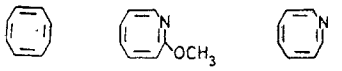
REACTIVITY OF π-EQUIVALENT MEDIUM-RING NITROGEN HETEROCYCLES. AZOCINES AND HOMOAZOCINES

L. A. Paquette

UDC 547.895

Cyclooctatetraene (I) has attracted the interest of organic chemists for a long time [1, 2], chiefly because of its central position as the smallest stable nonaromatic annulene. This 8π-electron system lacks meaningful resonance energy, has true polyolefinic character, and, in fact, adopts a tub conformation to minimize pπ overlap and strain. As a consequence, cyclooctatetraene displays an unequaled facility for structural rearrangement, a feature which has caused it to become the key starting material for synthetic entry to such important and interesting molecules as bullvalene [3], cyclobutadiene [4], and the cyclononatetraenide anion [5], to name but a few.

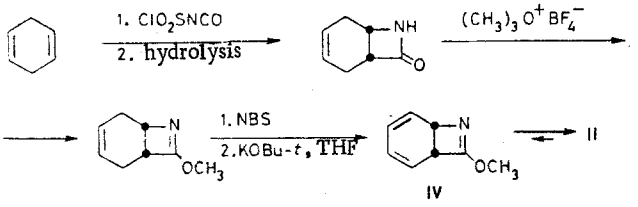


I II III

According to Hückel theory, π-equivalent [6] heterocyclic analogs of "aromatic" molecules should possess electronic properties comparable to the all-carbon systems. We believe that this conclusion can be equally applied to nondelocalized polyolefinic heterocycles, although unconventional physical and chemical properties are certain to accompany either structural modification. To probe these conclusions, there was devised some 10 years ago in this laboratory a general synthetic approach to 2-methoxyazocines (II) [7]. Incorporation of the imino ether functionality into II was dictated by our desire to avoid the anticipated lability of the parent azocine molecule (III) to air and moisture, and to gain entry to a relatively stable class of compounds. In actuality, II and its derivatives show good shelf stability whereas III, synthesized some time later by Hedaya and co-workers [8], has proved to be particularly labile [9].

As illustrated in Scheme I, the synthetic approach to 2-methoxyazocines begins with readily available 1,4-dihydrobenzene derivatives and requires but four laboratory manipulations. The sequence can be easily adapted to large scale reactions and is therefore particularly suitable for the ready preparation of large amounts of these compounds.

Scheme I



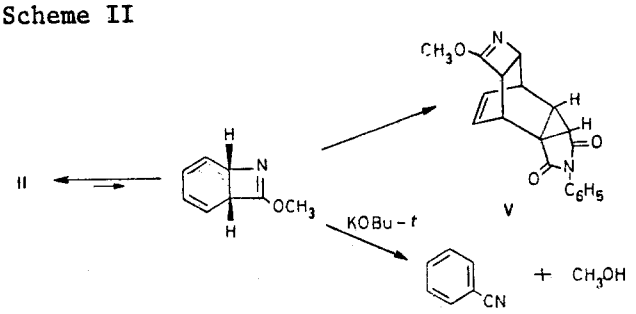
IV

Although the transient 7-azabicyclo[4.2.0]octatriene valence isomers (IV) never gain a concentration gradient which permits them to be spectroscopically detected, they can be trapped in Diels–Alder reactions. The conversion of II to V (Scheme II) is exemplary. The bicyclic forms also gain kinetic importance during the conversion of those azocines which carry a proton at C_3 to aryl nitriles [7]. These observations, in conjunction with the UV and ^1H NMR data, suggest that these hetero[8]annulenes likewise exist in strain-free tub conformations.

Evans Chemical Laboratories, Ohio State University, Columbus, Ohio, USA 43210.
Translation published in Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 147-157, February, 1978. Original article submitted March 21, 1977.

