intellectual equivalent of, for instance, the concept of sp^3 hybridization to the theory of hydrocarbons.

It is a pleasure to acknowledge the contributions of my colleagues mentioned in the references. Discussions with Dr. Jim Goble and his work in this area are especially appreciated. This research has been supported by the National Science Foundation, the Division of Chemical Sciences, Office of Basic Energy Sciences, U.S. Department of Energy, under Contract W-7405-Eng-48, and the Alfred P. Sloan Foundation.

1,2-Diazepines: A New Vista in Heterocyclic Chemistry

VICTOR SNIECKUS*

Guelph-Waterloo Centre for Graduate Work in Chemistry, University of Waterloo, Waterloo, Ontario, Canada N2L 3G1

JACQUES STREITH*

Laboratoire de Synthèse et de Photochimie Associé au CNRS, Ecole Nationale Supérieure de Chimie, Université de Haute Alsace, F-68093 Mulhouse Cedex, France

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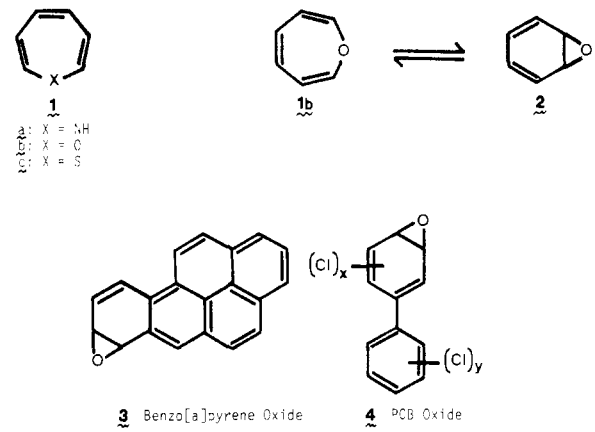
Chemists have long been familiar with five- and six-membered heteroaromatic substances, e.g., furan, pyrrole, and pyridine, as constituents of petroleum and coal tar and as characteristic structural frameworks of diverse natural products. In contrast, highly unsaturated seven-membered ring heterocycles are of recent, mainly synthetic, origin, and their evolution is linked to advances in theoretical and medicinal chemistry. In the 1960s as part of an intense inquiry into aromatic character, the question of potential antiaromaticity of the 8π-electron systems 1*H*-azepine (**1a**), oxepin (**1b**), and thiepin (**1c**) prompted serious efforts to synthesize these molecules.[1-3] Today, only **1c** remains for synthetic conquest[4] while the antiaromaticity question has been in large part answered in the negative on the basis of physicochemical evidence on derivatives of **1a-c**[1,2] and Hückel molecular orbital calculations.[5] The subsequent demonstration[1] of the oxepin (**1b**)-oxanorcaradiene (**2**) equilibrium was instrumental in establishing valence isomerization as a widely encompassing principle in organic chemistry[6,7] and significantly aided studies in unrelated areas: the mechanism of carcinogenesis of polycyclic aromatic hydrocarbons (**3**),[8] the metabolism of environmentally deleterious chemicals (**4**),[9] and the biosynthesis of certain natural products.[10]

In 1960, while pursuing a trail of structural misassignment, workers at Hoffmann-La Roche discovered the potent sedative and anxiolytic action of certain 1,4-benzodiazepines.[11] These findings resulted in a dominant market position for several therapeutic agents such as Librium (**5**) and catapulted synthetic activity toward other benzo- and dibenzo-annelated seven-membered-ring heterocycles.[12] Additional stimulus was



Victor Snieckus was born in Lithuania and spent his early childhood in Germany during World War II. As an undergraduate at the University of Alberta he, like many others before and after him, was inspired by Rube Sandin. Following graduate studies at the University of California, Berkeley (M.Sc. with D. S. Noyce), and the University of Oregon (Ph.D. with Virgil Boekelheide), he held a postdoctoral fellowship at the National Research Council of Canada, Ottawa (with Ted Edwards). He is currently interested in the development of new synthetic strategy and methods for complex organic molecules.

Jacques Streith was born in Thionville, France, and received the Baccalauréat and Licence ès-Sciences physiques at the University of Strasbourg. After the customary military service, he obtained the D.Sc. degree at Strasbourg in 1963 (with G. Ourisson). He has held a postdoctoral fellowship at Harvard (with E. J. Corey) and a Visiting Professorship at the Catholic University, Washington, D.C. His long-standing interest in diazepines has recently led him into areas of polyazaazulene, pyridocyclopropane, and azirine chemistry.

(1) Vogel, E.; Günther, H. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 385.
(2) Paquette, L. A. "Nonbenzenoid Aromatics"; Snyder, J. P., Ed.; Academic Press: New York, 1969; Vol. 1, p 249.
(3) Similar incentives catalyzed synthetic work on more unusual 7-membered unsaturated heterocycles of (a) phosphorus [Markl, G.; Schubert, H. *Tetrahedron Lett.* **1970**, 1273], (b) silicon [Barton, T. J.; Kippenhan, R. C.; Nelson, A. J. *J. Am. Chem. Soc.* **1974**, *96*, 2272], and (c) boron [Eisch, J. J.; Galle, J. E. *Ibid.* **1975**, *97*, 4436].
(4) 1*H*-Azepine (**1a**) has been recently characterized: Vogel, E.; Altenbach, H.-J.; Drossard, J.-M.; Schmickler, H.; Stegelmeier, H. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 1016. In contrast, only highly substituted thiepins are stable at low temperatures: Reinhoudt, D. N.; Kouwenhoven, C. G. *Tetrahedron* **1974**, *30*, 2093. Hess, B. A., Jr.; Schaad, L. J.; Reinhoudt, D. N. *Ibid.* **1977**, *33*, 2685.
(5) Dewar, M. J. S.; Trinajstic, N. *Tetrahedron* **1970**, *26*, 4269. Hess, B. A., Jr.; Schaad, L. J.; Holyoke, C. W., Jr. *Ibid.* **1972**, *28*, 3657.
(6) Maier, G. "Valenzisomerisierungen"; Verlag Chemie: Weinheim, 1972.
(7) For valence isomerization of substituted 1*H*- and 4*H*-azepines, see respectively: Prinzbach, H.; Babsch, H.; Fritz, H.; Hug, P. *Tetrahedron Lett.* **1977**, 1355. Göckel, U.; Hartmannsgruber, U.; Steigel, A.; Sauer, J. *Ibid.*, **1980**, 599.
(8) Gelboin, H., T'so, P., Eds., "Polycyclic Aromatic Hydrocarbons and Cancer"; Academic Press: New York, 1978.
(9) Forgue, S. T.; Preston, B. D.; Hargraves, W. A.; Reich, I. L.; Allen, J. R. *Biochem. Biophys. Res. Commun.* **1979**, *91*, 475.
(10) Johns, N.; Kirby, G. W. *J. Chem. Soc., Chem. Commun.* **1971**, 163.
(11) Sternbach, L. H. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 34. For a personal account, see: Sternbach, L. H. *J. Med. Chem.* **1979**, *22*, 1.

