for the disappearance of VI were calculated with a computer program which included a least-squares subroutine. The program for the calculation of activation parameters included a least-squares subroutine as well. A similar titrimetric method was used for the thermal decomposition of VI in chlorobenzene in the absence of amine. In this case the aliquots were quenched by addition to boiled distilled water. The rate of decomposition of *t*-butyl isopropyl peroxide (VIII) was determined by glpc. The reactants were sealed in capillary tubes with the internal standard, cyclohexane. Tubes were periodically removed from the thermostated bath and the glpc area ratios of VIII to cyclohexane were determined. First-order rate constants were calculated from these data.

Acknowledgment. This investigation was supported by a U. S. Army Research Office (Durham) grant and the Petroleum Research Fund, administered by the American Chemical Society.

Thermochemical Reactions of 1H-Azepine Derivatives. I. Dimerization[1]

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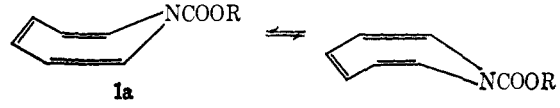
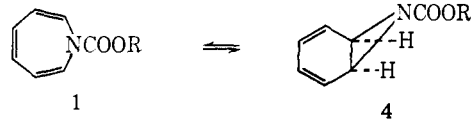
Abstract: Heating of several 1-substituted 1H-azepines at 120–130° for short periods of time has been found to afford crystalline dimers. Classification of these dimerizations as (6 + 4) π cycloadditions was based upon ultimate degradation of the unsubstituted dimers to ethylcyclodecane. The stereochemistry of the dimerization was established as *exo* by X-ray crystallographic structure determination of a derived methiodide. It is suggested that the transition states of such reactions are controlled to a significant extent by orbital symmetry factors since the *exo*-bonding process is favored on the basis of secondary orbital interactions. Thermolysis of the monomeric 1H-azepines or their low-temperature dimers at 200° for several minutes was observed to give rise to different dimers. These high-temperature dimers were shown to be derivatives of the highly symmetrical 13,14-diazatricyclo[6.4.1.1^{2,7}]-tetradeca-3,5,9,11-tetraene system. The mechanistic interrelationship of the two types of dimers is discussed.

From the purely structural viewpoint, the 1H-azepine nucleus (**1**) can be considered to be closely related to cycloheptatriene (**2**) since both molecules contain a fully conjugated triene unit in a seven-membered ring. From the electronic standpoint, however, 1H-azepines with their cyclic array of 8 π electrons are isoelectronic with cyclooctatetraene (**3**).[3] Since the effects of a wide range of temperatures (from −150 to *ca.* 600°) on both of these hydrocarbons have been examined by a variety of techniques, we were interested in the possibility that 1H-azepines may respond in equally interesting fashion to varied thermal energies. We have already commented on the fact that the nmr spectra of a diverse number of 1H-azepine derivatives remain invariant over a substantial temperature range (−90 to +130°).[6a] Therefore, the energy of activation for the conformational ring inversion of nonplanar structures **1a** and **1b**[6] appears to be less than that required in the case of cycloheptatriene (E_a = 5.7–6.3 kcal/mol)[7] or cyclooctatetraene.[8] These nmr studies also provide no evidence for the existence of benzenimine tautomers such as **4**, especially in the



1a **1b**

higher temperature (90–130°) regions. This is particularly significant since it is suggestive that **4** is relatively



1 **4**

less stable than benzene oxide,[9] a number of norcaradienes,[10] and bicyclo[4.2.0]octatetraene[11] relative to their respective monocyclic counterparts.

At somewhat more elevated temperatures, cycloheptatriene and 7-monosubstituted cycloheptatrienes are subject to a series of successive suprafacial 1,5-sigmatropic hydrogen shifts;[12] under the most drastic

(1) Unsaturated Heterocyclic Systems. LI. For previous paper, see I. C. Paul, S. M. Johnson, J. H. Barrett, and L. A. Paquette, *Chem. Commun.*, 6 (1969).

(2) National Institutes of Health Predoctoral Fellow, 1965–1968.

(3) According to a current convention,[4] these heterocycles would be termed π-excessive analogs of cyclooctatetraene.[5]

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

(5) For a recent synthesis of the first monocyclic π-equivalent heterocyclic congeners of cyclooctatetraene, see L. A. Paquette and T. Kakihana, *ibid.*, 90, 3897 (1968); L. A. Paquette and J. C. Philips, *ibid.*, 90, 3898 (1968).

(6) (a) L. A. Paquette, D. E. Kuhla, J. H. Barrett, and R. J. Haluska, *J. Org. Chem.*, *in* press. (b) Recent X-ray crystallographic studies have provided evidence that 1H-azepines preferably adopt the boat conformation (at least in the crystalline state): I. C. Paul, S. M. Johnson, L. A. Paquette, J. H. Barrett, and R. J. Haluska, *J. Am. Chem. Soc.*,, 90, 5023 (1968).

(7) (a) F. A. L. Anet, *ibid.*, 86, 458 (1964); (b) F. R. Jensen and L. A. Smith, *ibid.*, 86, 956 (1964).

(8) (a) F. A. L. Anet, *ibid.*, 84, 671 (1962); (b) F. A. L. Anet, A. J. R. Bourn, and Y. S. Lin, *ibid.*, 86, 3576 (1964).

(9) E. Vogel and H. Günther, *Angew. Chem. Intern. Ed. Engl.*, 6, 385 (1967).

(10) E. Ciganek, *J. Am. Chem. Soc.*, 89, 1454, 1458 (1967), and references therein for earlier literature.

(11) (a) A. C. Cope, A. C. Haven, Jr., F. L. Ramp, and E. R. Trumbull, *J. Am. Chem. Soc.*, 74, 4867 (1952); (b) R. Huisgen and F. Mietzsch, *Angew. Chem. Intern. Ed. Engl.*, 3, 83 (1964); (c) E. Vogel, H. Kiefer, and W. R. Roth, *ibid.*, 3, 442 (1964).

(12) (a) A. P. ter Borg, H. Kloosterziel, and N. van Meurs, *Proc. Chem. Soc.*, 359 (1962); *Rec. Trav. Chim.*, 82, 717 (1963), and related work from this group; (b) G. Büchi and E. M. Burgess, *J. Am. Chem.*

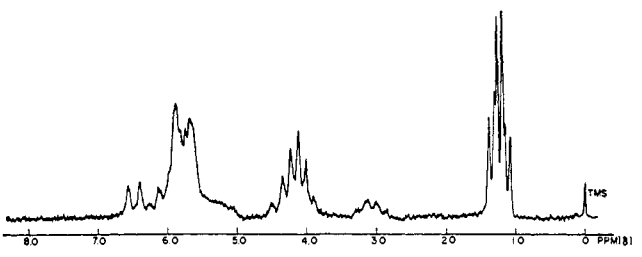
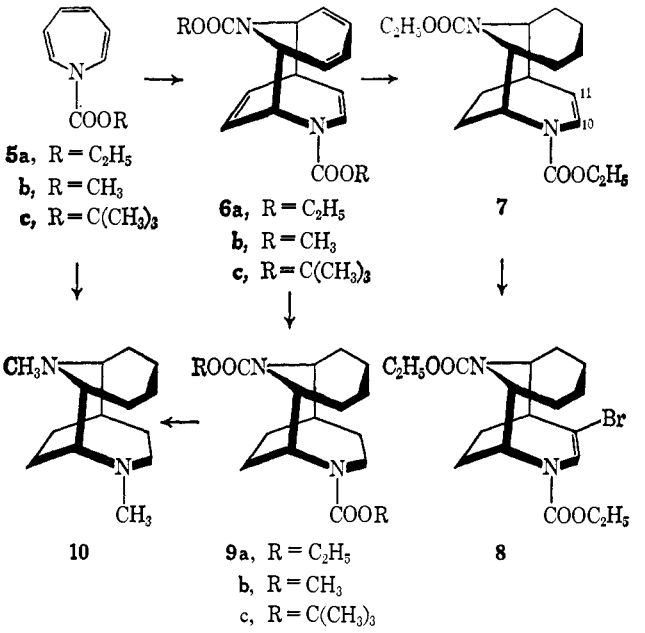


Figure 1. 60-MHz nmr spectrum of **6a** (CCl_4 solution).

conditions examined (approximately 400°), these tropilidenes give the derived aromatic products.[13] In contrast, 7,7-disubstituted cycloheptatrienes, when heated to 300°, undergo nonaromatizing skeletal rearrangements in which C-7 and its geminal substituents migrate around the periphery of the cyclohexadiene ring.[14] Also, heating of cyclooctatetraene at 100–170° forms four dimers of unusual structure.[15] Strikingly, pyrolysis of this same hydrocarbon in a flow system at *ca.* 540° gives an entirely different set of products from which dihydropentalene and lesser amounts of benzene and styrene have been isolated.[16]

In view of such spectacular thermally induced molecular changes exhibited by these hydrocarbon cognates of the 1H-azepine system, we have investigated the thermochemical reactions of the latter group of heterocycles. The present paper describes the dimerization of 1H-azepine derivatives[17] while the ensuing communication[18] reports on aromatization phenomena and sigmatropic rearrangements of the nitrogen atom.