0009-3122/78/1402-0111$07.50

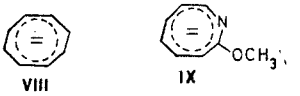
Scheme II



In this connection, 1,2-dihydroazocin-2-ones (VI) which are readily prepared from these azocines exist predominantly as β-lactams [10]. For example, VIIa dominates its equilibrium with VIa by 97-98% at 60°; the concentration level of VIIb under comparable conditions is 80%. The effect of an N-methyl substituent is to influence the position of equilibrium to an amazing extent. Thus, the NMR spectrum of VIc indicates the substance to be entirely bicyclic, i.e., in the form of VIIc, over a substantial temperature range. The factors at play in this altered ground state preference appear to be chiefly the result of lessened strain in a β-lactam relative to a 1-azetine ring, the electropositive character of the carbonyl carbon which should favor bonding to sp^3- rather than sp^2-hybridized carbon, and the increase in diene pπ-orbital overlap found in VII [10].

a R = R' = H ; b R = CH_3, R' = H ; c R = R' = CH_3

Hückel calculations on cyclooctatetraene indicate the molecule to possess a degenerate pair of singly occupied nonbonding levels (Table 1) and therefore to be particularly susceptible to two-electron reduction to give a delocalized 10π-electron dianion [11]. This species was predicted to be planar with a delocalization energy of −3.7β providing the compressional energy of flattening the ring is not appreciable (probably less than 2 kcal/mole) [12]. Katz's classic experiments dealing with the generation of VIII appeared in 1960 [13] and brought forth renewed interest in this area of chemistry. The energy levels of the hypothetical flat azocine system are also recorded in Table 1 for comparison purposes [14]. To the extent that these approximations are reasonable, the delocalization energy in the azocinyl dianion is anticipated to be about −5.1β. At the experimental level, treatment of II and its various



methylated derivatives with potassium metal in liquid ammonia, tetrahydrofuran, and dimethoxyethane led readily to dianions such as IX [14, 15]. On protonation with various active hydrogen sources, these species undergo preferential conversion to 3,4- and 3,6-dihydroazocines (Scheme III). Dihydro derivatives of type X and XI serve a useful function in the synthesis of cyclobutenopyridines [16]. For example, potassium tert-butoxide in tetrahydrofuran at room temperature transforms XI into X, the more extensively conjugated isomer. At the reflux temperature, X experiences further reaction with the base via its valence tautomer XII to give XIII. The driving force behind the relatively facile loss of methanol from XII is undoubtedly the incipient aromaticity of the resulting pyridine ring.

Scheme III

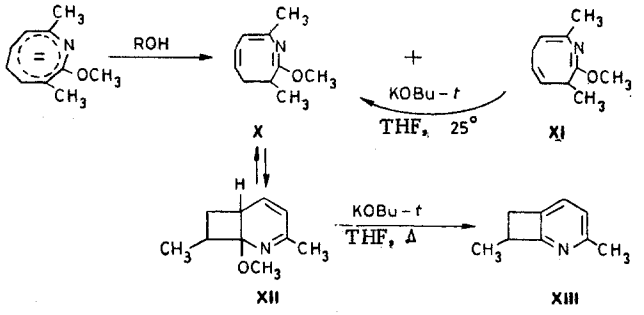
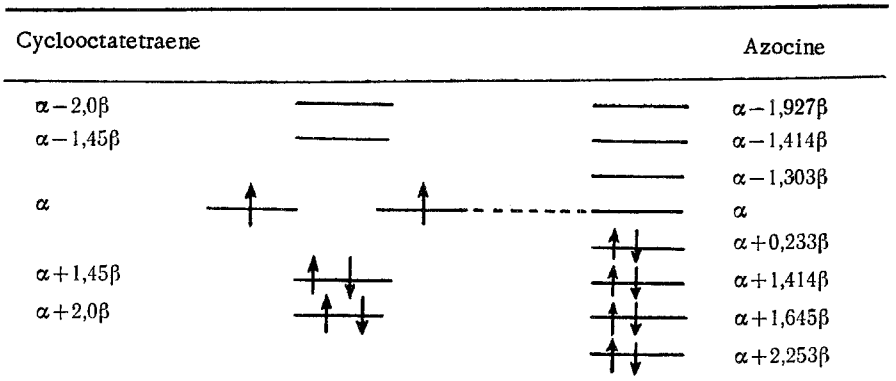
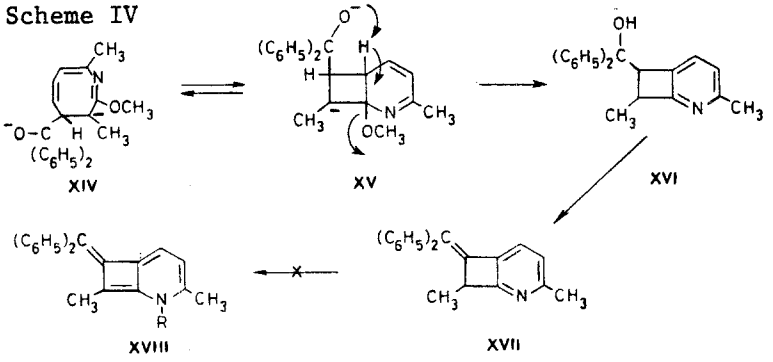