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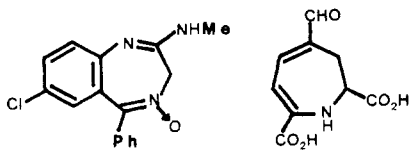
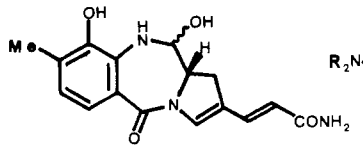
injected by the discovery of natural products exhibiting azepine [muscaflavin (**6**)[13]], benzazepine [rhoeadine,[12c] cephalotaxine[14]], and 1,4-benzodiazepine [anthramycin (**7**)[15]] skeletons. Not surprisingly, these findings also

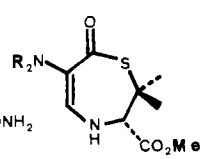


5 Librium

6 Muscaflavine



7 Anthramycin



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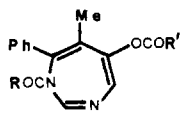
encouraged advances in the methodology of heterocyclic ring construction. Along similar lines, interest in 1,4-thiazepines (**8**) evolved connected with progress in the chemistry of the penicillin antibiotics.[16] The current literature offers ample evidence for an accelerating growth in our knowledge of seven-membered-ring heterocyclic compounds.[17]

Interest in diazepines is of recent vintage. The "quasi-aromatic" dihydro-1,4-diazepinium system **9** has



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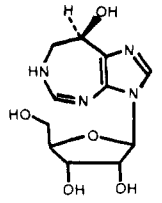
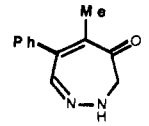


11 Conformycin



12

been extensively studied although attempts to prepare its fully unsaturated derivatives have failed.[18] The first 1,3-diazepine, **10**, has only recently been disclosed.[19] Nor does Nature like to program the biosynthesis of 1,3-diazepines, the unique example being the microbial metabolite conformycin (**11**) whose structural elucidation prompted the usual synthetic search for biologically active analogues.[20]

(12) (a) Kasparek, S. *Adv. Heterocycl. Chem.* **1974**, *17*, 45. (b) Kricka, L. J.; Ledwith, A. *Chem. Rev.* **1974**, *74*, 101. (c) Kametani, T.; Fukumoto, K. *Heterocycles* **1975**, *3*, 931.

(13) Barth, H.; Kobayashi, M.; Musso, H. *Helv. Chim. Acta* **1979**, *62*, 1231.

(14) Finlay, J. A. *Int. Rev. Sci. Org. Chem. Ser. 2* **1976**, *9*, 23.

(15) Hurley, L. H. *Acc. Chem. Res.* **1980**, *13*, 263.

(16) Stoodley, R. J. *Tetrahedron* **1975**, *31*, 2321.

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(18) Lloyd, D.; Cleghorn, H. P.; Marshall, D. R. *Adv. Heterocycl. Chem.* **1974**, *17*, 1.

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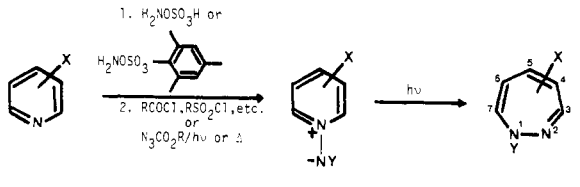
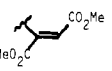
(20) Nakamura, H.; Koyama, G.; Iitaka, Y.; Ohno, M.; Yagisawa, N.; Kondo, S.; Maeda, K.; Umezawa, H. *J. Am. Chem. Soc.* **1974**, *96*, 4327. Thiellier, H. M. P.; Koomen, G. J.; Pandit, U. K. *Tetrahedron* **1977**, *33*, 2609 and references therein.

Scheme I



13 **14**

14								
X	H	H	H	H	3-CN	4,6-diMe	4-Br 6-Br
Y	CO_2R	CSNHMe		CN	CO_2Et	CO_2Et	COPh
Yield %	90-97	0	0	0	86	41	56 24

14						
X	5-NMe_2	5-CO_2Et	3,5,7-triPh	H	H	5-Me
Y	CO_2Et	CO_2Et	Ph	Ts	CO_2-3-cholesteryl	
Yield %	65	0	0	74	57	64

Activity in the area of highly unsaturated 1,2-diazepines was for a long time limited to the thorough investigations of compound **12** by Moore and his collaborators.[21] The discovery of a general and convenient photoinduced entry into 1,2(1*H*)-diazepines **14** initiated our studies on this class of heterocycles.[22] Like the root of any scientific discovery, our original finding exposed many unchartered branches. This Account relates those we have traced with varying degrees of success.

Synthesis

The pyridine *N*-oxides were one of the first groups of heterocyclic compounds which was infected by the principle "if the compound is on the shelf, blast it with light". These compounds showed multifaceted photoreactivity and raised interesting mechanistic questions which remain incompletely answered.[23] Working by analogy, it was a light jump to irradiate the isoelectronic pyridine *N*-imides **13** (Scheme I), the prototype of which (X = 2,4,6-Ph_3, Y = Ph) dates to Schneider's early provocative studies.[24] As is commonly observed in contemporary scientific work, several laboratories almost simultaneously demonstrated the smooth photoinduced rearrangement of **13** into the 1,2(1*H*)-diazepine system **14**.[25] With the introduction of the Tamura reagent (*O*-(mesitylenesulfonyl)hydroxylamine, MSH),[26] certain deficiencies in earlier preparative methods[24b] for the precursor *N*-aminopyridinium salts have been circumvented, and the scope of the photochemical synthesis has been expanded (Scheme I).[22] The initial

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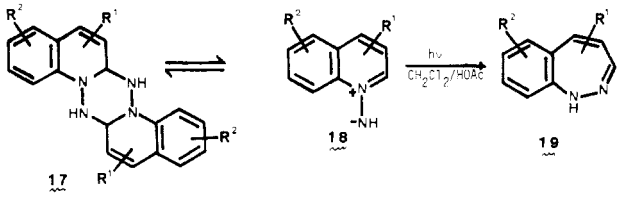
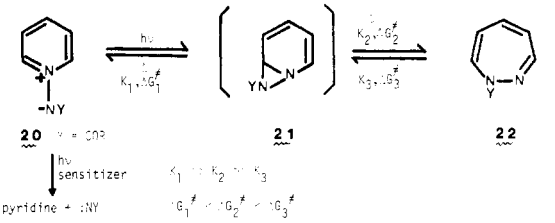
(26) Tamura, Y.; Minamikawa, J.; Ikeda, M. *Synthesis*, **1977**, 1.