Low-Temperature Dimerization. Thermolysis of a neat sample of N-carbethoxyazepine (**5a**) in a sealed ampoule at 130° for 2 hr produced a mixture containing chiefly a white crystalline dimer (**6a**), mp 78° (85% conversion), admixed with unreacted starting material and a small amount (8% conversion) of a second crystalline dimer **31a** (see below). The dimeric nature of **6a** was clearly evident from its mass spectrum which shows a molecular ion peak at *m/e* 330. Its ultraviolet absorption spectrum [λ_{max}^{EtOH} 213 mμ (ε 13,700)] was suggestive of, but of course not confirmatory for, the presence of α,β-unsaturated urethan[19] and medium-ring diene chromophores.[20] The nmr spectrum of **6a** (Figure 1) consists of a complex pattern in the δ 4.9–6.8 region



corresponding to ten protons, a five-proton multiplet at 3.7–4.6, a one-proton multiplet centered at 3.1, and two overlapping triplets (6 H) at 1.0–1.5. The presence of nonequivalent ethoxyl absorptions permits the rather important conclusion that the molecule lacks an element of symmetry.

Careful atmospheric pressure hydrogenation of **6a** resulted in a rapid uptake of 3 mol equiv of hydrogen. On the basis of spectroscopic and chemical criteria, the resulting hexahydro derivative (**7**) was readily characterized as an α,β-unsaturated urethan. Its ultraviolet spectrum showed a single absorption (in ethanol) at 226 mμ (ε 15,000) whereas a doublet centered at δ 6.9 (J = 9.5 Hz) corresponding to H-10 was distinct in the nmr spectrum. Bromination of **7** at −50° resulted in the rapid uptake of 1 equiv of the halogen; when the reaction mixture was allowed to warm to room temperature, hydrogen bromide was evolved spontaneously and vinyl bromide **8** was produced. That the bromine substituent in **8** occupied the 11 position was confirmed by the nmr spectrum in which H-10 now appears as a singlet at δ 7.41. The downfield shift of this vinyl proton ($\Delta\sigma$ = 0.51δ) is in excellent agreement with the expected effect of the C–Br bond anisotropy at that position.[21]

Catalytic reduction of **6a** at 50 psig proceeded with the uptake of 4 mol of hydrogen to give an octahydro bis urethan ultimately assigned structure **9a** whose nmr spectrum showed evidence for only five protons on carbon bearing nitrogen (see Experimental Section). This observation served to remove from further consideration a large number of alternative structures possible for dimer **6a** such as **11–13** whose perhydro derivatives would possess six or seven such protons. Lithium

Soc., 84, 3104 (1962); (c) E. Weth and A. S. Dreiding, *Proc. Chem. Soc.*, 59 (1964); (d) R. W. Murray and M. L. Kaplan, *J. Am. Chem. Soc.*, 88, 3527 (1966), and references therein.

(13) (a) W. G. Woods, *J. Org. Chem.*, 23, 110 (1958); (b) W. M. Halper, G. Gaertner, E. W. Swift, and G. E. Pollard, *Ind. Eng. Chem.*, 50, 1131 (1958); (c) J. H. Birely and J. P. Chesick, *J. Phys. Chem.*, 66, 568 (1962); (d) K. N. Klump and J. P. Chesick, *J. Am. Chem. Soc.*, 85, 130 (1963); (e) W. C. Herndon and L. L. Lowry, *ibid.*, 86, 1922 (1964); (f) A. G. Harrison, L. R. Honnen, H. J. Dauben, Jr., and F. P. Lossing, *ibid.*, 82, 5593 (1960).

(14) J. A. Berson and M. R. Wilcott, III, *ibid.*, 88, 2494 (1966); see also J. A. Berson, P. W. Grubb, R. A. Clark, D. R. Hartter, and M. R. Wilcott, III, *ibid.*, 89, 4076 (1967).

(15) For a summary of this work, see G. Schröder, "Cyclooctatetraene," Verlag Chemie, Weinheim/Bergstr., Germany, 1965, pp 60–62.

(16) (a) M. Jones, Jr., private communication; (b) M. Jones, Jr., and L. O. Schwab, *J. Am. Chem. Soc.*, 90, 6549 (1968); (c) see also I. Tanaka, *J. Chem. Soc. Japan, Pure Chem. Sect.*, 75, 212 (1954); *Chem. Abstr.*, 48, 4984*b* (1954).

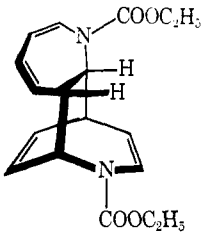
(17) A preliminary report of a portion of this work has appeared: L. A. Paquette and J. H. Barrett, *J. Am. Chem. Soc.*, 88, 2590 (1966).

(18) L. A. Paquette, D. E. Kuhla, and J. H. Barrett, *J. Org. Chem.*, in press.

(19) Reported λ_{max} values: 229–255 mμ (ε 4200–9000): (a) J. H. van den Hende and A. S. Kende, *Chem. Commun.*, 384 (1965); (b) A. S. Kende, P. T. Izzo, and J. E. Lancaster, *J. Am. Chem. Soc.*, 87, 5044 (1965); (c) J. E. Baldwin and R. A. Smith, *ibid.*, 87, 4819 (1965); (d) I. C. Paul, J. E. Baldwin, and R. A. Smith, *ibid.*, 88, 3653 (1966).

(20) (a) For example, 1,3-cycloheptadiene, λ_{max} 248 mμ (ε 7500): E. Pesch and S. L. Fries, *ibid.*, 72, 5756 (1950); (b) for a compilation of ultraviolet absorption data for cyclic medium-ring dienes, see L. A. Paquette and R. W. Begland, *ibid.*, 88, 4685 (1966).

(21) (a) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, pp 176–178; (b) L. A. Paquette, J. H. Barrett, R. P. Spitz, and R. Pitcher, *J. Am. Chem. Soc.*, 87, 3417 (1965).



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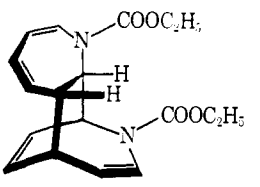

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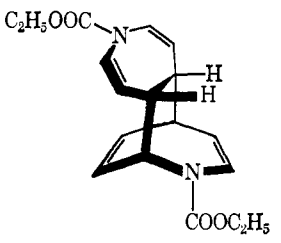

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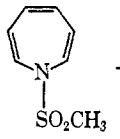
aluminum hydride reduction of **9a** afforded diamine **10** whose spectral characteristics served to reinforce these conclusions.

At this point, it should be mentioned that ancillary experiments have shown that the formation of dimers of type **6** appears to be a general property of simple N-substituted azepines. For example, both N-carbomethoxyazepine (**5b**) and N-carbo-*t*-butoxyazepine (**5c**) were smoothly converted to **6b** and **6c**, respectively, when heated without solvent for 2 hr at 130°. The structural similarity of dimers **6a–6c** was immediately apparent from the spectroscopic data (see Experimental Section). More conclusively, since exhaustive catalytic hydrogenation and lithium aluminum hydride reduction of **6b** and **6c** gave rise exclusively to diamine **10**, these compounds must necessarily be constructed of the identical carbon–nitrogen framework. In similar fashion, pyrolysis (122°, 2 hr) of N-methanesulfonylazepine (**14**) gave rise to a dimer (**15**, *m/e* 342) whose nmr spectrum is remarkably similar to those of **6** and is clearly indicative of eight vinyl protons, three protons on allylic carbon bearing nitrogen, and two nonequivalent methane-



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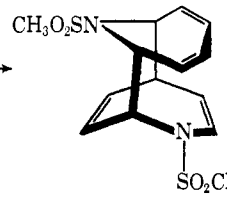

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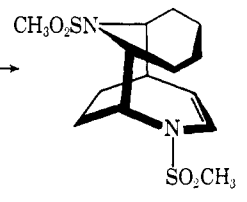


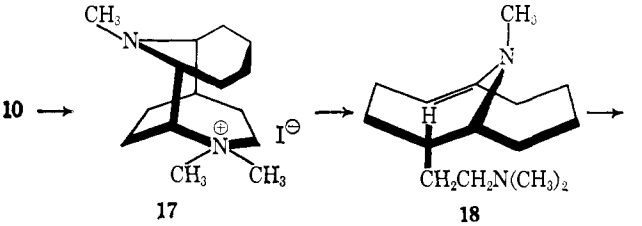
16

sulfonyl groups. The structural assignment follows entirely from the observed spectral parameters. As expected, partial hydrogenation of **15** afforded α,β-unsaturated urethan **16** (*m/e* 348); this material resisted further catalytic reduction. N-Cyanoazepine[22] and N-methylazepine[23] have also recently been reported to give rise to unsymmetrical dimers although at significantly lower temperatures (25–60° and 0–30°, respectively). Unfortunately the question of structural assignments to these dimers has not yet been resolved by these research groups.

