV spectra were recorded on a Perkin Elmer 571 spectrometer. VPC analyses were performed on a 2-m 20% SE-30 on chrom-W (AW and DMCS) column using a Hewlett-Packard 5750 research chromatograph equipped with a flame ionization detector. Satifactory elemental analyses (C,H,N) were obtained for all compounds listed in Tables I and II. Elemental analysis were performed by Midwest Microlabs Inc., Indianapolis, IN. All the aldehydes and ketones used in this study were obtained commercially. Melting points are uncorrected.

Unconjugated Azadienes. 1. Molecular Sieve Method. Acetophenone (12.0 g, 0.1 mol) and 2-propenylamine (8.6 g, 0.15 mol) were dissolved in 60 mL of cyclohexane. To this was added 80 g of molecular sieves (Davison type 3Å) and the mixture was left to stand at room temperature. The reaction progress was followed by gas chromatography. After the complete disappearance of acetophenone the mixture was filtered and the sieves were washed thrice with ether. The filtrates were combined, the solvents were distilled in vacuo, and the residue was distilled to give 13.5 g (85%) of (*E*)-2-phenyl-3-aza-2,5-hexadiene, bp 58–59 °C (0.3 mm).

Titanium Tetrachloride Method. A solution of 18.3 g (0.1 mol) of 4-benzoylpyridine and 35.0 g of 2-propenylamine (0.6 mol) in 300 mL of benzene was cooled to 0 °C. This was followed by the dropwise addition (1 h) of a solution of 8 g of $TiCl_4$ in 60 mL benzene. An immediate precipitation of TiO_2 was observed. The mixture was stirred overnight and then filtered. The filtrate was washed with saturated NaCl solution and dried (Na_2SO_4). The solvent was distilled in vacuo, and the (*E,Z*)-1-phenyl-1-(4-pyridyl)-2-aza-1,4-pentadiene product was used for the next re-

Table II. Melting Points of Pyrolysis Products, 3, or Their Derivatives, 6[a]

compd	formula	mp, °C	compd	formula	mp, °C
8a	$C_{10}H_{11}N$	liquid[b]	17c	$C_9H_{14}ClNS$	180-185
8b	$C_{11}H_{16}ClN$	175-178	17d	$C_{10}H_{16}ClNS$	166-168
11[c]	$C_{14}H_{13}N$	64-65	18[d]	$C_9H_{14}ClNS$	200-203
12	$C_{14}H_{16}ClN$	275-278	22a[f]	$C_{16}H_{15}N$	95-100
14a	$C_{11}H_{16}ClN$	190-195	22b[g]	$C_{14}H_{15}N_2$	136-137
14b[d]	$C_{12}H_{18}ClNO$	186-188	23[g]	$C_{15}H_{14}N_2$	83-85
14c	$C_{12}H_{18}ClN$	225-227	25b[d]	$C_{22}H_{20}N_8O_{14}$	199-200
14d[d]	$C_{11}H_{15}ClFN$	220-222	26a[d]	$C_{22}H_{20}N_8O_{14}$	157-159
14e[d]	$C_{11}H_{15}Cl_2N$	256-260	28	$C_{13}H_{18}ClN$	264-267
14f[e]	$C_{12}H_{12}N_2$	63-64	29[e]	$C_{12}H_{11}NO$	98
15	$C_{12}H_{18}ClN$	159-162	31	$C_{17}H_{22}N_4O_7$	176
17a	$C_{15}H_{16}N_4O_8$	185-187	34[e]	$C_{12}H_{18}ClN$	252-254

[a] Satisfactory elemental analyses (±0.4% for C, H, N) were obtained for all the compounds listed in the table. Compounds **6** were frequently isolated as mixtures of diastereoisomers. The pyrolysis reactions leading to the compounds listed in this table were worked up by method 3 (see Experimental Section) unless otherwise noted. [b] bp 195 °C. [c] Final purification was by sublimation. [d] The pyrolysate was purified by method 1. [e] The pyrolysate was purified by method 2. [f] The initial flash distillation of method 3 was omitted. [g] Compound **22b** crystallized directly and **23** was isolated by silica gel chromatography of the mother liquors (C_2H_5OH:$CHCl_3$, 1:10 elution).