TABLE 1. π-Electron Energy Levels for Cyclooctatetraene and Azocine [14]



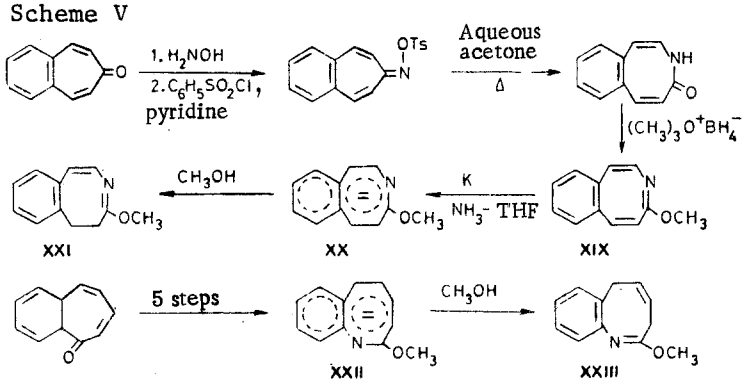
A novel intramolecular variant of the above reaction occurs upon treatment of these dianions with such nonenolizable ketones as benzophenone [16]. In these reactions, bonding of C_4 to the carbonyl group generates an alkoxide (XIV) which is similarly capable of valence isomerization to XV, 1,5 proton shift with concomitant ejection of methoxide ion, and aromatization (Scheme IV). Pyridine XVI has been isolated directly in 46% yield and dehydrated with acid to give XVII. This interesting heterocycle has so far resisted conversion to the novel system XVIII. Analogous reactions have not been observed with VIII.

Scheme IV

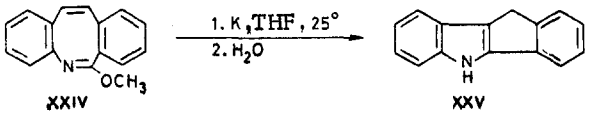


The widely differing chemical nature of dianions VIII and IX is best reflected in their electrochemical behavior. Cyclooctatetraene and its derivatives characteristically undergo two nearly Nernstian one-electron reductions [17]. In contrast, the azocines give rise to a single reduction wave, the diffusion current of which is clearly indicative of overall two-electron transfer [18]. These findings indicate that the azocine radical anions are more easily reduced than the parent heterocycles, resulting in the immediate introduction of a second electron to form the stable dianion. The rapid addition of a second electron in this manner required that an amount of stabilization equivalent to at least 0.4 V be available to the azocinyl radical anions. The azocines hold the unique position of being the first (and to this time the only) 4nπ-electron molecules capable of multielectron addition at the discharge potential. The factors contributing to this state of affairs are a favorable balance between electron repulsion, bond strain, and delocalization energy during the ring flattening process which is more optimal than in the cyclooctatetraene examples.

Scheme V

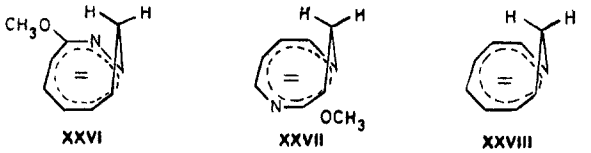


Electron delocalization of the azocinyl dianions is significantly altered by benzo fusion to the eight-membered ring [19], but not to the extent that aromatic character is lost [20]. The latter seemingly occurs, however, when the ring is homologated to the 1,6-methano[12]-annulene level [21]. The benzo azocines were prepared in rather classical fashion by Beckmann ring expansion of benzotropones (Scheme V). The alkali-metal reductions of such molecules frequently parallel the behavior of the parent system. For example, the protonation of XX proceeds exclusively at C_3 and C_4 to deliver XXI, while XXII reacts exclusively to give the 3,6-dihydro derivatives XXIII. Although this point will be returned to later in another context, we note at this time the fact that the benzylic and $-N{=}C(OCH_3){-}C<$ carbons are those which are invariably protonated. The imino ether function is also always retained. When such sites are blocked as in XXIV, an unprecedented transannular reaction resulting in formation of indole XXV is observed [19].



