Heterodienophiles. I. Stereoselectivity in the 1,4 Addition of Iminocarbamates to Cyclohexa-1,3-diene[1]

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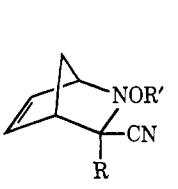
Abstract: The acid-catalyzed 1,4 addition of iminourethanes to cyclohexa-1,3-diene has been investigated in several solvents in order to determine reaction stereochemistry. Nmr analysis of 3-substituted-*N*-carbethoxy-2-azabicyclo[2.2.2]oct-5-enes (5,6-dehydroisoquinuclidines) utilizing long-range W-plan coupling and shift effects has indicated preferential formation of 3-exo adducts from acetyl and several aryl bisurethanes (Table I). Methyl, ethyl, benzyl, and phenyl benzalbiscarbamates also afforded major amounts of 3-exo adducts (Table II). Analysis of the stereochemistry of iminourethane cycloadditions suggests that a stepwise cyclic process involving protonated (*E*)-iminourethanes best explains the observed structural and stereochemical data. The mass spectral fragmentation patterns of *N*-carbethoxy-5,6-dehydroisoquinuclidines have been found to differ from previously reported patterns for ring cleavage of *N*-methyl-5,6-dehydroisoquinuclidines.

The Diels–Alder reaction, one of the most fundamental and useful reactions of the synthetic organic chemist, provides ready access to six-membered rings, especially bridged ones. Adding to the utility of this reaction is its remarkable stereoselectivity.[2] Among the several stereochemical aspects of this reaction,[2c,3] two principles derived from numerous studies are here worthy of note: (1) it has been observed that the geometric arrangement of substituents on the olefinic bond of the dienophile is preserved in the cyclic product; this has been generalized as the "principle of cis addition"; and (2) it has been noted that in the reaction of a cyclic diene and a substituted olefin, where the substituent of the dienophile can in principle enter either an exo (anti to the olefinic bond of the bicyclic product) or an endo position, there is a general kinetic preference arising from electronic and/or steric factors for endo addition.[3] Although a number of exceptions are known,[2a,3,4] this stereoselective observation has been generalized as the "Alder endo-rule."

While the six atoms involved in the formation of a ring are commonly all carbon atoms, it has been possible to synthesize heterocycles by inclusion of a heteroatom into either the diene or dienophilic components of the cycloaddition.[5] Consideration of the stereoselectivity noted in the all carbon Diels–Alder reaction renders it somewhat surprising, however, that little is known concerning the stereochemical outcome of 1,4 additions involving heterodienophiles. Biehler and Fleury[6] have synthesized a number of 2-azanorbornene derivatives **1** (R = COOEt, COOMe, $CONH_2$; R′ = SO_2PhCH_3-*p*, SO_2CH_3, $COPhNO_2$-*p*, COPh) *via* cycloaddition of sulfonyl or acyl isonitrosomalonoimines with cyclopentadiene. In all cases the evidence, mainly adduced from nmr shift parameters of the 7-syn and 7-anti hydrogens, has indicated kinetically controlled stereospecific formation of 3-exo cyano adducts **1**.



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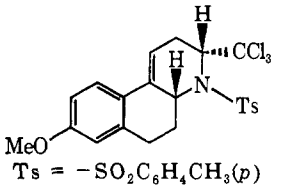

Ts = $-SO_2C_6H_4CH_3(p)$

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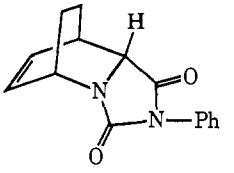

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The reaction of *N*-arylsulfonylimines of chloral with several dienes has recently been utilized in the synthesis of a number of functionally substituted tetrahydropyridines and piperidines.[7] X-Ray study of the adduct **2** has shown the trichloromethyl group to occupy a position trans to the bridge hydrogen.

Cyclohexadiene has been reacted with the imine formed upon acid-catalyzed decomposition of 5-methoxy-3-phenylhydantoin to form an adduct **3** which has been assigned the C-3 endo configuration on the basis of a 6-Hz deshielding of the phenyl group upon hydrogenation of the double bond of **3**.[8]

From analysis of the stereochemistry of imine cyclo-

(1) Presented in part at the 164th National Meeting of the American Chemical Society, New York, N. Y., Aug 1972.