action without further purification. ^{1}H NMR[19,20] for (*E*)-1 (R = CH_3, Ar = C_6H_5, 4-XC_6H_4, 3-XC_6H_4, or heterocyclic) δ 2.0 ± 0.2 (CH_3–C). ^{1}H NMR for (*Z*)-1 (R = CH_3, Ar = 2-$CH_3C_6H_4$) δ 2.3 ± 0.1 (CH_3–C). ^{13}C NMR[19,20] for (*E*)-1 (R = CH_3, Ar = C_6H_5, 4-XC_6H_4, 3-XC_6H_4 or heterocyclic) δ 15 ± 1 (CH_3–C), 54 ± 1 (NCH_2), 166 ± 2 (C=N). ^{13}C NMR for (*E*)-1 (R = C_6H_5, Ar = C_6H_5 or 4-pyridyl) δ 169 ± 1 (C=N). ^{13}C NMR for (*E*)-1 (R = CH_3, Ar = 2-$CH_3C_6H_4$) δ 13 ± 0.5 (CH_3–C). ^{13}C NMR for (*Z*)-1 (R = CH_3, Ar = 2-$CH_3C_6H_4$) δ 15 ± 0.5 (CH_3–C), 56 ± 1 (NCH_2). IR ($CHCl_3$) ν_{max} 1635 ± 15 cm^{-1} (*Z* or *E* C=N).

General Method for the Isomerization of 1 to the Conjugated Azadienes, 2. To a 0.1 M solution of 1 in benzene were added 0.22 g of powdered KOH and 50 mg of 18-crown-6 ether. The mixture was stirred and the reaction progress was followed by gas chromatography, observing the disappearance of 1. Most reactions were complete in 12–20 h. If there was no appreciable reaction after 20 h, the mixture was heated at reflux in an oil bath until complete disappearance of 1 was observed. The mixture was washed with saturated NaCl solution, and the solvent was distilled in vacuo. The residue was purified by vacuum distillation of recrystallization. Azadienes thus treated were sufficiently pure for pyrolysis. ^{1}H NMR[19,20] for (*E,Z*)- and (*E,E*)-2 (R = CH_3, Ar = C_6H_5, 4-XC_6H_4, 3-XC_6H_4, and heterocyclic) δ 2.2 ± 0.2 (CH_3–CN). ^{1}H NMR for (*Z,Z*)-2 (R = CH_3, Ar = 2-$CH_3C_6H_4$) δ 1.80 (CH_3C=C), 6.3 (NCH). ^{1}H NMR for (*Z,E*)-2 (R = CH_3, Ar = 2-$CH_3C_6H_4$) δ 1.65 (CH_3C=C). ^{13}C NMR[19,20] for (*E,Z*)-2 (R = CH_3, Ar = C_6H_5, 4-XC_6H_4, 3-XC_6H_4, or heterocyclic) δ 123 ± 2 (=CH—), 134 ± 2 (NCH), 160 ± 1 (C=N). ^{13}C NMR for (*E,E*)-2 (R = CH_3, Ar = C_6H_5, 4-XC_6H_4, 3-XC_6H_4, or heterocyclic) δ 134 ± 2 (NCH, but always downfield from the corresponding (*E,Z*)-2 isomer). ^{13}C NMR for 2 (R = C_6H_5, Ar = C_6H_5 or 4-pyridyl) δ 164 ± 2 (C=N). ^{13}C NMR for (*Z,E*)-2 (R = CH_3, Ar-2-$CH_3C_6H_4$) δ 19.2 (CH_3CN), 168.0 (C=N). IR ($CHCl_3$) ν_{max} 1600 ± 10 cm^{-1} (*Z* or *E* C=N). UV λ_{max} (log ϵ) in C_2H_5OH for (*E,E*)- and (*E,Z*)-**33c** are 216 (4.21) and 266 nm (4.07) and for (*Z,E*)- and (*Z,Z*)-**33** are 211 (4.14) and 240 nm (4.06).