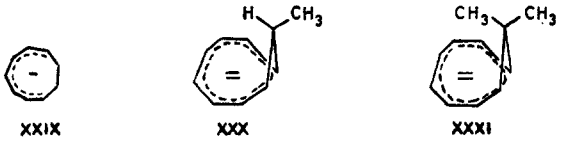
XXIV XXV

Having established that azocinyl dianions do possess considerable aromatic character, we turned our attention to the possibility that suitable homologs such as XXVI and XXVII might exhibit enhanced levels of homoaromatic delocalization. At the outset, the capability of carbocyclic dianion XXVIII to disperse charge was examined in some detail [22, 23]. It



XXVI XXVII XXVIII

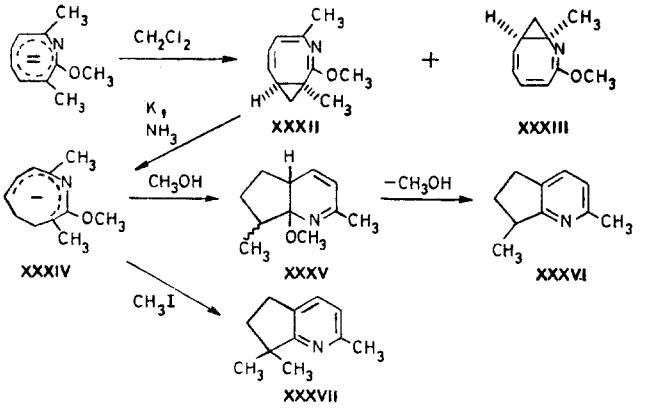
had previously been well established by the research groups of Winstein [24], Katz [25], and Smentowski [26] that one-electron reduction of cis-bicyclo[6.1.0]nona-2,4,6-triene did result in central bond rupture with formation of the nine-electron homoaromatic radical anion related to XXVIII. The trans isomer does not have the capability for symmetry-allowed disrotatory cyclopropane ring fission and is transformed under similar conditions simply to the bicyclic radical anion [27]. The susceptibility of the homoaromatic radical anion to further reduction was also clearly elucidated. However, the assignment of structure to this dianion as XXVIII was founded on a less-than-satisfactory analysis of 1,8 overlap and ring current effects by NMR spectroscopy. Our own reinvestigation [22, 23], and that of Okamura [28] and Bates [29], showed the concern regarding the authenticity of XXVIII as generated under the earlier conditions to be valid. However, dianion XXVIII can be generated satisfactorily and shown to approximate the structure given by XXVIII where minimization of angle and torsional strain and maintenance of maximum $p\pi$ overlap are delicately balanced. When produced in liquid ammonia at −65° to −78°, XXVIII is rapidly protonated by solvent to the parent cyclononatrienyl anion XXIX [22]. The positioning of methyl groups at C_9 as in XXX and XXXI effectively retards the rate of kinetically controlled protonation by solvent, thereby enabling direct spectral examination of these dianions.



XXIX XXX XXXI

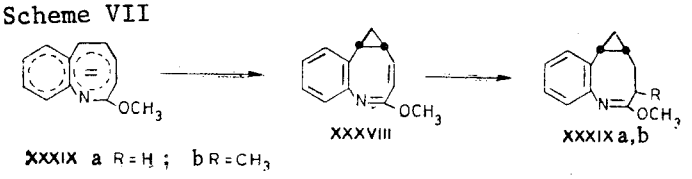
In view of the reduced basicity of XXX and XXXI, our work centered on derivation of 3,8-dimethyl-2-methoxyazocine. Addition of dichloromethane to the derived dianion afforded the pure homoazocines XXXII and XXXIII (Scheme VI) after column chromatography at low temperatures (–40° and below) [20]. Exposure of XXXII to the action of two equivalents of potassium in liquid ammonia as before leads to monoanion XXXIV. Mechanistically, it is possible that a dimethyl derivative of the homoaromatic anion XXVII was formed first and suffered rapid protonation by solvent to give XXXIV. However, no spectral confirmation of this claim is in hand. Upon treatment of XXXIV with methanol, charge neutralization takes place by protonation chiefly at the unsubstituted terminus of the azaheptatrienyl anion segment with formation of an unstable triene, electrocyclic closure of which to give XXXV is followed by aromatization with loss of methanol. The pyridine derivative XXXVI is thereby produced. Methylation proceeds analogously to give XXXVII [20]. The fate of XXXIII under comparable conditions is currently under investigation.