Scheme II

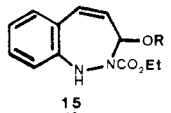


Scheme III



optimism associated with the projected generalization of a new synthetic method was soon deflated by observations that the ring expansion **13** → **14** suffered from competitive isomerization to 2-aminopyridines (Scheme VII) and fragmentation to pyridines and nitrene species (Scheme III). The pathway(s) followed was (were) found to be dependent on the nature of the substituents X and Y in **13**. In practice, the fragmentation mode can sometimes be avoided by the proper choice of the Y chromophoric "handle", wavelength, solvent, and the exclusion of a sensitizer.

Largely disappointing results awaited those who were tempted to irradiate *N*-imides of other nitrogen heteroaromatics in attempts to synthesize new and unusual heterocycles. As the rather extensive literature reveals,[27] N–N fragmentation and rearrangement to amino heteroaromatics are the rule, and ring expansion is the low-yield exception. We also yielded to the temptation and obtained mixed results. Photolysis of quinoline *N*-acylimides in CH_2Cl_2 resulted in the formation of quinoline and 2-(acylamino)quinoline;[28a] concurrently, Tamura and others showed that low yields of ring-expanded products, e.g., **15**, could be isolated from irradiation of quinoline *N*-imides in protic solvents.[28b] On the other hand, photolysis of quinoline *N*-imide dimers **17**, obtained by treatment of the corresponding monomeric salts with potassium carbonate, produced modest yields of 1,2(1*H*)-benzodiazepines **19** and only small amounts of fragmentation and rearrangement byproducts (Scheme II).[29] The equilibrium **17** ⇄ **18** is established in the photolysis medium (NMR evidence), suggesting that **19** is formed via the *N*-imide intermediate **18**. Our very able former collaborator, T. Tsuchiya, has made the a priori unexpected observation that 1-substituted isoquinoline *N*-acylimides are photoconverted into 1,3(1*H*)-benzodiazepines **16**.[30] These results provide adequate temptation for further effort in this area.



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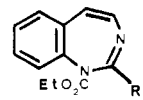

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A working hypothesis for the mechanism of the photoreaction **13** → **14** was stimulated by the photochemical investigations of the isoelectronic pyridine *N*-oxides.[23] We envisaged (Scheme III) that UV irradiation of *N*-imide **20** results in an electronic transition to an excited singlet state which undergoes an orbital symmetry controlled electrocyclization of its 4π 1,3 dipole to the 1,7-diazanorcaradiene intermediate **21**. This photoinduced process is followed by a thermally allowed disrotatory valence isomerization to the 1,2-(1*H*)-diazepine **22**. That a singlet-state excitation is involved in the transformation **20** → **22** was demonstrated by triplet-state sensitization studies of *N*-acylimides.[31] In the presence of photoexcited eosin or 3,4-benzopyrene, 1,2(1*H*)-diazepine formation was completely suppressed in favor of pyridine and acylnitrene products. In benzene solution, the released $:NCO_2Et$ may be trapped as 1-(ethoxycarbonyl)azepine. Further evidence for the intermediacy of triplet nitrene and therefore triplet *N*-imide (principle of conservation of spin) was derived from irradiation of **20**, Y = CO_2Et, in the presence of various concentrations of *cis*- and *trans*-4-methyl-2-pentene following in the footsteps of Lwowski's classical study.[32] In spite of the generally high chemical yields for the conversion **20** → **22**, the quantum yield is low (3% in MeCN at room temperature) and diminishes with decreasing temperature. Since diazepine is the exclusive product, this result suggests competing radiationless thermal processes for the intermediate **21**, viz., ring contraction to **20** and ring expansion to **22** with $\Delta G_2^{\ddagger} > \Delta G_1^{\ddagger}$. A rate factor $K_1/K_2 \approx 30$ would account for the low overall quantum yield of the photoreaction.

Attempts to detect or trap the postulated 1,7-diazanorcaradiene **21** have been unsuccessful in Mulhouse and in Waterloo.[33] For further probes into its nature, experiments using deuterated and ^{13}C-labeled *N*-imides were carried out in collaboration with H. Kwart.[34] Photoconversion of 2-deuteriopyridine *N*-benzoylimide into a mixture of 3- and 7-deuterated diazepines showed a large, inverse secondary deuterium isotope effect, $k_H/k_D = 0.911$.[34a] This result is indicative of a thermal transition state in which C-2 of the *N*-imide is undergoing rehybridization from sp^2 to sp^3. A second set of experiments, involving competitive irradiation of a mixture of unlabeled and 2,6-^{13}C-labeled pyridine *N*-benzoylimides to give the corresponding unlabeled and 2,7-^{13}C-labeled diazepines, also showed an inverse isotope effect, $k_{12C}/k_{13C} = 0.9876$.[34b] This result implies a greater bonding preference for the heavier isotope and can be reconciled only with a transition state of an

(27) See, inter alia, *N*-imides of triazolines [Bird, C. W.; Wong, D. Y.; Boyd, G. V.; Summers, A. J. H. *Tetrahedron Lett.* **1971**, 3187] benzo[c]cinnolines [Gait, S. F.; Peek, M. E.; Rees, C. W.; Storr, R. S. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1975 and references therein], quinazolines [Fetter, J.; Lempert, K.; Barta-Szalai, G.; Möller, J.; Parkany, L. *Acta Chim. Acad. Sci. Hung.* **1977**, *94*, 233].

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(29) Tsuchiya, T.; Kurita, J.; Snieckus, V. *J. Org. Chem.* **1977**, *42*, 1856. For alternate new routes to benzodiazepines, see the comprehensive studies of Sharp and co-workers: Reid, A. A.; Sood, H. R.; Sharp, J. T. *J. Chem. Soc., Perkin Trans. 1* **1976**, 362.

(30) Tsuchiya, T.; Enkaku, M.; Okajima, S. *Chem. Pharm. Bull. Jpn.* **1980**, *28*, 2602.

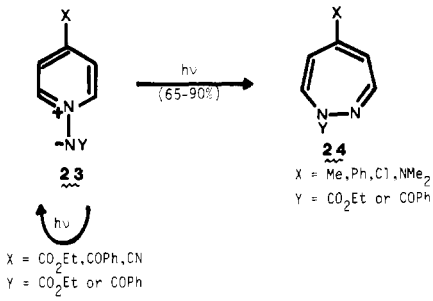
(31) Streith, J.; Luttringer, J. P.; Nastasi, M. *J. Org. Chem.* **1971**, *36*, 2962.

(32) McConaghy, J. S.; Lwowski, W. *J. Am. Chem. Soc.* **1967**, *89*, 4450.

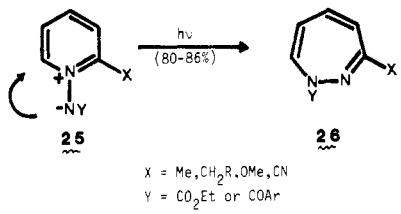
(33) (a) Allman, R.; Frankowski, A.; Streith, J. *Tetrahedron* **1972**, *28*, 581; (b) Snieckus, V., et al., unpublished results, 1973.