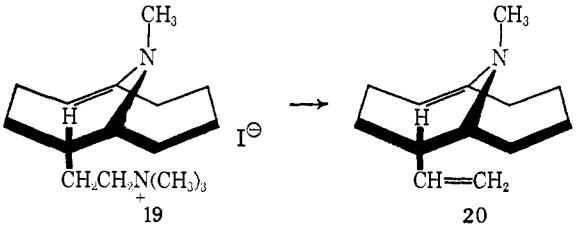
(22) (a) F. D. Marsh and H. E. Simmons, *J. Am. Chem. Soc.*, 87, 3529 (1965); (b) A. L. Johnson and H. E. Simmons, *ibid.*, 88, 2590 (1966); 89, 3191 (1967).

(23) K. Hafner and J. Mondt, *Angew. Chem.*, 78, 822 (1966); *Angew. Chem. Intern. Ed. Engl.*, 5, 839 (1966).

A final decision regarding the gross structure of the low-temperature dimers (**6**) was sought by recourse to exhaustive Hofmann degradation of **10**. To this end, heating an acetone solution of **10** with an excess of methyl iodide at 50° in a sealed tube led to the isolation of monomethiodide **17**. The position of quaternization (N-9 rather than N-14) was readily established by Hofmann elimination of **17**, a reaction which proved to be



17 18



19 20

highly regiospecific[24] and to lead only to bridgehead enamine **18**. The regiospecificity observed in this quaternary ammonium hydroxide decomposition can be attributed to the favorable proximity of the trigonal nitrogen center; by way of correlation, it should be mentioned that a similar directional influence of a first row element has recently been noted in an oxygen heterocycle.[25] From an intense band at 1645 cm^{-1} in the infrared spectrum of **18** the presence of an enamine double bond could be inferred. The ultraviolet absorption at 248 mμ (ϵ 3560) in isooctane lent additional support to the bridged enamine formulation.[26] The nmr spectrum, likewise compatible with structure **18**, displayed a lone vinyl proton as a doublet of doublets at δ 5.06 and two sharp singlets at 2.76 (3 H) and 2.19 (6 H) corresponding to an N-methylvinylamine and a saturated dimethylamino group, respectively.[27]

Quaternization of **18** in ether at ambient temperature proceeded in positionally selective fashion to give monomethiodide **19** in quantitative yield. When **19** was subjected to Hofmann degradation, a mixture of vinyl enamine **20** (30%) and the product of demethylation, **18** (70%), was obtained. Separation of the two components was readily achieved by reaction of the mixture with methyl iodide and filtration of the regenerated **19**. The integrity of the enamine function in **20** was established on the basis of a strong infrared band at 1660 cm^{-1} and ultraviolet absorption at 247.5 mμ (ϵ 4100) in isooctane. Of particular significance, the nmr spectrum of **20** revealed the presence of *four* vinyl protons.

Leaving aside for the moment the further degradation of **20**, let us return to the quaternization of **10**. If selec-

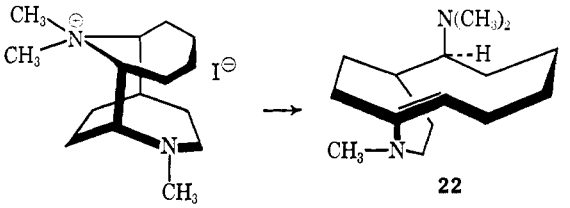
(24) A. Hassner, *J. Org. Chem.*, 33, 2684 (1968).

(25) L. A. Paquette and R. W. Begland, *ibid.*, 32, 2723 (1967).

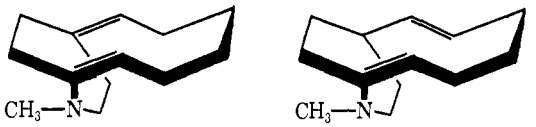
(26) Compare the spectral characteristics of 11-azabicyclo[4.4.1]-undec-$\Delta^{1,2}$-ene: (a) A. C. Cope, R. J. Cotter, and G. G. Roller, *J. Am. Chem. Soc.*, 77, 3590 (1955); (b) K. Biemann, G. Büchi, and B. H. Walker, *ibid.*, 79, 5558 (1957).

(27) The characteristic downfield shift associated with enamine N-methyl substituents when compared to methyl groups in saturated amines, produced by enamine resonance and consequent diminution of electronic density at the nitrogen center, has previously been recognized; see, for example, L. A. Paquette and M. Rosen, *ibid.*, 89, 4102 (1967).

tive reaction of N-14 would have actually occurred, then degradation of this monomethiodide (**21**) would very probably (because of regiospecificity) have produced enamine **22**, a structure equally compatible with the nmr characteristics of the isolated product because of the presence in this molecule of 12 protons on carbon bearing nitrogen and a lone vinyl proton. However,



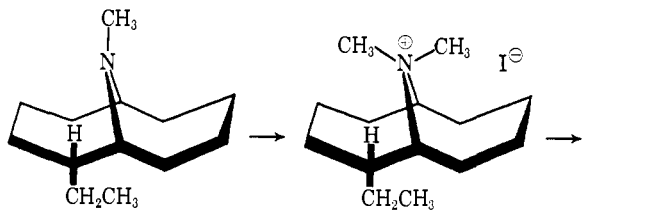
21 **22**



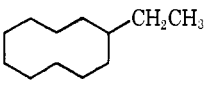
23 **24**

since further Hofmann degradation of **22** must necessarily lead to **23** or **24**, a practical decision between these structural alternatives and **20** becomes possible. Thus, inspection of the three structures quickly shows that **23** and **24** incorporate two and three vinyl protons, respectively, whereas only **20** is endowed with the four vinyl protons demanded by the nmr data.

The remainder of the degradation proved to be classical in nature and lacking in stereoselectivity. Hydrogenation of **20** furnished bridgehead amine **25**, the methiodide of which was seen to produce a mixture of five amines upon Hofmann elimination. The single major component (40%) was shown to be **25** resulting again from N-demethylation.[28] The largest fraction (58%)



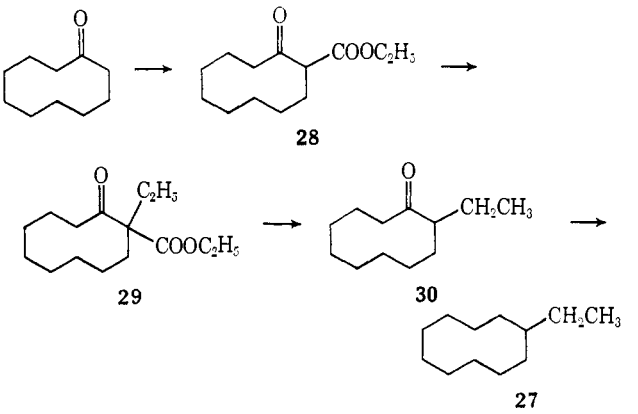
25 **26**



27

consisted of nearly equal quantities of two new amines, while two other basic nitrogen compounds were present in only minute amounts (2% combined yield). Because this mixture could not be separated readily by preparative scale vpc techniques, the degradation was continued without further purification. The mixture was hydrogenated,[29] resubmitted to a Hofmann elimination cycle, subjected to sequential acid–base treatment to separate the desired hydrocarbons from basic components, and finally hydrogenated. At this stage, there was obtained a lone hydrocarbon which was identified as ethylcyclodecane (**27**) on the basis of the following independent synthesis.

Treatment of cyclodecanone with sodium hydride and diethyl carbonate according to the procedure of Krapcho, *et al.*,[30] gave rise in 94% yield to β-keto ester **28** which could be conveniently ethylated and hydrolyzed under standard conditions. Reduction of the resulting ketone **30** by means of the Huang-Minlon modification[31] of the Wolff–Kishner reaction gave an excellent yield of authentic ethylcyclodecane (**27**) which was identical in all respects with the hydrocarbon obtained above.



28 **29** **30** **27**

The isolation of **27** serves as conclusive proof that the dimerization of simple unsubstituted 1H-azepines at moderate temperatures is the result of (6 + 4)π cycloaddition. Information relating to the stereochemistry of such dimers (**6**) was derived from a three-dimensional X-ray analysis of methiodide **17**.[32] The latter study has revealed that such cycloadditions clearly proceed in the *exo* sense demanded by orbital symmetry considerations operative during the bonding process. This point will be returned to in the Discussion section.

Lastly, it should be mentioned that dimers of type **6** have been found to be present in high concentration in samples of **5a** and **5b** which have been stored at ambient laboratory temperature for prolonged periods (6 months to 3 years). Such observations form the basis for the reasonable conclusion that (6 + 4)π cycloaddition constitutes the first step in the dimerization of 1H-azepines. In other words, it does not appear likely that additional transient intermediates intervene in the conversion of **5** to **6**.

High-Temperature Dimerization. When N-carbethoxyazepine (**5a**) was heated briefly in a sealed tube at 200°, it was rapidly and smoothly converted in 83% yield to a highly crystalline dimeric (*m/e* 330) solid. The nmr spectrum in this case showed two completely superimposable ethoxy groups at δ 4.08 (4 H, quartet, J = 7.5 Hz) and 1.29 (6 H, triplet, J = 7.5 Hz), a pseudosinglet absorption for eight vinyl protons at δ 5.88,[33] and a broad four-proton absorption at δ 4.7–5.1

(28) Such bridgehead methiodides appear to be particularly prone to N-demethylation under Hofmann conditions; *cf.* ref 26a.