General Method for the Pyrolysis of 2. Pyrolyses of 2 were carried out using a 1.0-cm O.D. quartz tube (250 cm long, coiled into a spiral of 30 cm in length) and maintained at 600 ± 20 °C inside a Lindberg heavy duty furnace. Auxiliary heating tapes were used to heat the inlet and outlet connections of the pyrolysis tube to prevent condensation of compounds in those regions. Compounds to be pyrolyzed were placed in a 25-mL pear-shaped flask, equipped with a capillary helium (He) inlet, which was heated by a heating mantle. The tip of the He inlet was placed below the surface of the liquid in the flask, and the He flow was controlled with a needle valve similar to those used in gas chromatographs to control gas flow. The pyrolysates were collected in a vacuum trap cooled to −78 °C. A second trap in series was used as a precautionary measure, but no pyrolysates ever escaped the first trap. The whole system was maintained under vacuum, normally at 0.1 mm, and the vacuum was controlled by varing the rate of He flow. In most pyrolyses, the compounds distilled into the pyrolysis zone at the rate of 1 g/h.

The pyrolysate was warmed to room temperature and purified by one of the following three methods: 1. The pyrolysate was fractionated using a spinning band or Vigreux distillation column. 2. The pyrolysate was chromatographed on silica gel and then distilled in vacuo. 3. The pyrolysate was flash distilled in vacuo to separate the product from polymers, and the distillate was dissolved in 6 N HCl. The acid solution was washed with ether and then made basic either with KOH or concentrated NH_4OH. The products were extracted with ether. Final purification was by simple distillation in vacuo.

The practice of distilling 2 into the pyrolysis zone led to the formation of distillation pot residues in many cases. This is, obviously, not the optimal method for introducing 2 into the pyrolysis zone. The yields reported in the text are based on the amount of 2 that distilled through the pyrolysis tube. ^{1}H NMR for 3 (R = CH_3) δ 2.3 ± 0.8 (CH_3C=N), 2.7 ± 0.3 (CH, shift dependent on conformation and group Ar), 3.45 ± 0.15 (NCH_2, quasiaxial H), 4.0 ± 0.25 (NCH_2, quasiequatorial H). ^{13}C NMR for 3 (R = CH_3) δ 17 ± 2 (CH_3CH), 23 ± 1 (CH_3CN), 23 ± 1 (quasiaxial CH_3CH), 29 ± 2 (quasiequatorial CH_3CH), 54 ± 2 (NCH_2), 163 ± 1 (C=N). ^{13}C NMR for 3 (R = H) δ 160 ± 2 (C=N). ^{13}C NMR for 3 (R = aryl) δ 166 ± 1 (C=N). IR ($CHCl_3$) ν_{max} 1620 ± 20 cm^{-1} (C=N). IR ($CHCl_3$) for 31 ν_{max} 1660 cm^{-1} (C=C).

General Method for the Sodium Borohydride Reductions. A mixture of 0.01 mol of 1, 2, or 3, 0.02 mol of $NaBH_4$, and 60 mL of 2-propanol were heated at reflux for 16–20 h. The reaction progress was followed by gas chromatography and the heating time was adjusted to allow complete disappearance of starting materials. The solvent was distilled in vacuo, the residue dissolved in water, and the product extracted with ether. The ether extracts were combined and dried. The ether solvent was then distilled, and the resulting amines were purified by simple vacuum distillation.

The amines were dissolved in ether and converted to their hydrochloride salts by adding hydrogen chloride gas. These salts were purified by recrystallization from ethanol–ether mixtures at 0 °C. In some cases picrate salt derivatives were prepared using a standard method.