(34) (a) Kwart, H.; Benko, D. A.; Streith, J.; Harris, D. J.; Schuppiser, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 6501. (b) Kwart, H.; Benko, D. A.; Streith, J.; Schuppiser, J. L. *Ibid.* **1978**, *100*, 6502.

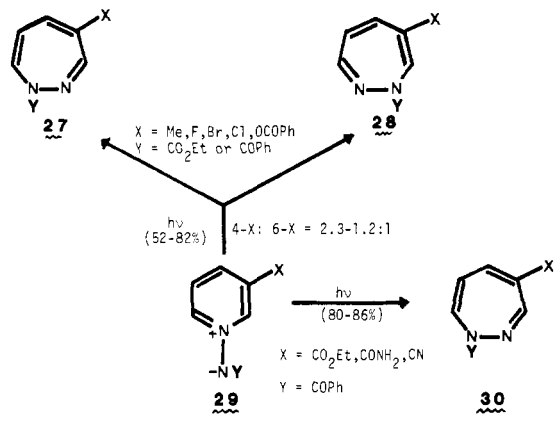
Scheme IV



Scheme V



Scheme VI

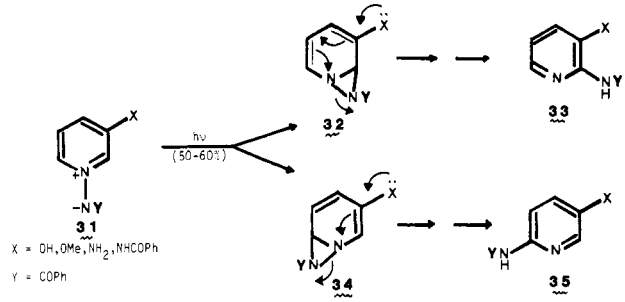


associative mechanism in which C-2 is fully bonded to each of the two nitrogens. Since inverse heavy-atom isotope effects are rarely observed, these results must be regarded as strong evidence for the intermediacy of the 1,7-diazanorcaradiene **21** in the photochemical transformation **20** → **22**.

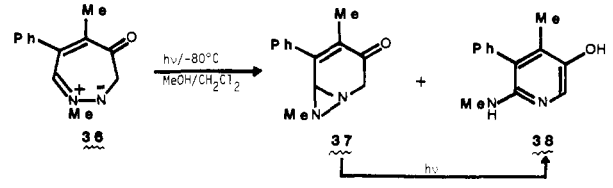
The effect of pyridine ring substituents on the photoreactivity, cursorily noted in the early work (Scheme I), invited a thorough examination. The results of irradiation experiments with 4-substituted *N*-imides **23** (Scheme IV) show that electron-donating groups lead to the expected 1,2-diazepines **24** while electron-withdrawing functions totally inhibit the photoinduced ring expansion.[25,31] Alkyl, methoxyl, and cyano substituents at C-2 (**25**, Scheme V) orient the primary photochemical process exclusively toward C-6, leading to 3-substituted 1,2-diazepines (**26**).[25,31,35] These rather incomplete results suggest that inductive and mesomeric effects of 2-substituents are overruled by steric effects.

An extensive study of the effect of 3-substituents was greatly facilitated by the preparative availability of a series of pyridine *N*-imides **29** (Scheme VI).[36] Weak

Scheme VII



Scheme VIII



electron-donating groups (Me, F, Cl, Br, OCOPh) act indiscriminantly, affording both 4- and 6-substituted diazepines, **27** and **28**, while electron-withdrawing groups (CO_2Et, CN, $CONH_2$) promote high-yield regiospecific ring expansion to 4-substituted diazepines **30**. These results may be rationalized by a qualitative HMO model.

As the work on substituent effects continued, our early observation[25e] that photolysis of a pyridine *N*-imide with a modestly electron-donating 3-substituent provides, in part, a 2-aminopyridine derivative became less of a curiosity. *N*-Imides bearing strongly electron-donating groups **31**, X = OH, OMe, NH_2, NHCOPh, undergo nonregiospecific isomerization to the corresponding 2- and 6-substituted pyridines **33** and **35** (Scheme VII).[36] Here we propose that preferential N–N bond scission in the intermediate 1,7-diazanorcaradienes **32** and **34** is triggered by electron donation from the X-substituents. The photochemical formation of **38** from the 1,7-diazabicyclo[4.1.0]heptanone **37**, itself derived by irradiation of the diazepinium betaine **36** (Scheme VIII),[37] may proceed by an enol analogous to **34**. Results consistent with the formation of the same intermediates **32** and **34** are available from thermolysis studies of 1,2(1*H*)-diazepines (cf. Scheme XI).

While contemplating ways by which *N*-alkyl and *N*-aryl-1,2(1*H*)-diazepines could be prepared, our attention was drawn to a report by Klingsberg on the reaction of pyrylium salts with hydrazines.[38] In cordial collaboration with Klingsberg, we confirmed and expanded the original observations. Treatment of thiapyrylium salts **39** with methylhydrazine was shown to give 3,5,7-triaryl-1-methyl-1,2(1*H*)-diazepines (**41**) in ~70% yield.[39] Unfortunately, the condensation of the corresponding pyrylium salts **40** with methylhydrazine provides only low yields of **41**, the major products being the *N*-aminopyridinium salt **43** and the pyrazole **44**. These heterocyclic ring contractions, which also occur from reactions of **39** and **40** with phenylhydrazine, may

(35) 3-Methoxy-1,2(1*H*)-diazepines (**26**, X = OMe, Y = COR) have been converted (Me_3SiCl, NaI) into the corresponding diazepin-3-ones, thus providing a general entry into these meagerly known derivatives: Kiguchi, T., Schuppiser, J.-L., Schwaller, J.-C., Streith, J. *J. Org. Chem.* **1980**, *45*, 5095.

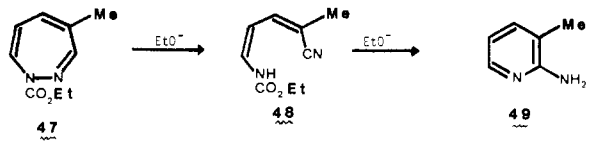
(36) Fritz, H.; Gleiter, R.; Nastasi, M.; Schuppiser, J.-L.; Streith, J. *Helv. Chim. Acta* **1978**, *61*, 2887.

(37) Pleiss, M. G.; Moore, J. A. *J. Am. Chem. Soc.* **1968**, *90*, 4738.

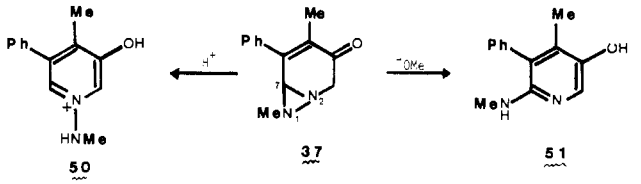
(38) Klingsberg, E. "Abstracts of Papers", 150th National Meeting of the American Chemical Society, Sept 1967; American Chemical Society: Washington, D.C., 1967; p 66S.

