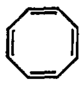
The Azacyclooctatetraene (Azocine) System[1,2]

Sir:

Cyclooctatetraene (**1**) is widely recognized for its blatant nonaromaticity which is reflected in its high reactivity and marked propensity for unusual rearrangement.[3] Despite unabated interest in the theoretical and practical aspects of cyclooctatetraene chemistry, eight-membered heterocyclic analogs of this hydrocarbon have not been reported, although unconventional physical and chemical properties can almost certainly be anticipated to be associated with such molecules. We wish now to report the successful synthesis of azacyclooctatetraenes **2a** and **2b**, the first monocyclic π-equivalent[4] congeners of **1**.



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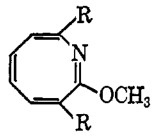
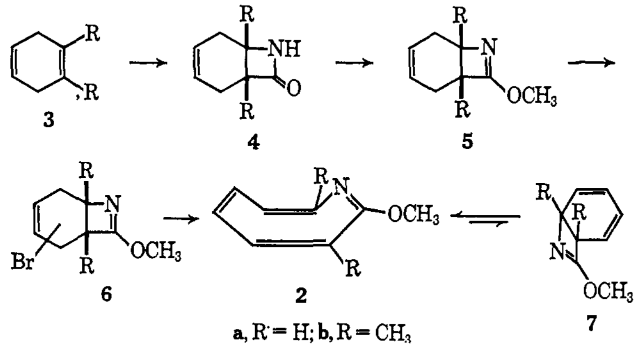
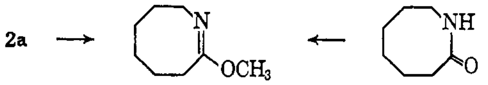


2a, R = H
b, R = CH$_3$

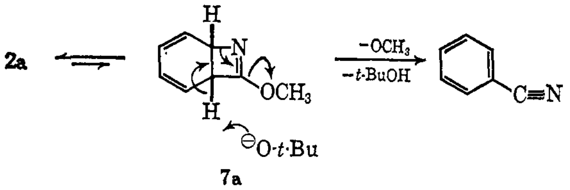
When 1,4-cyclohexadiene (**3a**) was treated with chlorosulfonyl isocyanate (CSI) in benzene solution at 70°, monocycloaddition[5,6] could be readily achieved. The resulting N-(chlorosulfonyl) β-lactam was reduced directly with thiophenol and pyridine in acetone at 0°[7] or with cold 4 *N* sodium hydroxide in acetone with loss of the chlorosulfonyl group to give **4a**,[8] mp 121.5–122.5°, ν_{max}^{KBr} 1740 and 1700 cm^{-1}, in 55% over-all yield. O-Methylation of **4a** with trimethyloxonium fluoroborate[9] in the manner previously described[10] led to the isolation of imino ether **5a** in 50% yield. The structure of this novel 1-azetine derivative[11] followed from its spectral parameters [ν_{max}^{neat} 1618 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 5.58–5.75 (multiplet, 2H, vinyl protons), 3.68 (singlet, 3 H, OCH$_3$), 3.62 (multiplet, 1 H, >C*H*N=, 3.41 (multiplet, 1 H, >C*H*C(OCH$_3$)=, and 1.97–2.42 (multiplet, 4 H, allylic protons)]. This compound was found to be extremely base sensitive and had to be handled with care to avoid its spontaneous exothermic decomposition. Monobromination of **5a** was effected with 1 equiv of N-bromosuccinimide in refluxing carbon tetrachloride solution; this monobromide (**6a**) was not characterized, and the position of entry of the halogen was not determined. Upon dehydrohalogenation of **6a** with potassium *t*-butoxide in tetrahydrofuran at 0° there was obtained a yellow oil, careful gas chromatography of which revealed the presence of two main components. Preparative vpc separation of the reaction mixture permitted the purification and isolation of the desired 2-methoxy-1-azocine (**2a**, 62%)[8] and benzonitrile (26%).[12] This azapolyene, a yellow liquid, exhibited pertinent infrared absorptions (neat) at 1675 (s), 1640 (m), and 1620 cm^{-1} (w), ultraviolet bands (isooctane) at 214 (ϵ 8750) and 305 mμ (ϵ 350), and the following nmr spectrum: $\delta_{TMS}^{CDCl_3}$ 6.54 (doublet, J = 8.5 Hz, 1 H), 5.75–6.05 (multiplet, 4 H), 5.12 (multiplet, 1 H), and 3.70 (singlet, 3 H). The structure of **2a** was established unequivocally by hydrogenation over 10% palladium on carbon at atmospheric pressure to give **8** which was prepared independently by the reaction of lactam **9** with trimethyloxonium fluoroborate.[13] Such informative spectroscopic and chemical data clearly indicate that the likely initial product of dehydrohalogenation, *i.e.*, **7a**, is subject to valence bond isomerization[14] and ready disrotatory ring opening to the favored azacyclooctatetraene tautomer.[15]





8 **9**

When **2a** was exposed to a slurry of potassium *t*-butoxide in tetrahydrofuran for 5 hr at 25°, a mixture consisting of 53% **2a** and 47% benzonitrile was obtained. This result indicated that the nitrile isolated in the preparative experiment resulted from interaction of **2a** with excess base, very probably by the pathway of eq 1 involving the bicyclo[4.2.0]tautomer **7a**.