(29) Failure to perform a hydrogenation at this step resulted in subsequent valence bond isomerization of the dienes thus produced. For analogy, *cf.* S. J. Rhoads, "Molecular Rearrangements, Part One," P. de Mayo, Ed., John Wiley & Sons, Inc., New York, N. Y., 1963, pp 684–706.

(30) A. P. Krapcho, J. Diamanti, C. Cayen, and R. Bingham, *Org. Syn.*, 47, 20 (1967).

(31) Huang-Minlon, *J. Am. Chem. Soc.*, 68, 2487 (1946).

(32) I. C. Paul, S. M. Johnson, J. H. Barrett, and L. A. Paquette, *Chem. Commun.*, 6 (1969).

(33) The appearance of a group of vinyl protons, which *a priori* would be expected intuitively to possess differing chemical shifts, as a simple pseudo-singlet nmr absorption is not unique to **31a** and many of its congeners, but has been reported for a number of polyunsaturated cyclic systems such as: (a) 1,3,5-cyclooctatrienes: W. von E. Doering,

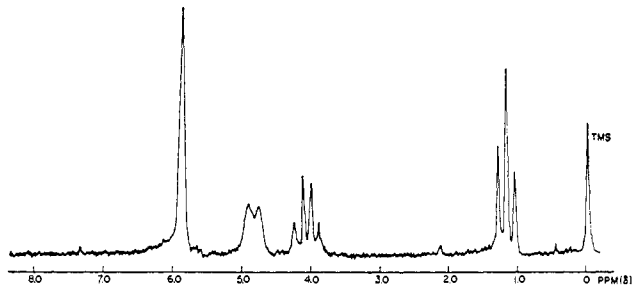
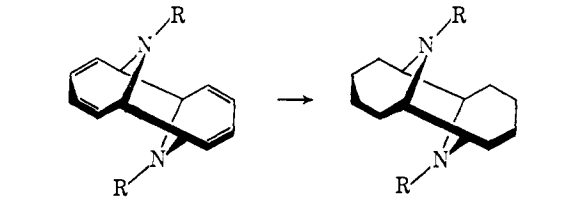


Figure 2. 60-MHz nmr spectrum of **31a** ($CDCl_3$ solution).

(Figure 2). These spectral features, when taken collectively with the ultraviolet absorption [λ_{max}^{EtOH} 232 (ϵ 14,100) and 237.5 mμ (ϵ 14,800)], Raman characteristics (intense band near 1620 cm^{-1} which is strongly depolarized by a parallel filter), and dipole moment data (0.91 D, in dioxane),[34] were fully compatible with the highly symmetrical structure **31a**.



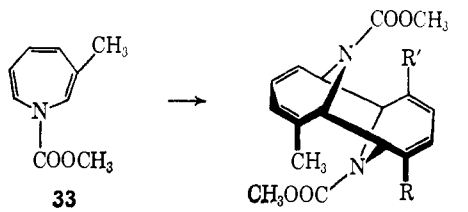
31a, R = $COOC_2H_5$
b, R = $COOCH_3$
c, R = $COOC(CH_3)_3$
d, R = CN
e, R = CH_3

32a, R = $COOC_2H_5$
b, R = $COOCH_3$
c, R = $COOC(CH_3)_3$
d, R = CH_3
e, R = H

Additionally, catalytic hydrogenation of **31a** proceeded with the uptake of 4 equiv of hydrogen to give **32a** which was reduced with lithium aluminum hydride to **32d** and hydrolyzed with anhydrous hydrogen bromide in glacial acetic acid to diamine **32e**.

The correctness of the structure assignment to **31a** was experimentally confirmed by chemical correlation with the high-temperature dimers of N-cyanoazepine (**31d**)[22] and particularly of N-methylazepine (**31e**),[23,35] the dihydrobromide of which has been the subject of a conclusive X-ray structure analysis.[36]

Additional experiments have shown that the N-carbomethoxy- (**5b**) and N-carbo-*t*-butoxyazepines (**5c**) likewise dimerize readily to **31b** and **31c**, respectively, at 200°. The interrelationship of these structures, although apparent from their nmr spectra (see Experimental Section), was verified in both instances by sequential hydrogenation and lithium aluminum hydride reduction to **32d**.[37] In like fashion, thermolysis of 3-methyl-N-carbomethoxyazepine (**33**) at 200° for 10 min in the absence of solvent produced in 24% yield a single dimer, mp 245–246.5°. The nature of the ring system as a 13,14-diazatricyclo[6.4.1.$1^{2,7}$]tetradeca-3,5,9,11-tetraene derivative (**34**) was immediately evident from the

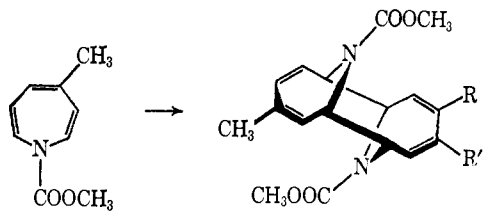


33

34a, R = H, R′ = CH_3
b, R = CH_3, R′ = H

nmr spectrum which shows, in particular, a broad six-proton vinyl absorption in the δ 5.62–6.08 region and a lone sharp methoxyl signal (6 H) at 3.76 and the ultraviolet absorption [λ_{max}^{EtOH} 239 (ϵ 14,615) and 246 mμ (ϵ 13,920)]. To the present time, however, it has not been possible to differentiate between isomers **34a** and **34b**, both of which are entirely compatible with the available data. It is noteworthy that Raman spectroscopy is not applicable to the solution of this problem. Specifically, since the groups at the two ends of **34a** and **34b** are essentially identical except for the symmetry of placement of the methyl substituents, the sole causative factor in the appearance of differing frequencies in the respective double bond regions would be coupling of the vibrations. Because the coupling ring in both cases is rather large and somewhat flexible, the interaction can be expected to be minimal. Therefore, the double bond frequencies should be about the same in both isomers and one would not expect to be able to distinguish with certainty between them.[38]

4-Methyl-N-carbomethoxyazepine (**35**) underwent equally facile dimerization at 200° to afford dimer **36a** or **36b** in 23% yield.[39]



35

36a, R = H; R′ = CH_3
b, R = CH_3; R′ = H

In an effort to obtain evidence which would indicate the operation of a multistep pathway in the high-temperature dimerization of 1H-azepines, a number of low-temperature dimers (**6**) were heated briefly at 200°. There were produced in high yield the corresponding symmetrical structures **31**, thereby strongly implicating the intermediacy of the kinetically controlled products (**6**) in the formation of dimers **31**. The propriety of this conclusion is discussed below.

Discussion

Cycloadditions between medium-ring polyenes and suitable olefins frequently lead to abnormal condensation products; yet, these reactions are almost always the result of kinetically controlled (4 + 2)π bonding processes (Diels–Alder reactions).[40] Such observations

G. Laber, R. Vonderwahl, N. F. Chamberlain, and R. B. Williams, *J. Am. Chem. Soc.*, 78, 5448 (1956); (b) cyclooctatetraene dimer, mp 53°: G. Schröder and W. Martin, *Angew. Chem. Intern. Ed. Engl.*, 5, 130 (1966); (c) the 1,6-cycloaddition product of nitrosobenzene with cycloheptatriene: J. Hutton and W. A. Waters, *Chem. Commun.*, 634 (1966).

(34) The authors are particularly indebted to Dr. A. L. Johnson (Du Pont) for the Raman and dipole moment measurements.

(35) We thank Professor K. Hafner for making available to us copies of the requisite comparison spectra.

(36) G. Habermehl and S. Göttlicher, *Angew. Chem.*, 79, 820 (1967); *Angew. Chem. Intern. Ed. Engl.*, 6, 805 (1967).

(37) Heating of **15** above 150° led only to decomposition.

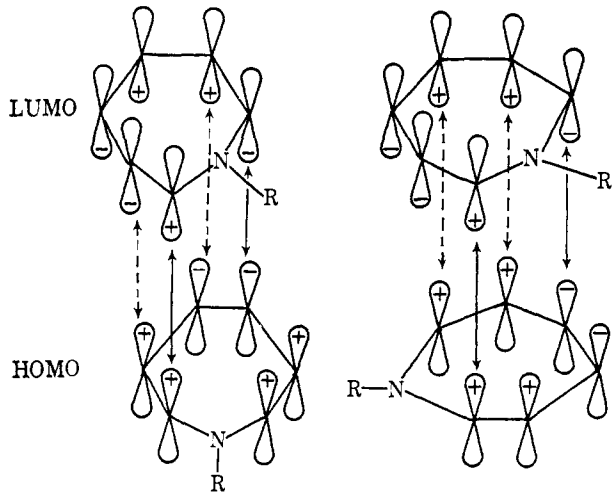
(38) We wish to acknowledge a helpful exchange of information with Professor R. C. Lord on this point.

(39) Since azepines **33** and **35**, when heated only to 125°, both gave rise to viscous oils consisting of inseparable mixtures of isomeric low-temperature dimers (structures inferred by nmr), these substances were not examined further.