Scheme VI



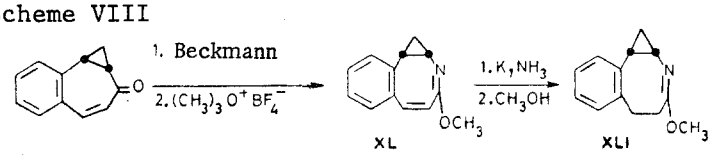
At this point, the effect of benzoannulation on the reductive ring opening of homoazocines became of interest. The first example studied was XXXVIII which can be readily prepared by the method shown in Scheme VII. When treated sequentially with potassium in ammonia and methanol, XXXVIII was converted to the dihydro derivative XXXIXa having an intact cyclopropane ring! If methyl iodide is substituted for methanol, then the isolated product was XXIXb. Evidently, the reduced form of XXXVIII has double negative charge concentrated chiefly at C_3 and C_4 in the unopened structure. Were disrotary cyclopropane bond fission to occur,

Scheme VII



benzenoid aromaticity would have to be temporarily disrupted. The energy demands for this reaction path are understandably too great. The results show that $XXXVIII^{2-}$ suffers protonation by ammonia at C_4 to give a monoanion having unit negative charge at C_3 where it is directly conjugated with imidate functionality.

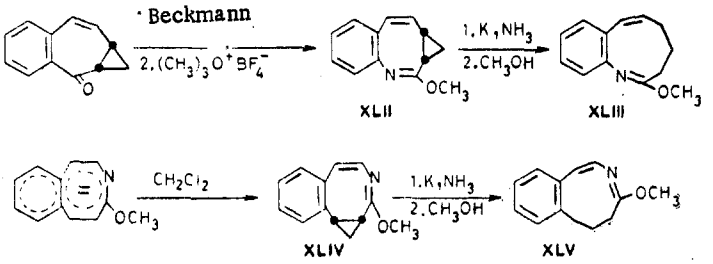
Scheme VIII



The behavior of XXXVIII is paralled closely by that of XL. When converted to its dipotassio derivative and subsequently protonated, XL is transformed uniquely to XLI (Scheme VIII). One might conclude on this basis that benzohomoazocinyl dianions strive to react in such a way as to preserve the integrity of the benzo and imino ether part structures, as well as

the cyclopropane ring. The first two conclusions are indeed correct, but the last is fallacious as revealed by the reactivity patterns of XLII and XLIV. In both of these examples, reduction led to clean scission of the central cyclopropane bond and formation of benzodihydroazocines (XLIII and XLV).

Scheme IX



A mechanistic rationalization of this apparently contradictory behavior is based on the premise that reduction of these systems proceeds in that direction which will place at least one of the pair of negative charges on that carbon immediately adjacent to the methoxyl bearing center. In the case of XXXVIII and XL, this state of affairs is reached simply by reduction of the lone unsubstituted double bond. Combined spectral and chemical data reveal that the resultant dianion is sufficiently basic to undergo rapid monoprotonation subsequent to its generation. The proton transfer occurs invariably at that carbanionic center that is not stabilized by the imidate functionality.

In XLII and XLIII, charge can be introduced adjacent to imidate carbon only by rupture of the three-membered ring and this appears to occur readily along the bond central to both rings. Clearly, the unique stabilizing capabilities of the $-N{=}C(OCH_3)-$ unit on a negative charge adjacent to the carbon (but not the nitrogen) atom has considerable control over the response of benzohomoazocines to reduction.

On a different subject, the thermal rearrangement of cis-bicyclo[6.1.0]nona-2,4,6-trienes to 3a,7a-dihydroindenes has presented a mechanistic enigma ever since Vogel's original discovery in 1961 [30]. Part of the difficulty arose because the unsubstituted hydrocarbon and anti-9-substituted derivatives rearrange mainly to cis-dihydroindenes while 9,9-dialkyl substitution serves to provide chiefly trans-fused products. Presently, these stereochemically distinct isomerizations (which generally occur at rather different rates) are believed to proceed from folded conformational arrangement XLVI except where this is sterically inhibited. This is the case with 9,9-disubstituted derivatives which are consequently forced to isomerize via the extended form XLVII. Although this rationalization nicely explains why 9,9-dialkyl derivatives fail to give cis products, it fails to interpret suitably the behavior of syn-9-substituted derivatives. These do not mimic their 9,9-disubstituted counterparts, but provide quantities of cis-dihydroindenes as do their epimers. This complication has recently been seemingly resolved by the finding that various syn-9-monosubstituted cis-bicyclo[6.1.0]-nonatrienes including the deutero example undergo facile epimerization at C_9 [31-34].