(1)

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[1] Unsaturated Heterocyclic Systems. XLIII. For previous paper in this series, see L. A. Paquette, G. R. Krow, J. R. Malpass, and J. J. Barton, *J. Am. Chem. Soc.*, **90**, 3600 (1968).

[2] We wish to express our gratitude to the National Institutes of Health for their generous financial support of this work.

[3] (a) G. Schröder, "Cyclooctatetraen," Verlag Chemie, Weinheim/Bergstr., Germany, 1965; (b) D. Lloyd, "Carbocyclic Non-Benzenoid Aromatic Compounds," Elsevier Publishing Co., New York, N. Y., 1966, pp 162–165; (c) R. A. Raphael, "Non-Benzenoid Aromatic Compounds," D. Ginsburg, Ed., Interscience Publishers, Inc., New York, N. Y., 1959, Chapter VIII.

[4] A. G. Anderson, Jr., W. F. Harrison, and R. G. Anderson, *J. Am. Chem. Soc.*, **85**, 3448 (1963).

[5] L. A. Paquette and T. J. Barton, *ibid.*, **89**, 5480 (1967).

[6] E. J. Moriconi and W. C. Crawford, *J. Org. Chem.*, **33**, 370 (1968).

[7] R. Graf, *Ann.*, **661**, 111 (1963). This reduction was initially performed by Dr. T. J. Barton.

[8] Satisfactory elemental analyses were obtained for all indicated new compounds.

[9] H. Meerwein, *Org. Syn.*, **46**, 120 (1966).

[10] L. A. Paquette, *J. Am. Chem. Soc.*, **86**, 4096 (1964), and references cited therein.

[11] At the time this work was performed, four-membered rings with an imino nitrogen were unknown. Since the completion of our synthesis, the preparation of several 1-azetines has been described: G. Pifferi, P. Consonni, G. Pelizza, and E. Testa, *J. Heterocyclic Chem.*, 4, 619 (1967).

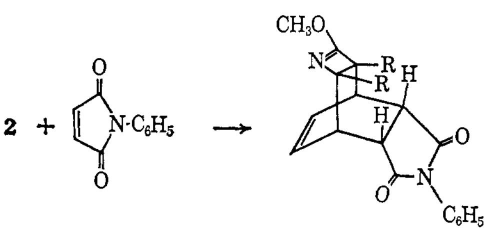
[12] The relative yields were somewhat variant with time. Minor contaminants which were present to the extent of approximately 10% were not characterized.

[13] Compare also W. Z. Heldt, *J. Am. Chem. Soc.*, **80**, 5880 (1958).

[14] (a) E. Vogel and H. Günther, *Angew. Chem. Intern. Ed. Engl.*, **6**, 385 (1967); (b) G. Maier, *ibid.*, **6**, 402 (1967).

[15] Spectra of a number of bracketed derivatives of 7 are presented in the accompanying communication: L. A. Paquette and J. C. Philips, *J. Am. Chem. Soc.*, **90**, 3898 (1968).

Further support for the existence of this reversible equilibrium was provided by the Diels–Alder reaction of **2a** with N-phenylmaleimide in refluxing toluene. The resulting colorless crystalline ((4 + 2)π) adduct, mp 205–207°,[8] exhibited spectral properties in unique agreement with structure **10a**: $\delta_{\mathrm{TMS}}^{\mathrm{CDCl_3}}$ 7.0–7.6 (multiplet, 5 H), 6.0–6.2 (multiplet, 2 H), 3.70 (singlet, 3 H), 2.9–3.6 (multiplet, 4 H), and ~1.9 (multiplet, 2 H). The product is formulated with the imide moiety *syn* to the double bond in accordance with established precedence.[3,16]