(40) For a further discussion of this point, *cf.* L. A. Paquette, D. E. Kuhla, J. H. Barrett, and L. M. Leichter, *J. Org. Chem.*, in press.

are readily understood in the light of orbital symmetry arguments resulting from molecular correlation diagrams[41] and the well-established criterion that reaction rates for Diels–Alder cycloadditions are faster as the diene component becomes increasingly planar.[42] In contrast, concerted cycloaddition processes involving larger numbers of π electrons in the reacting components are few in number at the present time (see below). The low-temperature $(6 + 4)\pi$ dimerization of simple 1H-azepines is therefore of considerable interest.

A priori, a Hoffmann–Woodward analysis[43] of the orbital symmetry relationships involved in the $(6 + 4)\pi$ cocycloaddition of two 1H-azepine molecules indicates that the reaction might take place through either of two alternative transition states. In the first alternative (**37**), the highest occupied molecular orbital (HOMO) of one azepine ring interacts with the lowest unoccupied (LUMO) of a second azepine molecule in the *endo* sense. The second transition state (**38**) is that which would ultimately lead to *exo* addition.[44] Inspection of these

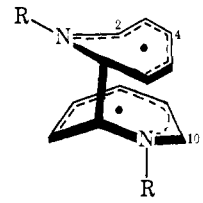


37 **38**

orbital diagrams clearly reveals the presence in **37** of repelling secondary nonbonding interactions (dashed lines; solid lines denote the primary bonding sites). By contrast, the secondary interactions in **38** are highly favorable and can be expected to lower the energy of this transition relative to **37**. As established above, the dimerization of 1H-azepines does indeed exhibit overwhelming preference for the *exo* $(6 + 4)\pi$ cycloaddition pathway.

The determinative role played by orbital symmetry factors in $(6 + 4)\pi$ cycloadditions has recently been uncovered in a limited number of such reactions. Thus, the reaction of tropone with cyclopentadiene[45] and the addition of dimethyldiphenylcyclopentadienone to cycloheptatriene and tropone[46] proceed exclusively to the respective *exo* adduct with virtual exclusion of the alternative *endo* isomer. Most interestingly, the 1H-azepine example represents the first instance wherein the same molecule functions as both the 6π and 4π components.

The thermally induced conversion of **6** to **31** is a transformation in which C-2 is seen to migrate from its original bonding site (C-1) to C-10 in a suprafacial manner. The selection rules advanced[47] for such [1,3] sigmatropic changes unmistakably reveal a serious energy impediment for the suprafacial pathway. Presumably, therefore, the migration in question is not concerted, but proceeds by way of intermediate diradical **39**.[48] Not surprisingly, homolytic cleavage of the C-1,2 bond is predicted to be facile due to the extensive delocalization



39

and attendant stabilization available to the uncoupled electrons. The ultimate formation of the C-2,10 bond is presumably favored in the thermodynamic sense because of the highly symmetrical geometry of the resulting structure (**31**). Interestingly, if a symmetry-allowed thermal suprafacial sigmatropic rearrangement of order [3,3][46] were occurring in **6** (*i.e.*, rupture of C-1,2 and rebonding at C-4,10), a structure identical with **6** would be found. In this sense, therefore, the latter rearrangement would be degenerate. Unfortunately, we have not found it possible to derive information relating to the operation of this alternative pathway.

Experimental Section[49]

Diethyl 9,14-Diazatricyclo[6.3.2.1^{2,7}]tetradeca-3,5,10,12-tetraene-9,14-dicarboxylate (6a). A 9.0-g (54.5 mmol) sample of **5a** was sealed in an ampoule and the tube was immersed in an oil bath preheated to 130°. After 2 hr, the resulting viscous oil was cooled and slurried in ether. The insoluble solid was filtered and dried to give 0.5 g (8% conversion) of **31a**.[50] The filtrate was brought to a volume of 200 ml with ether and the solution was decolorized (Darco G-60). The filtrate was concentrated to a volume of 15 ml

(41) R. Hoffmann and R. B. Woodward, *J. Am. Chem. Soc.*, **87**, 2046 (1965).

(42) For recent reviews of the Diels–Alder reaction, see: (a) A. Wasserman, "Diels–Alder Reactions," Elsevier Publishing Co., New York, N. Y., 1965; (b) J. Sauer, *Angew. Chem.*, 78, 233 (1966); 79, 76 (1967); *Angew. Chem. Intern. Ed. Engl.*, **5**, 211 (1966); **6**, 16 (1967).

(43) R. Hoffmann and R. B. Woodward, *J. Am. Chem. Soc.*, 87, 4388 (1965).

(44) For reasons of clarity and conciseness, we have utilized the LUMO only as the 6π donor and the HOMO exclusively as the 4π donor. It should be obvious that reversal of this pictorial formalism effects no alteration in the orbital symmetry argument.

(45) (a) R. C. Cookson, B. V. Drake, J. Hudec, and A. Morrison, *Chem. Commun.*, 15 (1966); (b) S. Ito, Y. Fujise, T. Okuda, and Y. Inoue, *Bull. Chem. Soc. Japan*, **39**, 1951 (1966).

(46) R. B. Woodward and K. Houk, unpublished work cited by R. B. Woodward, "Aromaticity," Special Publication No. 21, The Chemical Society, London, 1967, pp 242–246.

(47) R. B. Woodward and R. Hoffmann, *J. Am. Chem. Soc.*, 87, 2511 (1965).

(48) It should be pointed out that Woodward and Hoffmann have stated[47] that in the [*i,j*] sigmatropic rearrangements which they have considered, the σ orbital interacts with the π system in the transition state. They are careful to point out that if the migrating group possesses an available low-lying π orbital and is not so substituted as to create an impossible steric situation in the transition state, alternative allowed processes with reversed relationships may be possible. If the situation were present in the dimer rearrangement, the [1,3] shift would then be allowed.

(49) Melting points are corrected and boiling points are uncorrected. The microanalyses were performed by the Microanalytical Laboratory, Herlev, Denmark. Infrared spectra were determined with a Perkin-Elmer Model 237 spectrometer fitted with a sodium chloride prism. Ultraviolet spectra were recorded with a Cary Model 14 spectrometer. The nmr spectra were determined with Varian A-60 and A-60A spectrometers purchased with funds made available through the National Science Foundation. The mass spectra were measured with an AEI MS-9 mass spectrometer at an ionizing energy of 70 eV.

(50) This product is fully characterized later in the Experimental Section.

and 15 ml of petroleum ether (bp 80–100°) was added. After overnight storage at −10°, there was obtained 5.25 g (84.7% conversion) of **6a**. Concentration of the filtrate afforded 2.8 g of recovered **5a**. Dimer **6a** was obtained as a white crystalline solid, mp 78°; $\nu_{max}^{CCl_4}$ 1708 (>C=O) and 1665 cm^{-1} (>C=C<); λ_{max}^{EtOH} 213 (ε 13,700) and 241 mμ (ε 9350).

Anal. Calcd for $C_{18}H_{22}N_2O_4$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.46; H, 6.84; N, 8.40.

Dimethyl 9,14-Diazatricyclo[6.3.2.1^{2,7}]tetradeca-3,5,10,12-tetraene-9,14-dicarboxylate (6b). A 7.0-g (46.3 mmol) sample of **5b** was likewise heated for 2 hr at 130°. The viscous oil was slurried with ether and the insoluble solid was filtered and recrystallized from ethanol to give 2.12 g (30.3%) of **31b**, mp 297–298°.[50] The filtrate was decolorized and concentrated as above. The deposited crystals were recrystallized from methanol to give 4.38 g (62.5%) of **6b**, mp 137–138°; $\delta_{TMS}^{CDCl_3}$ 6.53 (doublet, 1 H, H-10), 4.9–6.3 (multiplet, 8 H, vinyl protons), 4.42 (multiplet, 1 H, H-11), 3.74, 3.62 (singlets, 3 H each, $-OCH_3$), and 3.12 (multiplet, 1 H, H-1).

Anal. Calcd for $C_{16}H_{18}N_2O_4$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.63; H, 6.29; N, 9.28.

Di-*t*-butyl 9,14-Diazatricyclo[6.3.2.1^{2,7}]tetradeca-3,5,10,12-tetraene-9,14-dicarboxylate (6c). Pyrolysis of 4.5 g (23.2 mmol) of N-carbo-*t*-butoxyazepine (**5c**)[1] at 130° for 2 hr in the manner described above gave rise to 2.1 g (46.6%) of **6c** as a white solid, mp 125–127° (from hexane); $\delta_{TMS}^{CCl_4}$ 6.51 (doublet, 1 H, H-10), 5.4–6.36 (multiplet, 8 H, vinyl protons), 4.40 (multiplet, 1 H, H-11), 3.18 (multiplet, 1 H, H-1), 1.52 and 1.42 (singlets, 9 H each, $-C(CH_3)_3$).

Anal. Calcd for $C_{22}H_{30}N_2O_4$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.14; H, 7.98; N, 7.29.