Scheme X

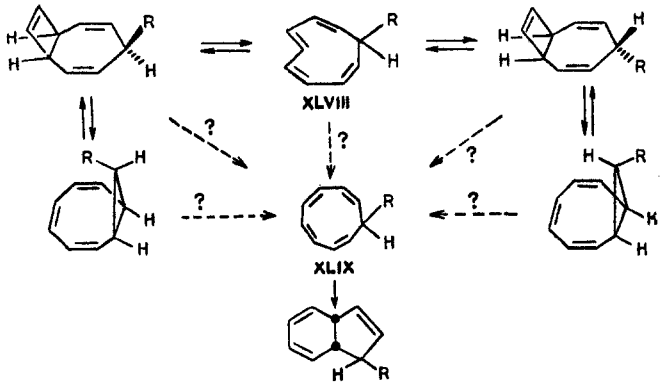


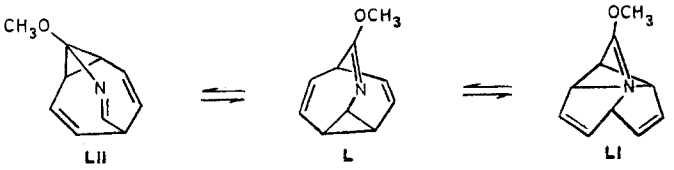
TABLE 2. Kinetic Data for Thermal Rearrangement of Homoazocines XXXII and XXXIII

Compound	Temperature, °C	$k \cdot 10^5$, sec^{-1}	Thermodynamic parameters
XXXII	70,0	1,05±0,01	
		1,16±0,02	
	80,1	3,38±0,05	$\Delta H^{\neq}$ = 28,3±0,7 kcal/mole
	80,4	3,61±0,07	$\Delta S^{\neq}$ = −1±2 cal/mole·deg
	80,5	3,99±0,08	(r = 0,998)
	90,9	12,6±0,02	
	90,9	12,8±0,02	
XXXIII	50,0	4,4±0,9	
		5,0±0,2	
	60,0	14,8±0,4	$\Delta H^{\neq}$ = 26,6±0,7 kcal/mole
		17,2±0,5	$\Delta S^{\neq}$ = 0,7±2 cal/mole·deg
	70,0	53±1	(r = 0,998)
		56±1	
		57,8±0,6	

The preferred epimerization pathway is believed to be that illustrated in Scheme X. The conversion to XLVIII is kinetically limiting and its rate of formation is double that of epimerization. This intermediate is therefore partitioned equally in both directions. The concentration gradient of XLVIII is generally such that it can be trapped (as a 2π component at the trans double bond) in cycloaddition reactions [2c].

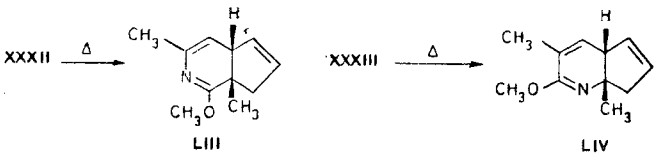
A remaining question concerns the mode of formation of XLIX, the ultimate precursor to cis-dihydroindene product. As indicated, it may arise from several different intermediates as well as the [6.1.0]bicyclic triene. In an attempt to gain information on this question, we have examined the response of XXXII and XXXIII to thermal activation.

The rates of rearrangement were determined between 50-90° in tetrachloroethylene solution with constant monitoring by ^1H NMR spectroscopy. The kinetic data, summarized in Table 2, compare very closely with those determined for various substituted homocyclooctatetraenes ($\Delta H^{\neq}$ = 24.6-32.4 kcal/mole). Thus, there is reason to believe that the imino ether linkage is not being disturbed in the rate-determining step of the rearrangement, since this should increase the energy barrier meaningfully. In the azabullvalene series [35, 36], for example, L and LI are separated by an activation energy of ∿12 kcal/mole [37], a value commonly seen in such systems [38]. The dramatic dampening effect of the imino ether bridge on the fluxional nature of this molecule (compared to bullvalene) is perhaps best reflected in the relatively large energy barrier (∿15-20 kcal/mole) [37] which separates L from LII. The conversion of L to LII has an exact parallel in the Cope rearrangement of XXXII and XXXIII (see Scheme X).