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Registry No. 1 (R = Ar = C_6H_5), 51411-28-0; (*E*)-1 (R = H; Ar = 1-naphthyl), 87869-49-6; (*E*)-1 (R = H; Ar = 2-naphthyl), 87869-50-9; (*E*)-1 (R = CH_3; Ar = C_6H_5), 87869-51-0; (*E*)-1 (R = CH_3; Ar = 3-BrC_6H_4), 87869-52-1; (*E*)-1 (R = CH_3; Ar = 3-FC_6H_4), 87869-53-2; (*E*)-1 (R = CH_3; Ar = 3-$MeOC_6H_4$), 87869-54-3; (*E*)-1 (R = CH_3; Ar = 2-MeC_6H_4), 87869-55-4; (*Z*)-1 (R = CH_3; Ar = 2-MeC_6H_4), 87869-56-5; (*E*)-1 (R = CH_3; Ar = 3-MeC_6H_4), 87869-57-6; (*E*)-1 (R = CH_3; Ar = 2-pyridyl), 87869-58-7; (*E*)-1 (R = CH_3; Ar = thiophen-3-yl), 87869-59-8; (*E*)-1 (R = C_2H_5; Ar = C_6H_5), 87869-60-1; (*E*)-1 (R = C_6H_5; Ar = 4-pyridyl), 87869-61-2; (*Z*)-1 (R = C_6H_5; Ar = 4-pyridyl), 87869-62-3; (*E,E*)-2 (R = H; Ar = 1-naphthyl), 87869-63-4; (*E,E*)-2 (R = H; Ar = 2-naphthyl), 87869-64-5; (*E,E*)-2 (R = CH_3; Ar = 3-BrC_6H_4), 87869-65-6; (*E,E*)-2 (R = CH_3; Ar = 3-FC_6H_4), 87869-66-7; (*E,E*)-2 (R = CH_3; Ar = 3-$MeOC_6H_4$), 87869-67-8; (*E,E*)-2 (R = CH_3; Ar = 3-MeC_6H_4), 87869-68-9; (*E,E*)-2 (R = CH_3; Ar = 2-pyridyl), 87869-69-0; (*E,E*)-2 (R = CH_3; Ar = thiophen-3-yl), 87869-70-3; (*E,E*)-2 (R = C_2H_5; Ar = C_6H_5), 87869-71-4; 4 (R = H; Ar = 2-furyl)·HCl, 87883-09-8; 4 (R = H; Ar = 1-naphthyl)·HCl, 87869-72-5; 4 (R = H; Ar = thiophen-2-yl)·HCl, 87869-73-6; 4 (R = CH_3; Ar = 3-BrC_6H_4)·HCl, 87869-74-7; 4 (R = CH_3; Ar = 4-ClC_6H_4)·HCl, 87869-75-8; 4 (R = CH_3; Ar = 3-FC_6H_4)·HCl, 87869-76-9; 4 (R = CH_3, Ar = 4-FC_6H_4)·HCl, 87869-77-0; 4 (R = CH_3; Ar = 3-$MeOC_6H_4$)·HCl, 87869-78-1; 4 (R = CH_3; Ar = 2-MeC_6H_4)·HCl, 87869-79-2; 4 (R = CH_3; Ar = 3-MeC_6H_4)·HCl, 87869-80-5; 4 (R = CH_3; Ar = 4-MeC_6H_4)·HCl, 87869-81-6; 4 (R = CH_3; Ar = 1-cyclohexen-1-yl)·HCl, 87869-82-7; 4 (R = CH_3; Ar = 2-furyl)·HCl, 87869-83-8; 4 (R = CH_3; Ar = 2-pyridyl)·2HCl, 87869-84-9; 4 (R = CH_3; Ar = 3-pyridyl)·2HCl, 87869-85-0; 4 (R = CH_3; Ar = 4-pyridyl)·2HCl, 87869-86-1; 4 (R = CH_3; Ar = thiophen-2-yl)·HCl, 87869-87-2; 4 (R = CH_3, Ar = thiophen-3-yl)·HCl, 87869-88-3; 4 (R = C_6H_5; Ar = 4-pyridyl)·2HCl, 87869-89-4; (*E*)-5, 87869-90-7; 5·HCl *N*,-α,5,6,-tetrahydro, 87869-91-8; 8, 86457-01-4; 8b·HCl 1,2-dihydro, 41565-86-0; (*E,E*)-9a, 87869-92-9; (*E,E*)-9b, 87869-93-0; 11, 87869-94-1; 12·HCl 3,4-dihydro, 87869-95-2; (*E,E*)-13a, 87869-96-3; (*E,Z*)-13a, 87869-97-4; (*Z,E*)-13a, 87869-98-5; (*Z,E*)-13b, 87869-99-6; (*Z,E*)-13c, 87870-00-6; (*Z,E*)-13d, 87870-01-7; (*Z,E*)-13e, 87870-02-8; (*Z,E*)-13f, 87870-03-9; 14·HCl 1,2-dihydro, 87870-04-0; 14b·HCl 1,2-dihydro, 25289-26-3; 14c·HCl 1,2-dihydro, 8870-05-1; 14d·HCl 1,2-dihydro, 87870-06-2; 14e·HCl 1,2-dihydro, 87870-07-3; 14f, 87870-08-4; 15·HCl 1,2-dihydro, 87870-09-5; (*Z,E*)-16a, 87870-10-8; (*Z,E*)-16b, 87870-11-9; (*Z,E*)-16c, 87870-12-0; (*Z*)-16d,