Diethyl 9,14-Diazatricyclo[6.3.2.1^{2,7}]tetradeca-10-ene-9,14-dicarboxylate (7). A solution of 3.3 g (10.0 mmol) of **6a** in 25 ml of ether was hydrogenated over 100 mg of 5% palladium on charcoal in an atmospheric pressure hydrogenator until 3 equiv of hydrogen was consumed. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. Molecular distillation gave 3.3 g (98.3%) of **7**, bp 110° (0.10 mm); $\nu_{max}^{CCl_4}$ 1706, 1686 (>C=O), and 1658 cm^{-1} (>C=C<); λ_{max}^{EtOH} 226 mμ (ε 15,000); $\delta_{TMS}^{CDCl_3}$ 6.90 (doublet, J = 9.5 Hz, 1 H, H-10), 4.5–5.5 (multiplet, 4 H, H-2,7,8,11), 3.9–4.4 (quartet, J = 7.0 Hz, 4 H, overlapping $-OCH_2-$), 2.2–2.8 (multiplet, 1 H, H-1), 1.8–2.2 (multiplet, 12 H), and 1.28 (triplet, J = 7.0 Hz, 6 H, overlapping $-CH_3$).

Anal. Calcd for $C_{18}H_{28}N_2O_4$: C, 64.26; H, 8.39; N, 8.33. Found: C, 64.63; H, 8.25; N, 8.43.

Diethyl 11-Bromo-9,14-diazabicyclo[6.3.2.1^{2,7}]tetradeca-10-ene-9,14-dicarboxylate (8). To a cold (−50°) solution of 2.0 g (5.95 mmol) of **7** dissolved in 20 ml of methylene chloride was added a solution of 0.85 g (5.95 mmol) of bromine in 10 ml of the same solvent. Upon completion of the addition, the reaction mixture was allowed to warm to room temperature during the course of which hydrogen bromide was evolved.[51] The solvent was removed under reduced pressure and the residue was subjected to repeated molecular distillation. Monobromide **8** was obtained as a colorless oil, bp 150° (0.08 mm); $\nu_{max}^{CCl_4}$ 1727, 1705 (>C=O), and 1672 cm^{-1} (>C=C<); $\delta_{TMS}^{CDCl_3}$ 7.41 (singlet, 1 H, vinyl proton), 4.5–5.5 (multiplet, 3 H, >C*H*N–), 3.8–4.5 (multiplet, 4 H, nonoverlapping $-OCH_2-$ groups), 2.75–3.2 (multiplet, 1 H, H-1), 1.3–2.5 (multiplet, 12 H), and 1.28 (multiplet, 6 H, nonoverlapping $-CH_3$).

Anal. Calcd for $C_{18}H_{27}BrN_2O_4$: C, 52.05; H, 6.55; N, 6.75; Br, 19.24. Found: C, 52.51; H, 6.73; N, 6.60; Br, 18.59.

Diethyl 9,14-Diazatricyclo[6.3.2.1^{2,7}]tetradecane-9,14-dicarboxylate (9a). A solution of 51.0 g (0.154 mol) of **6a** in 200 ml of anhydrous methanol was hydrogenated for 64 hr at 60 psig over 10% palladium on charcoal. The resulting colorless oil was distilled, bp 110° (0.01 mm); $\nu_{max}^{CCl_4}$ 1685 cm^{-1} (>C=O).

Anal. Calcd for $C_{18}H_{30}N_2O_4$: C, 63.88; H, 8.94; N, 8.28. Found: C, 64.28; H, 9.15; N, 8.31.

Hydrogenation of 1.5 g (5.0 mmol) of **6b** in similar fashion gave a quantitative yield of **dimethyl 9,14-diazatricyclo[6.3.2.1^{2,7}]tetradecane-9,14-dicarboxylate (9b)** as a colorless oil.

Anal. Calcd for $C_{16}H_{26}N_2O_4$: C, 61.91; H, 8.44; N, 9.03. Found: C, 62.25; H, 8.47; N, 8.83.

9,14-Dimethyl-9,14-diazatricyclo[6.3.2.1^{2,7}]tetradecane (10). To a rapidly stirred slurry of 12.0 g (0.30 mol) of lithium aluminum hydride in 500 ml of anhydrous tetrahydrofuran was added dropwise a solution of 50.8 g (0.15 mol) of **9a** in 200 ml of the same solvent. The mixture was refluxed for 20 hr, cooled, and treated sequentially with 12 g of water, 12 g of 30% sodium hydroxide solution, and 36 g of water. When the reaction mixture had turned completely white, 15 g of powdered magnesium sulfate was added. The solids were separated by filtration and washed well with hot tetrahydrofuran. The combined filtrates were concentrated and the residue was sublimed to give 31.2 g (91.5%) of **10**, mp 88–90°. This diamine afforded a dipicrate, mp 202–204° dec (from ethanol).

Anal. Calcd for $C_{20}H_{29}N_5O_7$: C, 45.88; H, 4.74; N, 16.47. Found: C, 46.00; H, 4.81; N, 16.54.

Reduction of 1.0 g (3.2 mmol) of **9** in similar fashion afforded 670 mg (93.7%) of **10**, identical in all respects with the above material.

Analogously, a 1.0-g (2.66 mmol) sample of **6c** was hydrogenated and, without purification, subjected directly to hydride reduction. The crystalline product (470 mg, 81.7%) was identical with the samples of **10** prepared above.

Dimerization of N-Methanesulfonylazepine.[52] A 1.76-g (10.3 mmol) sample of **14**[1] was placed in a sealed thick wall tube and heated at 122° for 2 hr. Chromatography of the crude product on Florisil gave 952 mg (54%) of **15** as a waxy solid which resisted a number of attempts at recrystallization; *m/e* 342; $\delta_{TMS}^{CDCl_3}$ 4.2–6.4 (multiplet, 11 H, vinyl and >C*H*N< protons), 3.1–3.55 (multiplet, 1 H, bridgehead proton), 2.81 and 2.93 (singlets, 3 H each, CH_3SO_2-).

Hydrogenation of 586 mg of **15** over 10% palladium on carbon in ethyl acetate at 50 psig for 24 hr afforded after chromatography on Florisil 367 mg (61.6%) of **16** as large white needles from ether, mp 139.5–141°; *m/e* 348; $\delta_{TMS}^{CDCl_3}$ 6.59 (doublet, 1 H, H-10), 4.38–5.16 (multiplet, 4 H, H-2,7,8,11), 3.03 and 3.06 (singlets, 3 H each, CH_3SO_2-), 2.3–2.8 (multiplet, 1 H, H-1), and 1.5–2.2 (multiplet, 12 H).

Anal. Calcd for $C_{14}H_{24}N_2O_4S_2$: C, 48.25; H, 6.94; N, 8.04. Found: C, 48.50; H, 6.99; N, 8.31.

9,9,14-Trimethyl-14-aza-9-azoniatricyclo[6.3.2.1^{2,7}]tetradecane Iodide (17). A solution of 4.4 g (0.02 mol) of **10** and 5 ml of methyl iodide in 50 ml of acetone was heated at 50° with rapid stirring for 15 hr. The white crystals which separated on cooling were recrystallized from methanol–acetone to give 7.0 g (96.5%) of **17**, mp 211–212° dec.

Anal. Calcd for $C_{15}H_{29}IN_2$: C, 49.45; H, 8.02; N, 7.67. Found: C, 49.38; H, 7.89; N, 7.45.

5-[2-(Dimethylamino)ethyl]-11-methyl-11-azabicyclo[4.4.1]undec-1-ene (18). To a solution of 14.0 g (38.4 mmol) of **17** in 100 ml of methanol–water (1:1) was added 8.9 g (38.4 mmol) of freshly prepared silver oxide and the mixture was stirred for 2 hr. The solids were removed by filtration and washed with methanol. The combined filtrate and washings were concentrated under reduced pressure to a volume of *ca.* 15 ml and the resulting oil was distilled at 160° (0.15 mm). The crude distillate was dissolved in ether; after drying over magnesium sulfate, the ether solution was evaporated and the oil redistilled to give 6.4 g (70.4%) of colorless liquid, bp 85° (0.15 mm), $n^{25}D$ 1.5077; $\nu_{max}^{CCl_4}$ 1645 cm^{-1} (>C=C(N<)–); $\lambda_{max}^{isooctane}$ 248 mμ (ε 3560); $\delta_{TMS}^{CDCl_3}$ 5.14 (doublet of doublets, 1 H, vinyl proton), 2.78 (singlet, 3 H, >NCH_3), 2.21 (singlet, 6 H, $-N(CH_3)_2$), 0.80–2.80 (multiplet, remaining protons).

Anal. Calcd for $C_{15}H_{28}N_2$: C, 76.21; H, 11.95; N, 11.85. Found: C, 75.89; H, 11.90; N, 11.87.

5-[2-(Trimethylazonia)ethyl]-11-methyl-11-azabicyclo[4.4.1]undec-1-ene Iodide (19). A solution of 1.0 g (4.13 mmol) of **18** and 5 ml of methyl iodide in 20 ml of anhydrous ether was stirred at room temperature for 5 min. The white precipitate, mp 195–200°, was recovered by filtration (1.6 g, 100%) and recrystallized from acetone–ether to yield pure **19**, mp 200–201° dec; $\nu_{max}^{CHCl_3}$ 1655 cm^{-1} (>C=C(N<)–); λ_{max}^{EtOH} 219.5 (ε 14,750) with a singlet shoulder at 250 mμ; $\delta_{max}^{CDCl_3}$ 5.12 (multiplet, 1 H, vinyl proton), 3.45 (singlet, 10 H, >C*H*N$(CH_3)_3^+$), 2.78 (singlet, 3 H, >NCH_3), and 0.80–2.70 (multiplet, 17 H).