(2) For general discussions of the Diels–Alder reaction, see (a) A. Wasserman, "Diels-Alder Reactions," Elsevier, Amsterdam, 1965; (b) J. Sauer, *Angew. Chem., Int. Ed. Engl.*, **5**, 211 (1966); **6**, 16 (1967); (c) A. S. Onishchenko, Diene Synthesis, D. Davey, New York, N. Y., 1964.

(3) For a discussion of the stereochemistry of the Diels–Alder reaction, see J. Martin and R. Hill, *Chem. Rev.*, **61**, 537 (1961).

(4) See, for example: (a) K. Alder and Gunzl, *Chem. Ber.*, **93**, 809 (1960); (b) H. Stockman, *J. Org. Chem.*, **26**, 2025 (1961); (c) J. A. Berson, Z. Hamlet, and W. A. Mueller, *J. Amer. Chem. Soc.*, **84**, 297 (1962); (d) Y. Kobuke, T. Sugimoto, J. Furukawa, and T. Fueno, *ibid.*, **94**, 3633 (1972).

(5) Reactions of dienes with dienophiles containing heteroatoms have been reviewed by (a) S. Needleman and M. C. Kuo, *Chem. Rev.*, **62**, 405 (1962); (b) Y. Arbuzov, *Russ. Chem. Rev.*, **33**, 407 (1964); (c) Y. Titov, *ibid.*, **31**, 267 (1962).

(6) J. Biehler and J. Fleury, *J. Heterocycl. Chem.*, **8**, 431 (1971).

(7) P. Rijsenbrij, R. Loven, J. Wijnberg, W. Speckamp, and H. Huisman, *Tetrahedron Lett.*, 1425 (1972).

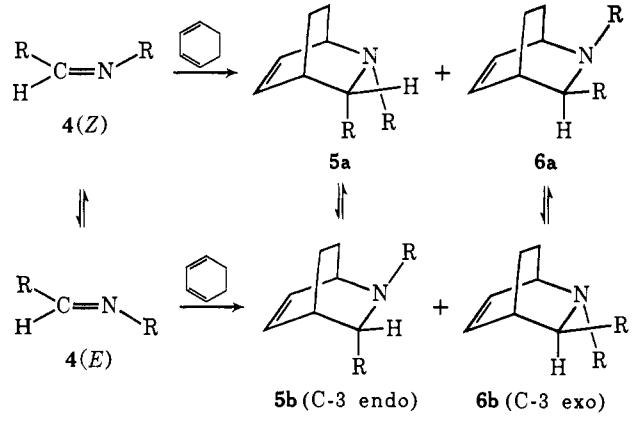
(8) (a) D. Ben-Ishai and E. Goldstein, *Tetrahedron*, **27**, 3119 (1971). (b) E. Goldstein and D. Ben-Ishai, *Tetrahedron Lett.*, 2631 (1969). (c) We have obtained **3** as a single stereoisomer in which the C-3 proton does not exhibit long-range W-plan coupling.[9] This proton is likely exo and the C-3 substituent is thus endo oriented.

(9) (a) A. Rassat, C. W. Jefford, J. M. Lehn, and B. Waegell, *Tetrahedron Lett.*, 233 (1964); (b) M. Barfield and B. Chakrabarti, *Chem. Rev.*, **69**, 757 (1969); (c) S. Sternhell, *Rev. Pure Appl. Chem.*, **14**, 15 (1964); (d) A. Rassat and P. Rey, *Tetrahedron*, **28**, 741 (1972).

additions, it is obvious that nitrogen inversion introduces a number of parameters not found in the all-carbon Diels–Alder reaction. Firstly, the principle of cis addition cannot be confirmed by inspection of the configurations of starting imine and product bicyclic amine since the nitrogen lone pair may be free to invert in both instances. Secondly, since in considering the imine component only the configuration at the imine carbon becomes configurationally fixed in product, it is difficult in many instances to determine if addition to dienes has occurred *via* the *Z* or *E* form of the imine. In the absence of this knowledge, it is difficult to apply the Alder endo-rule to predict the preferred stereochemistry at carbon in imine cycloadditions. Thirdly, the polarity of the imine bond may increase the likelihood of stepwise rather than concerted cycloadditions.