10a, R = H
b, R = CH_3

In similar fashion, 1,2-dimethyl-1,4-cyclohexadiene (**3b**) afforded **4b**, mp 91–92°,[8] in 72% yield. The derived imino ether **5b** was quite stable in this instance and afforded a perchlorate salt, mp 139–140°.[8] The two-step dehydrogenation of **5b** proceeded without difficulty, and **2b** was obtained as a stable yellow oil: bp 47° (0.35 mm);[8] $\nu_{\mathrm{max}}^{\mathrm{neat}}$ 1670 (s), 1640 (m), and 1625 cm^{-1} (w); $\lambda^{\mathrm{isooctane}}$ 212 (ε 12,900) and 297 mμ (ε 590); $\delta_{\mathrm{TMS}}^{\mathrm{C_6H_6}}$ 5.72 (singlet, 3 H), 4.95 (broad singlet, 1 H), and three three-proton singlets at 3.63, 1.92, and 1.82. The two methyl groups serve to protect the azocine from base-induced aromatization reactions but do not exert an influence which favors the bicyclic valence tautomer **7b**.[14b] However, the facile conversion of **2b** to **10b**, mp 194–195.5°,[8] attests to the existence of a spectroscopically undetectable equilibrium of the tetraene with **7b**.

The striking similarity of the C=C bond stretching frequencies of azocines **2a** and **2b** with those reported for **1**[17] and the excellent correspondence of the ultraviolet spectra of **2a** and **1**[18] suggest that these hetero analogs likewise exist in the strain-free puckered "tub" conformation known to be preferred by the hydrocarbon.[17,19]

The availability of azacyclooctatetraenes by means of this direct and apparently general synthesis now causes these heterocycles to become an attractive focus of further synthetic manipulations. Presently under active investigation are studies which deal with their photolability, their capability to support dianion (10π electron) character and to serve as precursors of azacyclobutadienes, and the various other phenomena which are logical consequences of these and related concepts.

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(16) J. G. Martin and R. K. Hill, *Chem. Rev.*, **61**, 537 (1961).

(17) E. R. Lippincott, R. C. Lord, and R. S. McDonald, *J. Am. Chem. Soc.*, **73**, 3370 (1951).

(18) A. C. Cope and C. G. Overberger, *ibid.*, **70**, 1433 (1948).

(19) (a) W. B. Person, G. C. Pimentel, and K. S. Pitzer, *ibid.*, **74**, 3437 (1952); (b) I. L. Karle, *J. Chem. Phys.*, **20**, 65 (1952).

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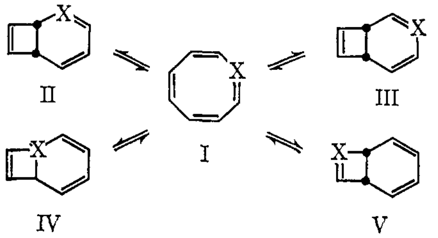
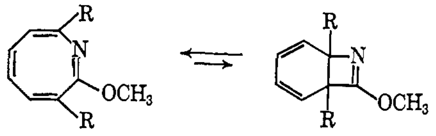
Concerning Azacyclooctatetraene Valence Tautomerism. Preparation of Annelated 7-Azabicyclo[4.2.0]octa-2,4,7-trienes[1,2]

Sir:

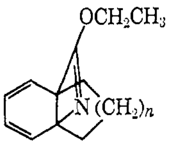
According to generalized theory, an unsubstituted π-equivalent heterocyclic congener of cyclooctatetraene such as I may theoretically be characterized by dynamic equilibrium with four structurally distinct valence bond tautomers (II–V). In actual fact, only one of the heteroatomic bicyclo[4.2.0]octatrienes is likely to be preferred for reasons such as more advantageous electronic interactions, more favorable conformational environments, and the like. However, placement of one or more substituents on the eight-membered ring could affect the original position of equilibrium sufficiently to cause an alternative bicyclic isomer to be more stable. The recent synthesis of the azacyclooctatetraene system[1] has permitted the first practical assessment of such a set of electrocyclic changes.



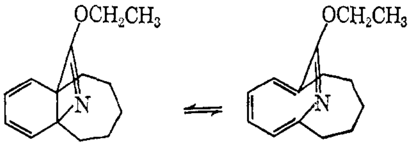
In 2-methoxyazocine (**1a**) and its 3,8-dimethyl analog (**1b**), the azacyclooctatetraene form is sufficiently stabilized that the proportion of valence tautomer in the equilibrium is below the spectroscopic detection limit (<5%). However, both substances readily form adducts with N-phenylmaleimide derived from the azetine form **2**.[1] This tautomer also appears to be the reacting species in the base-induced conversion of **1a** to benzonitrile.[1] Therefore, a detailed investigation of the spectral and chemical properties of such azetines was deemed advisable. This interest in valence bond tautomerizations has led us to prepare the annelated derivatives **3–5**.



1a, R = H
b, R = CH_3
2



3, *n* = 1
4, *n* = 2



5a
5b

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(1) Unsaturated Heterocyclic Systems. XLIV. For the previous paper in this series, see L. A. Paquette and T. Kakihana, *J. Am. Chem. Soc.*, **90**, 3897 (1968).

(2) We wish to express our gratitude to the National Institutes of Health for their generous financial support of this work.