(19) Karabatsos, G. J.; Lande, S. S. *Tetrahedron* **1968**, *24*, 3907–3922.

(20) Only those chemical shifts are reported which are not similar to corresponding shifts in analogous configurational isomers of compounds reported in ref 1, and these are reported herein only once. For 2, the configuration of the C=N is indicated first; eg., 7a is shown in the *E,E* configuration. Further, no unusual chemical shifts were seen for group Ar in 1, 2, or 3 and these are also not reported herein.

87870-13-1; **17a** 6,7-dihydro picrate, 87870-15-3; **17b**, 87870-16-4; **17c**·HCl 6,7-dihydro, 87870-17-5; **17d**·HCl 6,7-dihydro, 87870-18-6; **18**·HCl 4,5-dihydro, 87870-19-7; (*E*)-**21a**, 83575-90-0; (*Z*,*E*)-**21b**, 87870-20-0; **22a**, 87870-21-1; **22b**, 87870-22-2; **23**, 87870-23-3; (*Z*,*E*)-**24a**, 87870-24-4; (*Z*,*E*)-**24b**, 87870-25-5; **25a**, 87870-26-6; **25b** 1,2-dihydro dipicrate, 87870-28-8; **26a** 5,6-dihydro dipicrate, 87870-30-2; (*Z*,*E*)-**27a**, 87870-31-3; (*Z*,*E*)-**27b**, 87870-32-4; **28**·HCl 1,9a-dihydro, 87870-33-5; **29**, 87870-34-6; (*Z*,*E*)-**30**, 87870-35-7; **31** 1,2-dihydro picrate, 87870-37-9; (*E*,*E*)-**33**, 87870-38-0; (*E*,*Z*)-**33**, 87870-39-1; (*Z*,*E*)-**33**, 87870-40-4; (*Z*,*Z*)-**33**, 87870-41-5; **34**·HCl 1,2-dihydro, 87870-42-6; acetophenone, 98-86-2; 2-propenylamine, 107-11-9; 4-benzoylpyridine, 14548-46-0.

Notes

Structure of the *Bugula neritina* (Marine Bryozoa) Antineoplastic Component Bryostatin 3[1]

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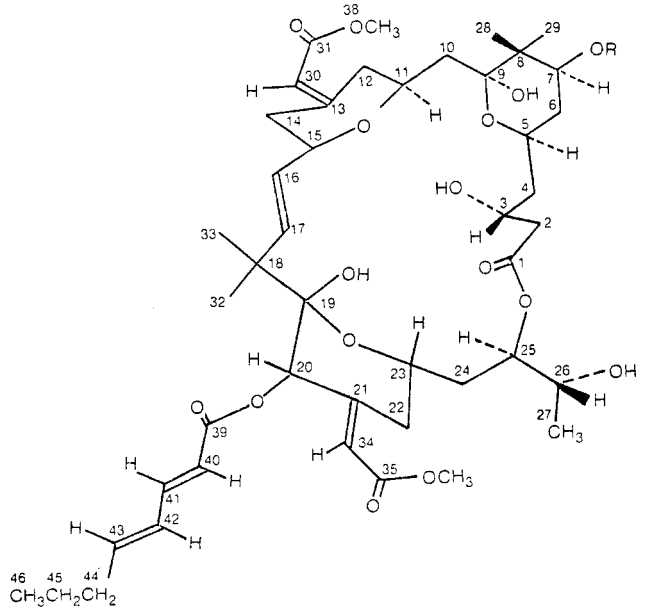
The marine Bryozoan *Bugula neritina* (Linnaeus) was formally described in 1758 and is now recognized as a common fouling organism on marine facilities and equipment. Colonies of this very cosmopolitan species may reach a height of 10 cm, where each tiny animal unit ranges from a width of 0.2–0.3 mm to a length of 0.6–0.8 mm.[2] In preceding reports[3] we summarized the discovery of 17 exceptionally potent *B. neritina* antineoplastic constituents and structures for the first two members of the series: bryostatins 1 (**1a**)[3a] and 2 (**1b**).[3b] These extraordinary