(39) Harris, D. J.; Kan, G. Y.-P.; Snieckus, V.; Klingsberg, E. *Can. J. Chem.* **1974**, *52*, 2798.

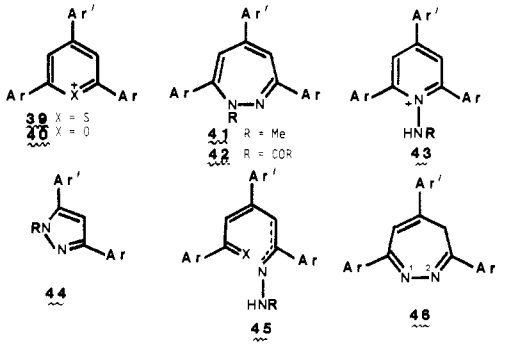
Scheme IX



Scheme X



be visualized as proceeding via open-chain, in some cases isolable, species (**45**).[40]



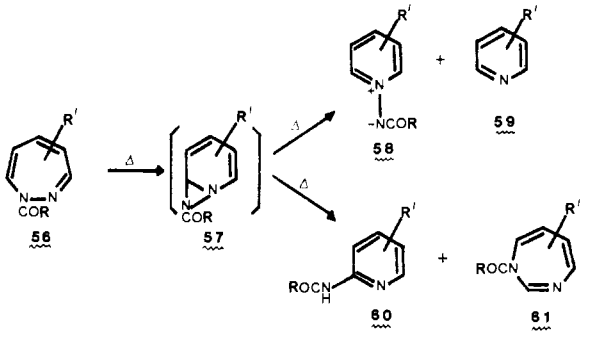
A general synthesis of 1-acylated-3,5,7-triaryl-1,2-(1*H*)-diazepines (**42**) as well as an alternate, more convenient route to **41**[39] also followed from Klingsberg's original finding[38] that pyrylium salts **40** undergo smooth reaction with hydrazine to yield 3,5,7-triaryl-1,2(4*H*)-diazepines **46**. The broad range of available 1,2(4*H*)-diazepines,[40,41] including some condensed and 3,5,7-trialkyl systems, and their facile alkylation[39,42] assure ready access to many 1,2(1*H*)-diazepine derivatives **42**.

Reactivity

Spectral data amassed to date[22b] lead to the portrayal of the 1,2(1*H*)-diazepine ring as a cyclic polyolefin having no propensity to achieve planar (and therefore antiaromatic) character or to equilibrate with the 1,7-diazanorcaradiene valence isomer **21**.[33a] Not surprisingly, 1,2(1*H*)-diazepines and 1*H*-azepines[2] show very similar physicochemical properties. The shape and geometry of the 1,2(1*H*)-diazepine ring as defined by the X-ray crystal structure of the 1-tosyl derivative shows a highly flexible, boat-shaped conformation, localized double bonds, a particularly short (1.26 Å) C–N double bond, and the N-1 electron density delocalized toward the tosyl substituent.[33a]

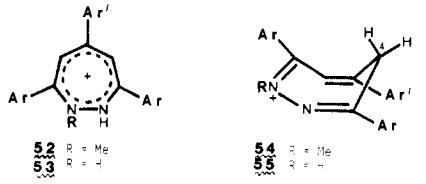
As a logical point of departure in chemical reactivity studies, we examined the behavior of 1,2(1*H*)-diazepines in acidic and basic solutions. In refluxing acetic acid, simple[19,31,43] and highly substituted (**42**)[33b] 1-acylated 1,2(1*H*)-diazepines undergo isomerization to the corresponding pyridine *N*-imides. Similarly, the 1-methyl-

Scheme XI



1,2(1*H*)-diazepines **41** and the 1,2(4*H*)-diazepinium salt **54** give the ring contraction product **43**, R = Me.[44] A common 1,7-diazanorcaradiene intermediate is suggested for these reactions by analogy with many similar rearrangements of seven-membered heterocycles to six-membered aromatic systems.[40] On the other hand, treatment of 1,2(1*H*)-diazepines with base results in rapid ring opening to (*Z*,*Z*)-dienaminonitrile derivatives, e.g., **47** → **48** (Scheme IX).[31] This reaction is triggered by proton abstraction from the polarized C–N double bond, a familiar theme in base-catalyzed reactions of isoxazole, pyrazole, and related heterocycles. Extended treatment of **48** (or **47**) with ethoxide yields the 2-aminopyridine **49**, suggesting that a 1,7-diazanorcaradiene is not involved. The significant observations of Pleiss and Moore[37] that the 1,7-diazabicyclo[4.1.0]-heptanone **37** (Scheme X) is smoothly converted under acidic and basic conditions into the *N*-aminopyridinium salt **50** and 2-aminopyridine **51**, respectively, provide evidence for the intervention of a common 1,7-diazanorcaradiene intermediate in the corresponding reactions of 1,2(1*H*)-diazepines. The formation of **50** is rationalized by N-1 protonation of **37** which induces preferential C–N bond cleavage while the production of **51** is initiated by rapid enolate formation followed by N–N bond cleavage as in the thermolysis of certain 1,2(1*H*)-diazepines (Scheme XI).

As a side excursion, we reexamined[44] the interesting suggestion[38] that protonation of **41** and **46** provides the planar species **52** and **53**, respectively. ^{1}H NMR studies

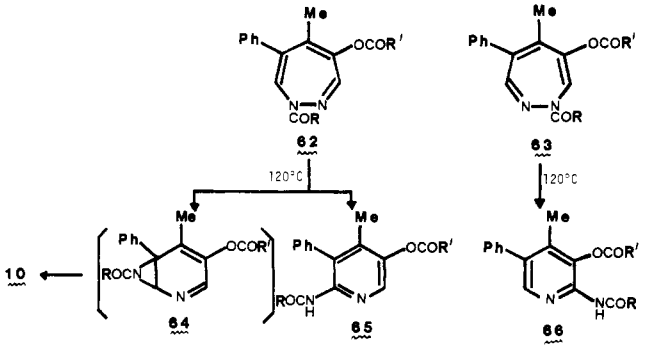


clearly showed rather that the 1,2(4*H*)-diazepinium salts **54** and **55** are formed. Variable-temperature NMR studies of **55** (and **54**) yielded evidence for ring inversion with an activation energy less than that of the corresponding free base **46**. This difference ($\Delta\Delta G^{\ddagger}$ = 7 kcal/mol) is attributed to a repulsive N–N lone pair interaction in the transition state of **46** which is relieved by protonation.