Anal. Calcd for $C_{16}H_{31}IN_2$: C, 50.79; H, 8.26; N, 7.41. Found: C, 50.59; H, 8.38; N, 7.35.

11-Methyl-5-vinyl-11-azabicyclo[4.4.1]undec-1-ene (20). A solution of 10.6 g (28 mmol) of **19** in 75 ml of anhydrous methanol was added to a stirred slurry of 12.95 g (28 mmol) of freshly prepared silver oxide in 50 ml of the same solvent. After 30 min, the solids were removed by filtration and the filtrate was concentrated under

(51) In subsequent experiments, slightly more than 1 equiv of acetamide was added to trap the evolved hydrogen bromide. This modification was advantageous because it gave a cleaner product, presumably because the acid was conveniently removed as the insoluble acetamide hydrobromide.

(52) This experiment was performed by R. J. Haluska whom we thank.

reduced pressure. Bulb-to-bulb distillation of the residue at 200–300° (10 mm) gave a mixture of **18** and **20** (ratio 70:30, vpc analysis). This mixture of amines (5.62 g) was dissolved in 150 ml of ether and 10 ml of methyl iodide was added. After stirring for 3 hr, the precipitated **19** (6.28 g) was filtered and the filtrate was concentrated to give 1.70 g (77.8% conversion) of **20**. An analytical sample was prepared by preparative scale vpc using a 5 ft 5% SF 96 on Chromosorb G column at 180°; $\nu_{max}^{CCl_4}$ 1667 (>C=C(N<)–) and 1647 cm^{-1} (>C=C<); $\lambda_{max}^{isooctane}$ 247.5 mμ (ε 4100); $\delta_{TMS}^{CDCl_3}$ 4.8–6.0 (multiplet, 4 H, vinyl protons), 2.75 (singlet with broad base, 4 H, >C*H*NCH_3), and 0.80–2.6 (multiplet, 13 H).

Anal. Calcd for $C_{13}H_{21}N$: C, 81.61; H, 11.06. Found: C, 81.85; H, 11.10.

2-Ethyl-11-methyl-11-azabicyclo[4.4.1]undecane (25). Hydrogenation of 1.41 g (7.3 mmol) of **20** in 50 ml of tetrahydrofuran containing 200 mg of 10% rhodium on carbon catalyst at 50 psig for 48 hr gave 1.42 g (99.7%) of **25** of 95% purity (vpc analysis). Preparative scale vpc on the same column as above at 180° afforded the analytical sample.

Anal. Calcd for $C_{13}H_{25}N$: C, 79.93; H, 12.90. Found: C, 80.33; H, 12.95.

2-Ethyl-11,11-dimethyl-11-azoniabicyclo[4.4.1]undecane Iodide (26). A solution of 1.0 g (5.12 mmol) of **25** and 3 ml of methyl iodide in 3 ml of acetone was sealed in an ampoule and heated at 100° for 8 hr. The solution was concentrated and the resulting solid was recrystallized from acetone to give 1.6 g (93.7%) of **26**, mp 214–215°.

Anal. Calcd for $C_{14}H_{28}IN$: C, 49.85; H, 8.37; N, 4.15. Found: C, 49.82; H, 8.37; N, 4.06.

Hofmann Degradation of 26. A mixture of 6.75 g (0.02 mol) of **26**, 4.65 g (0.02 mol) of freshly prepared silver oxide, and 100 ml of methanol was stirred for 30 min and filtered. The solids were washed with 100 ml of methanol and the combined filtrates were evaporated. Bulb-to-bulb distillation of the residue (20 mm, open flame) yielded 3.78 g of a mixture of products. This mixture was dissolved in tetrahydrofuran and hydrogenated at 50 psig over 10% palladium on charcoal. The saturated amine mixture (3.81 g) was heated with 12 ml of methyl iodide and 12 ml of acetone in a sealed tube at 100° for 16 hr. The resulting mixture of methiodides (6.44 g) was stirred with 4.65 g (0.02 mol) of freshly prepared silver oxide in 100 ml of methanol for 30 min. The normal work-up followed by bulb-to-bulb distillation gave 2.81 g of product. Dissolution of this material in 100 ml of tetrahydrofuran and hydrogenation as above yielded 2.84 g of a mixture of a hydrocarbon and saturated amines. This mixture was similarly heated with 9 ml of methyl iodide and 9 ml of acetone at 100° for 8 hr. The solvent was carefully evaporated at reduced pressure and the oil was extracted with ether. The ether solution was carefully concentrated to give 1.47 g of ethylcyclodecane (**27**), identical in all respects with the authentic sample described below.

Anal. Calcd for $C_{12}H_{24}$: C, 85.63; H, 14.37. Found: C, 85.52; H, 14.30.

2-Carbethoxycyclodecanone (28). To a rapidly stirred refluxing mixture of 11.8 g (0.10 mol) of diethyl carbonate and 3.3 g (0.138 g-atom) of sodium in 75 ml of dry benzene was added dropwise a solution of 7.0 g (0.045 mol) of cyclodecanone[53] in 35 ml of the same solvent during 3.5 hr. After cooling to room temperature, the mixture was neutralized by the addition of 8.2 ml of glacial acetic acid. The resulting precipitate was dissolved by the addition of 75 ml of water. The organic layer was separated and the aqueous layer was extracted twice with 20-ml portions of ether. The combined organic layers were dried, filtered, and evaporated. Distillation of the residue afforded 9.6 g (93.7%) of **28**, bp 108° (0.3 mm), n^{27}D 1.4855; $\nu_{max}^{CCl_4}$ 1748 (ester >C=O), 1712 (ring >C=O), 1647 (enol, β-keto ester), and 1608 cm^{-1} (>C=C< of enol).

Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.96; H, 9.89.

2-Ethylcyclodecanone (30). To a solution of 8.6 g (0.038 mol) of **28** in 100 ml of dry benzene was added 1.37 g (0.057 mol) of 60% sodium hydride–mineral oil suspension (previously washed free of the oil). The mixture was stirred rapidly at 80° for 2 hr and 5.94 g (0.038 mol) of ethyl iodide in 10 ml of dry benzene was added in one portion. Heating was continued for 8 hr and then 1.2 ml of acetic acid was added to the cooled reaction mixture. Water was added and the organic layer was processed in the usual fashion. The crude alkylation product (**29**) was used directly (9.1 g, 94.3%) without further purification.

A mixture of 2.54 g (0.01 mol) of crude **29**, 30 ml of glacial acetic acid, and 25 ml of 48% hydrobromic acid was refluxed overnight with stirring. The mixture was cooled, diluted with 50 ml of water, and extracted with two 25-ml portions of petroleum ether (bp 80–100°). The extracts were dried and carefully evaporated to give 1.53 g of **30**; the 2,4-dinitrophenylhydrazone was obtained as yellow-orange needles from ethanol, mp 77–78°.

Anal. Calcd for $C_{18}H_{26}N_4O_4$: C, 59.65; H, 7.32; N, 15.46. Found: C, 59.96; H, 7.24; N, 15.37.

Ethylcyclodecane (27). A solution of **30** (1.0 g, 5.5 mmol), 0.88 ml of hydrazine hydrate (99–100%), and 1.23 g (22 mmol) of potassium hydroxide in 10 ml of diethylene glycol was refluxed for 1.5 hr. At the end of this period, the temperature was allowed to rise to 195–200° and water and excess hydrazine hydrate were seen to distil. The temperature was held between 195 and 200° for 4 hr. To the cooled reaction mixture was added the above distillate and 10 ml of water. The mixture was extracted with three 25-ml portions of pentane and the organic extracts were processed in the normal fashion. The oil thus obtained was seen by vpc to contain 92% of **27** and 8% of cyclodecane. A sample purified by preparative scale vpc on a 5 ft 10% SF 96 on Chromosorb W column at 140° was identical in all respects with that obtained in the above degradation.

Diethyl 13,14-Diazatricyclo[6.4.1.1^{2,7}]tetradeca-3,5,9,11-tetraene-13,14-dicarboxylate (31a). A 6.45-g (0.04 mol) sample of **5a** was sealed in an ampoule under a nitrogen atmosphere and heated for 25 min at 200° in an oil bath. Upon cooling, the contents of the ampoule crystallized. Recrystallization of the material from ethanol gave 5.36 g (83.1%) of **31a**, mp 196–197°.

Anal. Calcd for $C_{18}H_{22}N_2O_4$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.43; H, 6.80; N, 8.59.

In similar fashion, thermolysis of 1.0 g (6.61 mmol) of **5b** yielded 910 mg (91%) of **31b** as a highly crystalline white solid, mp 297–298° (from methanol); ν_{max}^{KBr} 1700 cm^{-1} (>C=O). This compound was too insoluble in the common solvents for an nmr spectral determination.

Anal. Calcd for $C_{16}H_{18}N_2O_4$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.55; H, 6.16; N, 9.33.

Similarly, heating of 1.25 g (6.48 mmol) of **5c** for 3 min at 188–195° afforded 1.01 g (80.8%) of **31c** as white needles from ethanol, mp 204–205°; λ_{max}^{EtOH} 233 (ε 13,650) and 238 mμ (ε 14,290); $\delta_{TMS}^{CDCl_3}$ 5.68 (singlet, 8 H, vinyl protons), 4.72 and 4.53 (broad peaks, 4 H, bridgehead protons), and 1.34 (singlet, 18 H, *t*-butyl groups).