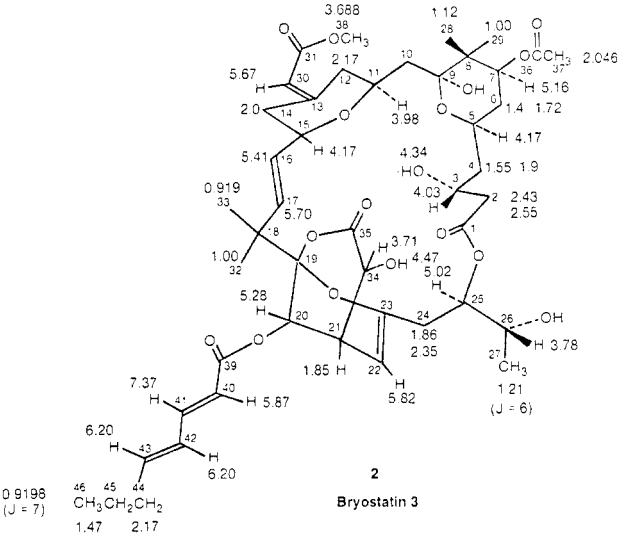


1a, R = $CO\text{-}CH_3$

b, R = H

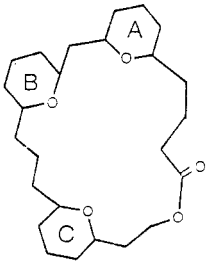
20-membered-ring lactones suggest that an intriguing series of biochemical events may be responsible for their powerful antineoplastic activity. Indeed, the possibility of affecting cellular membranes with such cyclic ionophores[4] suggests the added prospect of tumor destruction at the cellular level.[5] In pursuit of such important questions and the prospect of further defining structure/activity relationships, we have studied another novel *B. neritina* antineoplastic component herein designated bryostatin 3.

We now report the bioassay (PS system) guided isolation (81.5 mg, 1.6×10^{-7} % yield) and structural elucidation of bryostatin 3 (**2**) from *Bugula neritina*. Isolation of crude



2

Bryostatin 3



3

Bryopyran

bryostatin 3 was performed by employing the general route summarized for obtaining bryostatin 1.[3a] Bryostatin 3 (**2**) was found to strongly inhibit (life extension of 63% at 30

(1) Antineoplastic Agents. 93. For part 92 refer to: Pettit, G. R.; Holzapfel, C. W.; Cragg, G. M.; Herald, C. L.; Williams, P. *J. Nat. Prod.*, in press.

(2) Morris, R. H.; Abbott, D. P.; Haderlie, E. C. "Intertidal Invertebrates of California"; Stanford University Press: Stanford, CA, 1980; p 96.

(3) (a) Pettit, G. R.; Herald, C. L.; Doubek, D. L.; Herald, D. L.; Arnold, E.; Clardy, J. *J. Am. Chem. Soc.* **1982**, *104*, 6846. (b) Pettit, G. R.; Herald, C. L.; Kamano, Y.; Gust, D.; Aoyagi, R. *J. Nat. Prod.* **1983**, *46*, 528.

(4) We have observed bryostatins 1–3 to complex strongly with silver ion in FAB mass spectrometry experiments (see ref 1). Alternatively, this might only be due to the diene side chain at C-20.

(5) Gros, L.; Ringsdorf, H.; Schupp, H. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 305.

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