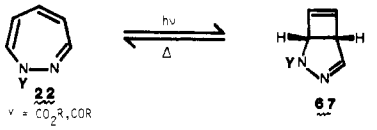
The thermal reversion (>150 °C) of 1,2(1*H*)-diazepines **56** (Scheme XI) into the corresponding pyridine *N*-imides **58** constituted an early finding in both laboratories. This reaction has been observed for 1-acyl-

(40) Van der Plas, H. C. "Ring Transformations of Heterocycles"; Academic Press: New York, 1973; Vol. 2, p 1.
(41) (a) Reissenweber, G.; Sauer, J. *Tetrahedron Lett.* **1977**, 4393. (b) Harris, D. J.; Kan, G. Y.-P.; Tschamber, T.; Snieckus, V. *Can. J. Chem.* **1980**, *58*, 494.
(42) Bemi, L.; Thomas, M. T.; Snieckus, V. *Synthesis* **1979**, 130.
(43) Nastasi, M.; Streith, J. *Bull. Soc. Chim. Fr.* **1973**, 635.
(44) Harris, D. J.; Thomas, M. T.; Snieckus, V.; Klingsberg, E. *Can. J. Chem.* **1974**, *52*, 2805.

Scheme XII



Scheme XIII



1,2(1*H*)-diazepines with no,[31,43] 3-, 5-, or 7-,[45] 3,5,7-,[46] and 4- or 6-electron-withdrawing group[19,45] substitutions. The last two groups also produce some pyridine (**59**) and 2- and 6-aminopyridine (**60**) derivatives, respectively. In contrast, 1,2(1*H*)-diazepines bearing electron-donating substituents at the 4- and 6-positions yield mainly 2- and 6-aminopyridines **60** together with varying amounts of the previously unknown fully unsaturated 1,3-diazepines **61**.[19,45] The thermodynamic parameters ($\Delta G^{\ddagger}$ = 24–27 kcal/mol, $\Delta S^{\ddagger}$ = −7 to −8 eu) observed in the rearrangement of 3-methyl-1,2(1*H*)-diazepines[47] are of similar magnitude to those exhibited by the thermal electrocyclization of 1,3,5-hexatriene to 1,3-cyclohexadiene, suggesting, by analogy, the intermediacy of the 1,7-diazanorcaradiene **57** in the thermal chemistry of **56**. The dichotomy of products **58** vs. **60** must be due to the absence or presence of four- or six-electron-donating substituents. Thus in the thermolysis of **62** and **63** (Scheme XII),[19] electron release by the acyloxy group assists cleavage of the weak N–N bond intermediates in the corresponding 1,7-diazanorcaradienes, leading to the 2-aminopyridines **65** and **66**, respectively. These results, considered side by side with our observations on the *photochemical* formation of 2-aminopyridines (Scheme VII), are fully consistent with the formation of the same 1,7-diazanorcaradienes either thermally from 1-acyl-1,2(1*H*)-diazepines or photochemically from pyridine *N*-imides. In the absence of electron-releasing 4- and 6-substituents, 1,2-(1*H*)-diazepines rearrange into pyridine *N*-imines **58**, the driving force for the C–N bond cleavage in the 1,7-diazanorcaradiene **57** being aromatization. Pyridines **59** may arise from the *N*-imides **58** or directly from the species **57**. The formation of the 1,3-diazepines **10** may be rationalized by a "walk rearrangement", i.e., to **64**, followed by ring expansion.

In common with many seven-membered-ring unsaturated heterocyclic systems,[48] 1-acyl-1,2(1*H*)-diazepines undergo photochemical disrotatory electrocyclization to give 2,3-diazabicyclo[3.2.0]heptadienes **67** (Scheme XIII).[31,45,46] The only exception to this general result was observed in the irradiation of the 1-methyl-1,2-(1*H*)-diazepine **41** which gave 1-methyl-3,5-diphenylpyrazole, presumably by nonconcerted loss of phenylacetylene from the bicyclic intermediate corresponding to **67**. Thermolysis of **67** affords 1,2(1*H*)-diazepines (**22**),[31] pyridine *N*-imides,[46] and 1,3-diazepines[45] depending on ring substitution.

1,2(1*H*)-Diazepines undergo a broad spectrum of cycloaddition reactions (Scheme XIV).[22a] The highly reactive dienophiles TCNE and 4-phenyl-1,2,4-triazoline-3,5-dione gave normal Diels–Alder adducts, e.g., **69**[25b] and this pathway was also followed by singlet oxygen, yielding the rather stable epidioxides **70**.[49] Dissolution of 1-(ethoxycarbonyl)-1,2(1*H*)-diazepines in formic acid (or boron trifluoride etherate) produced endo Diels–Alder dimers **71**.[50] The driving force for this interesting cycloaddition may be protonation at N-2 which lowers the LUMO energy level of the C-6–C-7 dienophile, thereby allowing an efficient interaction with the HOMO level of the butadiene portion of a nonprotonated diazepine.

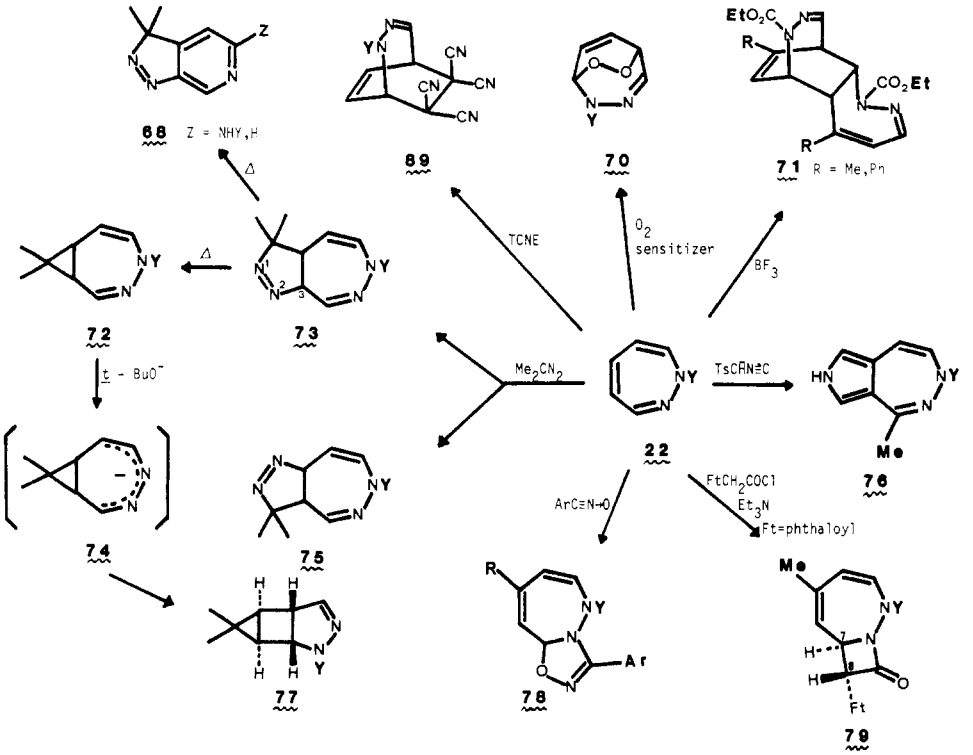
The reaction of 1,2(1*H*)-diazepines with diazoalkanes leads nonregioselectively to the 1-pyrazoline adducts **73** and **75**. Compounds **75** undergo facile tautomerization into the corresponding 2-pyrazolines which we currently view as potential precursors of tetraazaazulenes.[51] On the other hand, the thermolysis of 1-pyrazolines **73** provided, as expected from considerable precedent, entry into the homodiazepines **72**. Although these compounds proved to be stable to thermal Cope rearrangement, a reaction well documented for corresponding carbocyclic systems,[6] they suffered an interesting base-induced rearrangement to **77**, possibly by disrotatory electrocyclization of the 6π anion **74**.[52] Recently, a detailed investigation[53] of the reaction products from the thermolysis of the 2-pyrazolines corresponding to **73** has led to the additional isolation of pyrazolopyridines **68**, potential precursors of pyridocyclopropenes. TOSMIC anion behaves analogously to diazoalkanes, yielding pyrrolodiazepines **76**.[54] The strongly basic conditions required for this reaction preclude the use of 1,2(1*H*)-diazepines unsubstituted at C-3. Since nitrile oxides have been shown to undergo 1,3-dipolar cycloaddition with both olefins and imines, it was of interest to find that their reaction with 1,2-(1*H*)-diazepines proceeds site specifically and regiospecifically to the oxadiazoline cycloadducts **78** in good yield.[55] The imine double bond also participates in formal (2 + 2)π cycloaddition with ketene derivatives, providing stereospecifically the β-lactam diazepines **79**.[56] Thus the cycloaddition chemistry of 1,2(1*H*)-diazepines (Scheme XIV) offers flexible pathways to diverse new heterocycles.