Certain stereochemical predictions for heterodienophilic cycloadditions might be made, however, by making reasonable assumptions based on the all-carbon Diels–Alder reaction. As applied to imines the principle of cis addition implies that in a Diels–Alder transition state *Z*(*E*) imine initially leads to product with the same *Z*(*E*) orientation of substituents. It can be further assumed that the steric course of kinetically controlled dienophilic imine cycloadditions is governed by steric and electronic factors qualitatively similar to those found for dienophilic olefins. The cis-endo principle can then be applied in the following manner as shown in Scheme I. For a cycloaddition of

Scheme I

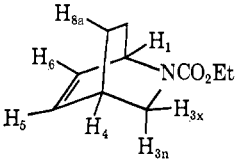


a hypothetical imine **4** with cyclohexadiene, cycloaddition *via* either the *Z* form, *E* form, or *via* both forms concurrently might occur. For cycloaddition *via* the *Z* form, the cis-endo rule predicts predominant kinetic formation of product **5** with the endo configuration at C-3, and only minor amounts of exo C-3 isomer **6**. However, if cycloaddition *via* the *E* form of **4** occurs, a competition between the substituent on imine carbon and the substituent on imine nitrogen for the endo position can result in a continuum of possibilities at C-3 from total endo adduct **5** to total exo adduct **6**.

If adducts **1–3** are formed *via* cyclic transition states the stereospecific introduction of the bulkier substituent of the imine carbon into the endo position indicates one or a combination of two possibilities: (1) addition occurs endo *via* the *Z* configuration of the imine, or (2) addition occurs from the *E* configuration of an imine in which the bulkier substituent on carbon is favored endo over the substituent on nitrogen. A complete analysis of the additions to form **1** and **2** would be speculative at this time since it is possible that small amounts of minor exo isomer were undetected due to the nmr method[6] of analysis of **1** or by isomeric enrichment of **2** before X-ray structure determination.[7] Although a rigorous stereochemical assignment[8] to **3** has not been made, the adduct **3** was obviously formed from an imine locked into the *Z* configuration as part of a ring.

With this historical background in mind, we decided to investigate the stereochemistry of 3-substituted-*N*-carbethoxy-5,6-dehydroisoquinuclidine[10] formation *via* the acid-catalyzed reaction of iminourethanes with cyclohexa-1,3-diene. The rigid nature of the azabicyclic system promised to be most suitable for stereochemical determinations because of the relative ease of determining nmr shift parameters.[11] Further, the ease of formation of 5,6-dehydroisoquinuclidines by this route indicated that our results could be of some synthetic utility.[12]

Assignment of Stereochemistry by Nmr Methods. In order to determine if nmr coupling parameters would enable a distinction to be made between the 3-exo and 3-endo positions of a 5,6-dehydroisoquinuclidine, the nmr spectrum of *N*-carbethoxy-2-azabicyclo[2.2.2]oct-5-ene (**7**) was analyzed. Of special interest to the



7

present study were the nmr ($CDCl_3$) resonances (Figure 1) for H_{3x} at δ 3.26 (sharp doublet of doublets, $J_{3n,3x}$ = 10.5 Hz, $J_{3x,4}$ = 2.2 Hz) and for H_{3n} at δ 3.04 (doublet of triplets, $J_{3n,8a} = J_{3n,4}$ = 2.2 Hz). A long-range W-plan[9] coupling between H_{8a} and H_{3n} was confirmed by irradiation of H_{8a} (δ 1.15) whereupon H_{3n} collapsed to a doublet of doublets. The olefinic region of **7** centered at δ 6.32 consisted of a narrow (11-Hz peak width at half-height) pattern for H_5 and H_6. The similar environment for the olefinic hydrogens indicating a lack of unequal anisotropic shift contributions to these hydrogens is consistent with the carbethoxyl in other than an endo configuration.[13]

To apply the W-plan coupling phenomena to stereochemical determination of a 3-substituted 5,6-dehydroisoquinuclidine an exo–endo mixture of 3-acetyl-*N*-carbethoxy-2-azabicyclo[2.2.2]oct-5-ene (**8a,b**) was synthesized.[10b] The major *exo*-acetyl isomer **8a** was identified by the nmr ($CDCl_3$) resonance for H_{3n} at δ 3.83 (quartet, $J_{3n,4}$ = 2.8 Hz, $J_{8a,3n}$ = 1.5 Hz). The couplings were confirmed by irradiation at H_4 (δ 2.96) which col-