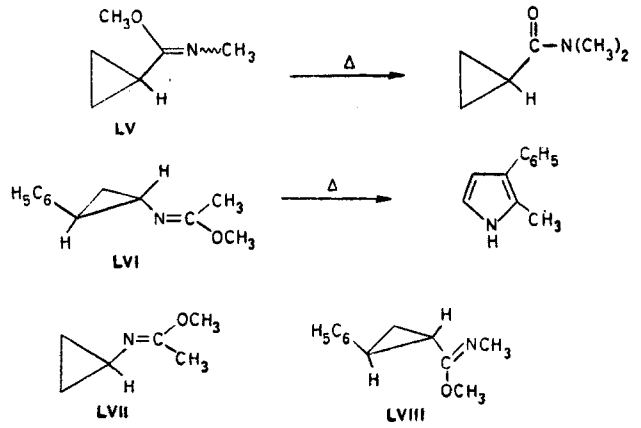


LII L LI

If the same mechanism is followed, then this step cannot be rate limiting. To cause this phenomenon, one may find it advantageous to study the syn 9-methyl derivatives of these homoazocines because Cope rearrangement is known to be much slower in the hydrocarbon analog [39]. Such research is in progress.



LIII LIV



Both homoazocines are cleanly isomerized to cis[4.3.0]bicyclic systems (LIII and LIV) at these temperatures. The overall reaction is therefore fully analogous. The comparative ease of these rearrangements relative to those observed for the simpler models LV-LVIII is particularly striking. The latter uniformly require temperatures in excess of 300°C and are not particularly susceptible to vinylcyclopropane rearrangement. Imino ether LV, for example, finds it more expedient to undergo the Chapman rearrangement than cleavage of the cyclopropane ring! Accordingly, the multiple unsaturation in XXXII and XXXIII does open low-energy reaction channels not directly accessible to structurally simpler imino ethers.

In conclusion, it is confidently stated that the chemistry of azocines and homoazocines promises considerable excitement for the future. Their ready accessibility, coupled with their predilection for unusual structural changes under relatively mild conditions, should cause them to be a focal point for new advances in the heterocyclic chemistry field.

Acknowledgment. We are grateful to the National Science Foundation and the National Institutes of Health whose generous financial support of our programs has made this research possible.

LITERATURE CITED

1. The initial synthesis of I was reported by R. Willstätter and E. Waser, Dtsch. Chem. Ges., 44, 3423 (1911); R. Willstätter and M. Heidelberger, ibid., 46, 517 (1913). The current commercial method of production was developed by W. Reppe, O. Schlichting, K. Klager, and T. Toepel, Ann., 560, 1 (1948).
2. For reviews of this subject, consult: (a) G. Schröder, "Cyclooctatetraen," Verlag Chemie, GmbH, Weinheim/Bergstr. (1965); (b) L. A. Paquette, Trans. N. Y. Acad. Sci., 357 (1974); (c) L. A. Paquette, Tetrahedron, 31, 2855 (1975).
3. G. Schröder, Angew. Chem., 75, 722 (1963); Chem. Ber., 97, 3140 (1964).
4. G. F. Emerson, L. Watts, and R. Pettit, J. Am. Chem. Soc., 87, 131 (1965); L. Watts, J. D. Fitzpatrick, and R. Pettit, ibid., 87, 3253 (1965).
5. T. J. Katz and P. J. Garratt, J. Am. Chem. Soc., 85, 2852 (1963); E. A. Lalancette and R. E. Benson, ibid., 85, 2853 (1963).
6. A. G. Anderson, Jr., W. F. Harrison, and R. G. Anderson, J. Am. Chem. Soc., 85, 3448 (1963).
7. L. A. Paquette and T. Kakihana, J. Am. Chem. Soc., 90, 3897 (1968); L. A. Paquette, T. Kakihana, J. F. Hansen, and J. C. Philips, ibid., 93, 152 (1971).
8. D. W. McNeil, M. E. Kent, E. Hedaya, P. F. D'Angelo, and P. O. Schiessel, J. Am. Chem. Soc., 93, 3817 (1971).
9. 1,2-Diazocine also shares this sensitivity: B. M. Trost and R. M. Cory, J. Am. Chem. Soc., 93, 5573 (1971).
10. L. A. Paquette, T. Kakihana, J. F. Kelly, and J. R. Malpass, Tetrahedron Lett., 1455 (1968); L. A. Paquette, T. Kakihana, and J. F. Kelly, J. Org. Chem., 36, 435 (1971).
11. H. L. Strauss, T. J. Katz, and G. K. Fraenkel, J. Am. Chem., Soc., 85, 2360 (1963).
12. L. C. Snyder, J. Phys. Chem., 66, 2299 (1962); C. A. Coulson, Tetrahedron, 12, 193 (1961); N. L. Allinger, J. Org. Chem., 27, 443 (1962).
13. T. J. Katz, J. Am. Chem. Soc., 82, 3784, 3785 (1960).
14. L. A. Paquette, J. F. Hansen, and T. Kakihana, J. Am. Chem. Soc., 93, 168 (1971).
15. L. A. Paquette, T. Kakihana, and J. F. Hansen, Tetrahedron Lett., 529 (1970).
16. L. A. Paquette and T. Kakihana, J. Am. Chem. Soc., 93, 174 (1971).
17. L. B. Anderson and L. A. Paquette, J. Am. Chem. Soc., 94, 4915 (1972) and references contained therein.