Anal. Calcd for $C_{22}H_{30}N_2O_4$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.45; H, 8.09; N, 7.09.

13,14-Dimethyl-13,14-diazatricyclo[6.4.1.1^{2,7}]tetradecane (32d).

A. From 31a. Catalytic hydrogenation of 4.8 g (14.5 mmol) of **31a** in 95 ml of ethanol containing prereduced platinum oxide at 26° (740 mm) gave 4.9 g (99.7%) of **32a**, mp 87–88° (from hexane); $\nu_{max}^{CCl_4}$ 1688 cm^{-1} (>C=O).

Anal. Calcd for $C_{18}H_{30}N_2O_4$: C, 63.88; H, 8.94; N, 8.28. Found: C, 63.91; H, 8.93; N, 8.25.

Reduction of 4.0 g (11.75 mmol) of **32a** with lithium aluminum hydride (0.95 g, 25.0 mmol) in refluxing tetrahydrofuran as described above afforded a solid which was sublimed at 60° (0.20 mm) to give 2.46 g (94%) of **32d**, mp 148–150°; $\delta_{TMS}^{CS_2}$ 2.63 (broad peak, 4 H, >C*H*N<), 2.53 (singlet, 6 H, >NCH_3), and 1.1–2.3 (multiplet, 16 H).

Anal. Calcd for $C_{14}H_{26}N_2$: C, 75.61; H, 11.79. Found: C, 75.70; H, 11.82.

B. From 31b. Hydrogenation of 1.0 g (3.31 mmol) of **31b** as above followed by hydride reduction of this product yielded 460 mg of **32d** identical with the sample prepared above.

C. From 31c. Sequential hydrogenation and hydride reduction of 1.0 g (2.58 mmol) of **31c** likewise led to the isolation of 350 mg of **32d**.

13,14-Diazatricyclo[6.4.1.1^{2,7}]tetradecane (32e). To 10 ml of glacial acetic acid previously saturated with anhydrous hydrogen bromide was added 1.0 g (3.0 mmol) of **32a** and the stirred solution was heated at 60° for 16 hr. The resulting precipitate was separated by filtration and dried to give 1.02 g (97.2%) of the dihydrobromide salt of **32e**, mp >315°. Treatment of 0.5 g of this salt with aqueous sodium hydroxide afforded pure **32e**, mp 60–61° (sealed tube).

Anal. Calcd for $C_{12}H_{22}N_2$: C, 74.17; H, 11,41. Found: C, 73.99; H, 11.34.

Thermal Conversion of 6a to 31a. A 130-mg (0.39 mmol) sample of **6a** in a sealed ampoule was heated for 5 min at 200°. The resulting solid was recrystallized from ethanol to give 80 mg (61.5%) of **31a**, mp 196–197°.

(53) E. W. Garbisch and J. Wohlebe, *J. Org. Chem.*, 33, 2157 (1968).

Dimerization of 3-Methyl-N-carbomethoxyazepine (33). An 850-mg (5.15 mmol) sample of **33**[1] was sealed in an ampoule and heated for 10 min at 200°. The resulting black gummy solid was recrystallized from methanol (charcoal decolorization) to give 205 mg (24%) of white crystals of **34**, mp 245–246.5°; $\nu_{max}^{CHCl_3}$ 1692 cm^{-1}; λ_{max}^{EtOH} 239 mμ (ε 14,615); $\delta_{TMS}^{CDCl_3}$ 5.62–6.08 (broad multiplet, 6 H, vinyl protons), 4.49–5.14 (multiplet, 4 H, >C*H*N<), 3.76 (singlet, 6 H, $-OCH_3$), 1.86–2.06 (multiplet, 6 H, $\geqslant CCH_3$).

Anal. Calcd for $C_{18}H_{22}N_2O_4$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.69; H, 6.64; N, 8.45.

Dimerization of 4-Methyl-N-carbomethoxyazepine (35). Heating of 1.10 g (6.65 mmol) of **35** in the above manner gave, after recrystallization from methanol, 248 mg (22.6%) of **36** as a highly crystalline white solid, mp 228–230°; $\nu_{max}^{CHCl_3}$ 1695 cm^{-1}; λ_{max}^{EtOH} 238 mμ (ε 14,190); $\delta_{TMS}^{CDCl_3}$ 5.50–5.91 (multiplet, 6 H, vinyl protons); 4.47–4.91 (multiplet, 4 H, >C*H*N<), 3.67 (singlet, 6 H, $-OCH_3$), and 1.81 (singlet, 6 H, $\geqslant CCH_3$).

Anal. Calcd for $C_{18}H_{22}N_2O_4$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.41; H, 6.75; N, 8.47.

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The Detection of a Schiff Base Intermediate in the Formation of Acetone-oxytocin[1]

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Abstract: Treatment of oxytocin with 60% aqueous acetone at 0° and at a pH of approximately 5 leads to the rapid formation of a Schiff base of oxytocin which has been trapped by reduction with sodium borohydride to give [1-(N-isopropylhemi-L-cystine)]-oxytocin (N-isopropyl-oxytocin). The reduction of the Schiff base was accomplished without reduction of the disulfide bond of oxytocin. Treatment of the hormone with acetone under the same conditions for 24 hr without the addition of borohydride affords acetone-oxytocin in aproximately 50% yield. N-Isopropyl-oxytocin possesses only a trace (~0.1 unit/mg) of oxytocic activity and does not exhibit avian vasodepressor activity. The preparation of N,N′-diisopropyl-L-cystine is also described.

The inactivation of oxytocin by aqueous acetone[3] with the formation of an isopropylidene derivative has been reported. This isopropylidene derivative, referred to as acetone-oxytocin, has been found to possess a 2,2-dimethyl-4-imidazolidinone ring structure in which the isopropylidene group from acetone forms a bridge between the nitrogen atom of the amino group of the half-cystine residue at position 1 of oxytocin and the nitrogen of the peptide bond between this half-cystine residue and the tyrosine residue at position 2, as shown in Figure 1.[4]

From a consideration of the mechanism of formation of the imidazolidinone derivative, it appeared likely that a Schiff base might be an intermediate. If the Schiff base were formed, it might be possible to detect its presence by treating the reaction mixture with sodium borohydride and trapping the Schiff base as [1-(N-isopropylhemi-L-cystine)]-oxytocin (N-isopropyl-oxytocin). It has been found that disulfide bonds in proteins are readily reduced by borohydride.[5] Since oxytocin contains a disulfide bond, it was necessary to find conditions suitable for reduction of the Schiff base without reduction of the disulfide bond. It was found that sulfhydryl formation was almost negligible at pH 5. Furthermore, at a pH of approximately 5 in 60% aqueous acetone, oxytocin is converted to acetone-oxytocin in 50% yield after 24 hr. The trapping experiment was therefore carried out in the following manner.

A solution of oxytocin in 60% aqueous acetone at pH 4.9 and 0° under nitrogen was treated over a 1-hr period with a large excess of sodium borohydride while the pH was maintained at 4.8–5.5 by addition of glacial acetic acid. Determination of the sulfhydryl content by the method of Ellman[6] was performed at various intervals during the addition of sodium borohydride. At no time was more than a trace of sulfhydryl detected.

The solid material obtained after neutralization of the reaction mixture and removal of the solvents *in vacuo* was purified twice by partition chromatography on Sephadex G-25[7] in the solvent system 1-butanol–3.5% acetic acid in 1.5% aqueous pyridine (1:1). N-Isopropyl-oxytocin was obtained in 75% yield as a white, lyophilized powder from the fractions comprising the peak with R_f 0.35. Oxytocin and acetone-oxytocin have R_f values of 0.24 and 0.76, respectively,[3] in the solvent system used. No oxytocin was detected in the partition chromatogram and only a trace of material was present at the position of acetone-oxytocin.

N-Isopropyl-oxytocin gave satisfactory values in the elemental and amino acid analyses. For the amino acid analysis, a 48-hr hydrolysis time was required due to the difficulty in the hydrolysis of the N-isopropyl-cystinyl–tyrosine peptide bond. It is interesting to note the high negative rotation of $[\alpha]^{23}D$ −88.3° (*c* 0.5, 1 *N*

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(3) D. Yamashiro, H. L. Aanning, and V. du Vigneaud, *Proc. Natl. Acad. Sci. U. S.*, **54**, 166 (1965).

(4) V. J. Hruby, D. Yamashiro, and V. du Vigneaud, *J. Amer. Chem. Soc.*, in press; D. Yamashiro and V. du Vigneaud, *ibid.*, **90**, 487 (1968).

(5) A. M. Crestfield, S. Moore, and W. H. Stein, *J. Biol. Chem.*, **238**, 622 (1963).

(6) G. L. Ellman, *Arch. Biochem. Biophys.*, **82**, 70 (1959).

(7) (a) D. Yamashiro, *Nature*, **201**, 76 (1964); (b) D. Yamashiro, D. Gillessen, and V. du Vigneaud, *J. Amer. Chem. Soc.*, 88, 1310, (1966).