(10) (a) M. P. Quan, T. K. B. Karns, and L. D. Quin, *Chem. Ind. (London)*, 1553 (1964); (b) H. Harter and S. Liisberg, *Acta Chem. Scand.*, 22, 2685 (1968); (c) M. P. Cava and C. Wilkens, *Chem. Ind. (London)*, 1422 (1964); (d) M. Cava, C. Wilkens, D. Dalton, and K. Bessho, *J. Org. Chem.*, 30, 3772 (1965); (e) for a survey of reactions of *N*-ethoxycarbonylimines, see H. E. Zaug, *Synthesis*, 2, 64 (1970).

(11) G. Krow, E. Michener, and K. Ramey, *Tetrahedron Lett.*, 3653 (1971).

(12) G. Krow, R. Rodebaugh, M. Grippi, and R. Carmosin, *Synthetic Commun.*, 2, 211 (1972).

(13) (a) P. Laszlo and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **86**, 1171 (1964); (b) K. Tori, Y. Takano, and K. Kitahonoki, *Chem. Ber.*, 97, 2798 (1964). Both upfield and downfield shifts of olefinic proton resonances have been observed in substituted norbornenes and bicyclo[2.2.2]octene derivatives.

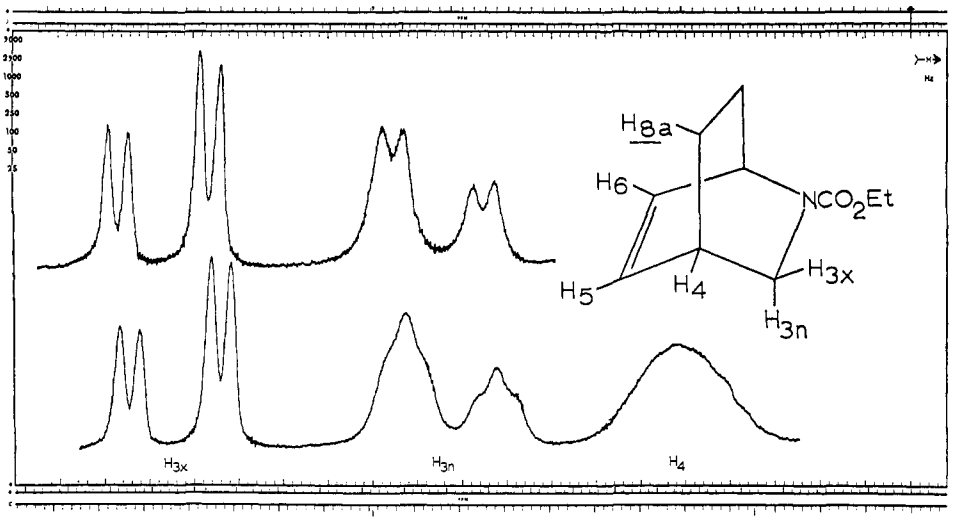
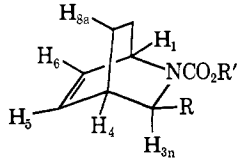
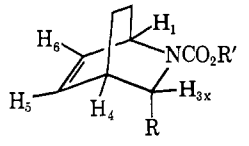


Figure 1. Compound **7** ($CDCl_3$): lower, doublet of triplet pattern for H_{3n}; upper, irradiation of H_{8a} (δ 1.15) collapses H_{3n} to a doublet of doublets.



8a, R = COMe; R' = Et
9a, R = Ph; R' = Me



8b, R = COMe; R' = Et
9b, R = Ph; R' = Me

lapsed the major 2.8-Hz coupling and irradiation at H_8 (δ 1.25) which collapsed the minor 1.5-Hz interaction. The long-range W-plan coupling $J_{8a,3n}$ and the narrow olefinic absorption for H_5–H_6 at δ 6.44 (peak width at half-height = 11 Hz) are in agreement with assignment of **8a** as the *exo*-acetyl isomer.