18. L. A. Paquette, J. F. Hansen, T. Kakihana, and L. B. Anderson, Tetrahedron Lett., 533 (1970); L. B. Anderson, J. F. Hansen, T. Kakihana, and L. A. Paquette, J. Am. Chem. Soc., 93, 161 (1971).
19. L. A. Paquette, L. B. Anderson, J. F. Hansen, S. A. Lang, Jr., and H. C. Berk, J. Am. Chem. Soc., 94, 4907 (1972).
20. S. V. Ley and G. D. Ewing, unpublished work in this laboratory.
21. L. A. Paquette, H. C. Berk, and S. V. Ley, J. Org. Chem., 40, 902 (1975).
22. S. V. Ley and L. A. Paquette, J. Am. Chem. Soc., 96, 6670 (1974).
23. L. A. Paquette, S. V. Ley, S. G. Traynor, J. T. Martin, and J. M. Geckle, J. Am. Chem. Soc., 98, 8162 (1976).
24. R. Rieke, M. Ogliaruso, R. McClung, and S. Winstein, J. Am. Chem. Soc., 88, 4729 (1966); S. Winstein, G. Moshuk, R. Rieke, and M. Ogliaruso, ibid., 95, 2624 (1973).
25. T. J. Katz and C. Talcott, J. Am. Chem. Soc., 88, 4732 (1966).
26. F. J. Smentowski, R. M. Owens, and B. D. Faulion, J. Am. Chem. Soc., 90, 1537 (1968).
27. G. Moshuk, G. Petrowski, and S. Winstein, J. Am. Chem. Soc., 90, 2179 (1968).
28. W. H. Okamura, T. I. Ito, and P. M. Kellett, Chem. Commun., 1317 (1971); T. I. Ito, F. C. Baldwin, and W. H. Okamura, ibid., 1440 (1971).
29. M. Barfield, R. B. Bates, W. A. Beavers, I. R. Blacksburg, S. Brenner, B. I. Mayall, and C. S. McCulloch, J. Am. Chem. Soc., 97, 900 (1975).
30. E. Vogel and H. Kiefer, Angew. Chem., 73, 548 (1961); E. Vogel, Angew. Chem. Intern. Ed. Engl., 2, 1 (1963).
31. M. B. Sohn, M. Jones, Jr., and B. Fairless, J. Am. Chem. Soc., 94, 4774 (1972).
32. A. G. Anastassiou and R. C. Griffith, Chem. Commun., 1301 (1971); 399 (1972); Tetrahedron Lett., 3067 (1973); J. Am. Chem. Soc., 95, 2379 (1973).
33. J. M. Brown and M. M. Ogilvy, J. Am. Chem. Soc., 96, 292 (1974).
34. C. P. Lewis and M. Brookhart, J. Am. Chem. Soc., 97, 651 (1975).
35. L. A. Paquette and T. J. Barton, J. Am. Chem. Soc., 89, 5480 (1967); L. A. Paquette, T. J. Barton, and E. B. Whipple, ibid., 89, 5481 (1967); L. A. Paquette, J. R. Malpass, G. R. Krow, and T. J. Barton, ibid., 91, 5296 (1969).
36. L. A. Paquette and J. R. Malpass, J. Am. Chem. Soc., 90, 7151 (1968); L. A. Paquette, J. R. Malpass, and G. R. Krow, ibid., 92, 1980 (1970).
37. H. Klose and H. Günther, Chem. Ber., 102, 2230 (1969).
38. G. Schröder, J. F. M. Oth, and R. Meranyi, Angew. Chem. Intern. Ed. Engl., 4, 752 (1965).
39. A. G. Anastassiou and R. C. Griffith, Chem. Commun., 1301 (1971).