Organometallic 1,2(1*H*)-Diazepines

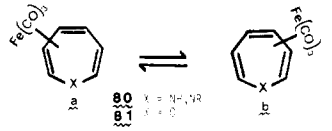
Certain transition metal π complexes with additional sites of conjugated unsaturation exhibit rapid and re-

(45) Tsuchiya, T.; Kurita, J.; Kojima, H. *J. Chem. Soc., Chem. Commun.* **1980**, 444.
(46) Kan, G.; Thomas, M. T.; Snieckus, V. *J. Chem. Soc., Chem. Commun.* **1971**, 1022.
(47) Goursot, P.; Kwart, H.; Strub, H.; Streith, J. unpublished results.
(48) Snieckus, V.; Harris, D. J. "Photochemistry of Heterocyclic Compounds"; O. Buchardt, Ed.; Wiley: New York, 1976, p 288.
(49) Tsuchiya, T.; Arai, H.; Hasegawa, H.; Igeta, H. *Chem. Pharm. Bull. Jpn.* **1977**, *25*, 2749.
(50) Willig, B.; Streith, J. *Tetrahedron Lett.* **1973**, 4167.
(51) Frost, J. R.; Streith, J. *J. Chem. Soc., Perkin Trans. 1*, **1978**, 1297.
(52) Klinger, F.; Strub, H.; Streith, J. *Tetrahedron Lett.* **1980**, 1223.
(53) Gesche, P.; Klinger, F.; Streith, J.; Strub, H. *Tetrahedron Lett.* **1980**, 4507.
(54) Harris, D.; Syren, S.; Streith, J. *Tetrahedron Lett.* **1978**, 4093.
(55) Streith, J.; Wolff, G.; Fritz, H. *Tetrahedron* **1977**, *33*, 1349.
(56) Streith, J.; Wolff, G. *Heterocycles* **1976**, *5*, 471.

Scheme XIV



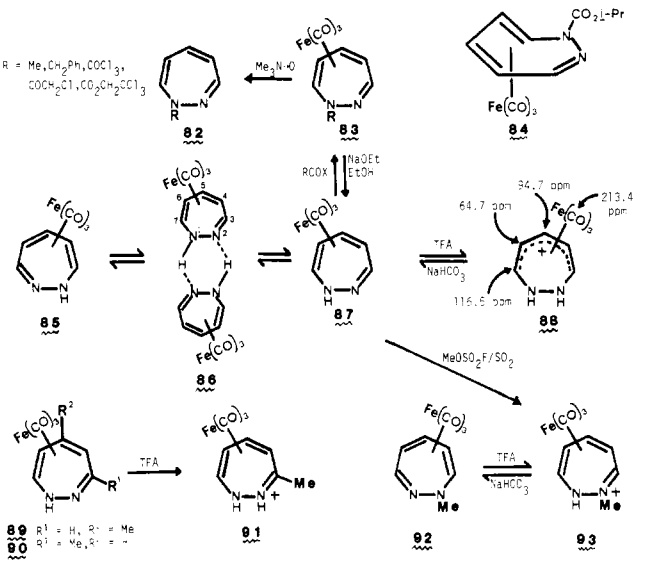
versible "fluxional" processes which convey a time-averaged symmetry plane to these molecules.[57] The knowledge that 1*H*-azepine–$Fe(CO)_3$ (**80**) and oxepin–$Fe(CO)_3$ (**81**) are fluxional[58] as depicted by **80**, **81** (a ⇄



b) encouraged us to prepare analogous complexes of 1,2(1*H*)-diazepines. In fact, the reaction of the diazepines with $Fe_2(CO)_9$ in benzene at room temperature smoothly led to air-stable, protic solvent insensitive complexes **83**, R = CO_2R, COR, SO_2Ar (Scheme XV).[22a,59] Higher than mono-ring complexes **83** cannot be prepared, presumably owing to steric effects and the reluctance to assume the more planar conformation necessitated by complexation.

In contrast to 1*H*-azepine and oxepin complexes, the 1-substituted 1,2(1*H*)-diazepine–$Fe(CO)_3$ adduct **83** cannot achieve a time-averaged symmetry plane by $Fe(CO)_3$ migration because of the inherent nonequivalency of the two alternate π-diene sites. This expectation is supported by ^1H NMR spectroscopy between −40 and +100 °C in solution and corroborated by X-ray crystallographic studies of 1-(isopropoxycarbonyl)-1,2-(1*H*)-diazepine–$Fe(CO)_3$ complex **84**.[33a] As deduced both from the X-ray data and ^1H NMR studies, com-

Scheme XV



plexation brings about flattening of the N-2–N-1–C-7 atom system and an upward folding of the C-5–C-6 bridge. Similarity in the coupling constants of 1-acetyl-1,2(1*H*)-diazepine–$Fe(CO)_3$ and the corresponding complexes of 1*H*-azepine (**80**) and oxepin (**81**) suggests conformational resemblance in these organometallic heterocycles. An interesting difference is the observation of restricted rotation about the N–CO bond in 1-(ethoxycarbonyl)-1*H*-azepine–$Fe(CO)_3$ ($\Delta G^{\ddagger}_{-28°C}$ = 13 kcal/mol)[58b] for which no corresponding phenomenon in 1-acetyl-1,2(1*H*)-diazepine–$Fe(CO)_3$ was detected down to −40 °C.

Following the path cleared by Fischer and Rühle on 1-(ethoxycarbonyl)-1*H*-azepine–$Fe(CO)_3$,[60] we treated

(57) Cotton, F. A. In "Dynamic Nuclear Magnetic Resonance Spectroscopy"; Jackman, L. M., Cotton, F. A., Eds., Academic Press: New York, 1975; p 377.

(58) (a) Review: Pannell, K. H.; Kalsotra, B. L.; Parkanyi, C. *J. Heterocycl. Chem.* **1978**, *15*, 1057. Seminal papers: for **80**: (b) Günther, H.; Wenzl, R. *Tetrahedron Lett.* **1967**, 4155. For **81**: (c) Aumann, R.; Averbeck, H.; Krüger, C. *Chem. Ber.* **1975**, *108*, 3336.

(59) Reinvestigation of this reaction on the 1-arylsulfonyl-1,2(1*H*)-diazepines has led to the isolation of pyrrole derivatives as the major products in addition to the complexes **83**: Bellamy, F.; Schuppiser, J.-L.; Streith, J. *Heterocycles* **1978**, *11*, 461.

(60) Fischer, E. O.; Rühle, H. *Z. Anorg. Allg. Chem.*, **1965**, *341*, 137.

the complexes **83**, R = CO_2Et, COMe, with base to give the unsubstituted complex **87** in high yield.[61] Although reactivity studies on **87** have not been rewarding, they have been balanced by interesting physicochemical observations. Variable-temperature ^1H NMR spectroscopy clearly demonstrated the fluxional behavior, **87** ⇄ **85**, of the bare 1,2(1*H*)-diazepine–$Fe(CO)_3$ complex. This fluxionality necessarily involves simultaneous prototropy and valence isomerization. The prototropic component may contribute little to the total energy barrier of the fluxional process since the activation energies for the complexes **87** ($\Delta G^\ddagger$ = 13.7 kcal/mol),[61a] **80**, X = NCO_2Et ($\Delta G^\ddagger$ = 15.5 kcal/mol),[58b] and 2,7-dimethyloxepin–$Fe(CO)_3$ ($\Delta G^\ddagger$ = 15.8 kcal/mol)[58c] are very similar in magnitude. Static ^1H NMR parameters of **87** (**85**) (observed at −32 °C) are comparable to those of the 1-acylated derivatives **83**, thus implying like overall geometries for the two systems.

IR dilution measurements on **87** indicated the presence of intermolecular hydrogen-bonded species while solvent-dependent ^1H NMR studies revealed that the relative fluxional rates decrease as the hydrogen-bonding ability of the solvent increase in the order liquid SO_2 > CD_2Cl_2 > CD_3OD.[61b] On the basis of these results, we proposed that the mechanism of the overall fluxional process **87** ⇄ **85** involves intermolecular proton transfer via a dimeric species **86**.[62] Monomeric species analogous to **86** have been advanced to explain the fluxional behavior of 1*H*-azepine– and oxepin–$Fe(CO)_3$ complexes.[58c] This interpretation is consistent with the observations that the 5-methyl complex **89** is fluxional ($\Delta G^\ddagger$ = 15 kcal/mol) while the 3-methyl derivative **90** is nonfluxional (a 3-methyl structure corresponding to **86** is expected to be static by a simple partial π-dienyl cation stability argument).[63]

The mechanistic picture depicted by **86** predicts that the rate of fluxionality should be strongly enhanced by acid catalysis which would break up intermolecularly hydrogen-bonded species by rapid proton exchange at N-sites. In agreement with this expectation, the ^{13}C NMR spectrum of **87** (**85**) in CD_2Cl_2–TFA at 0 °C is consistent with a fluxional, monomeric imminium species **88**.[61b] The relative chemical shifts at $C_{3,7}$, $C_{4,6}$, and C_5 are similar to those observed for dienyl cations rather than the corresponding $Fe(CO)_3$ complexes[63] and may reflect charge distribution which is strongly influenced by N lone-pair interaction. The equivalency of the carbonyl carbons in **88** indicates that the basal–apical carbonyl exchange process[57] is fast at 0 °C. The structure of the protonated species was fully defined by the X-ray determination of the trifluoroacetate of **88**, which confirmed the site of protonation at the intrinsically less basic N-2 site and clearly showed the attachment of the $Fe(CO)_3$ moiety at C-4 through C-7.[64]

The X-ray study also showed that **88** is significantly flatter than other azepine and 1,2(1*H*)-diazepine–$Fe(CO)_3$ (**84**) complexes, a result in concurrence with the lower activation energy of fluxionality for **88** compared to complexes **80** and **81**.

The derived mechanistic picture predicts that it should be possible to prevent fluxional behavior by blocking the intermolecular prototropy. In agreement, we found that methylation produced species **93** which is static on the ^1H NMR time scale to +30 °C.[61b] Somewhat surprisingly, the same species **93** is produced in the acid-catalyzed equilibration of the **1**-methyl complex **92**, presumably by protonation at the less basic nitrogen. On the other hand, treatment of the 3-methyl complex **90** with TFA yields the nonfluxional species **91**, acid catalysis apparently being insufficient to effect rearrangement to the less stable isomer.

A discontinuously reappearing objective of our studies has been the preparation or detection of the parent 1,2(1*H*)-diazepine heterocycle. This goal has been frustrated by inaccessibility of diazepines bearing N substituents which may be dislodged under mild conditions (Scheme I). The finding[65] that 1,2(1*H*)-diazepine–$Fe(CO)_3$ (**87**) undergoes smooth alkylation and acylation to give complexes **83** promises a new avenue of attack on this problem. Decomplexation using Shvo's excellent method[66] leads to compounds (**82**) which include the first known simple 1-alkyl-1,2(1*H*)-diazepines. The preparation of 1,2(1*H*)-diazepine from some of the attractive precursors **82** or by decomplexation of **87** has not been successful to date.[65b] Reference to the recent characterization of 1*H*-azepine[4] suggests that the root of the problem may be an inherent lability of the bare 1,2(1*H*)-diazepine.

Conclusion

The discovery of a new heterocyclic system innocently invites investigation of its properties and reactivity principles. Such studies tend to weave in and out of areas of established knowledge and unknown territory in heterocyclic chemistry. With the 1,2(1*H*)-diazepine system as a vehicle, we have been rewarded by observations of new physicochemical parameters, surprising rearrangements and cycloadditions, and unusual fluxional organometallic derivatives. It will be of interest to see how further studies of 1,2-diazepines will contribute to other new vistas in heterocyclic chemistry.

The study of diazepines marked our initiation into independent academic research. A number of students and colleagues have travelled with us from pyridinium ylides to diazepines and beyond. We hope this Account reflects their enthusiasm, dedication, and persistence, but foremost, our indebtedness to them. Our efforts have been made possible by the support of the Natural Sciences and Engineering Research Council of Canada and Bristol Laboratories (to V.S.), the Centre National de la Recherche Scientifique, Dêlêgation Gênêrale à la Recherche Scientifique et Technique, Ciba-Geigy, Hoffmann-LaRoche, Rhone-Poulenc and Roussel-Uclaf (to J.S.), and NATO (International collaboration grant to V.S. and J.S.).

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