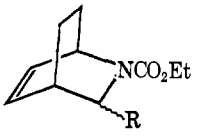
The minor *endo*-acetyl isomer **8b** showed separate olefin absorptions for H_6 at δ 6.54 and H_5 at δ 6.20, consistent with shielding of H_5 by an *endo*-acetyl group.[13] The signal for proton H_{3x} at δ 4.01 (doublet, $J_{3x,4}$ = 2.0 Hz) overlapped slightly with the ethoxyl methylene in $CDCl_3$, but could be observed in CCl_4 at δ 3.86. Irradiation at H_4 collapsed the H_{3x} resonance to a singlet. The 18-Hz upfield position of the resonance for H_{3x} in the endo isomer **8b** relative to H_{3n} in the exo isomer **8a** is consistent with the expected shielding of the endo proton by the neighboring π bond.[13] Integration of the olefinic region permitted determination of the exo–endo ratio as 67:33 in favor of the exo isomer **8a**.

An exo–endo mixture of 3-phenyl-*N*-carbomethoxy-2-azabicyclo[2.2.2]-oct-5-ene (**9a,b**) was synthesized from benzalbis(methyl carbamate) and cyclohexa-1,3-diene. Nmr (acetone-d_6) of the major *exo*-phenyl isomer **9a** showed a narrow multiplet olefinic region for H_5 and H_6 centered at δ 6.50. Proton H_{3n} at δ 4.38 (quartet, $J_{3n,4}$ = 2.5 Hz, $J_{8a,3n}$ = 1.2 Hz) showed long-range W-plan coupling to H_{8a} characteristic of the 3-endo proton. Irradiation of H_4 and H_{8a} (δ 0.92) confirmed the assigned couplings.

The minor endo isomer **9b** showed separate olefinic absorptions for H_6 at δ 6.56 and H_5 at δ 5.88 consistent with shielding of H_5 by the endo phenyl. Proton H_{3x} at δ 4.70 (doublet $J_{3x,4}$ = 1.7 Hz), which did not show long-range W-plan coupling as found in the *exo*-phenyl isomer, was decoupled to a singlet by irradiation of H_4 (δ 2.90). The ratio of **9a**:**9b** was shown to be 80:20 in favor of the *exo*-phenyl isomer **9a** by integration of the two olefinic regions.[14]

Reaction Parameter Effects on Stereoisomer Ratios. The observation of long-range W-plan coupling and an upfield position for 3-endo hydrogens in 3-*exo*-phenyl-5,6-dehydroisoquinuclidine (**9a**) and of the complementary upfield shift of the H_5 olefinic proton in the 3-*endo*-phenyl-5,6-dehydroisoquinuclidine (**9b**) has facilitated determinations of stereoisomer ratios for a number of aryl-5,6-dehydroisoquinuclidines. In Table I the results of a probe of reaction stereoselectivity as a function of aryl substitution for a number of aryl iminourethanes are indicated. Table II shows the stereoselectivity obtained upon variation of carbamate substituents. In Table III the effects of solvent and choice of acid catalyst on the stereoselectivity of 3-phenyl-5,6-dehydroisoquinuclidine (**14**) formation are presented.

Table I. Stereochemical Preferences in the Synthesis of 3-Substituted-*N*-carbethoxy-2-azabicyclo[2.2.2]oct-5-enes[a]



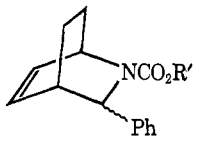
Compd	R	Exo adduct (%)
8	$COCH_3$	67
14	Ph	80
10	Ph-*p*-NO_2	80
11	Ph-*p*-CH_3	85
12	Ph-*o*-CH_3	83
13	Ph-3,4-$(OCH_3)_2$	79

[a] Reactions were run in benzene using boron trifluoride as catalyst.

Confirmation of Kinetic Origin of Stereoisomer Ratios. Before analyzing the data in Tables I–III, it was first

(14) Details of the spectral analysis have been reported in G. Krow and R. Rodebaugh, *Org. Magn. Resonance*, 5, 73 (1973).

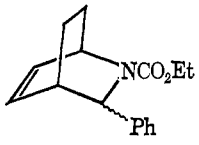
Table II. Stereochemical Preferences in the Synthesis of 3-Phenyl-*N*-substituted-2-azabicyclo[2.2.2]oct-5-ene Carbamates[a]



Compd	R′	Exo adduct (%)
9	CH_3	82
14	CH_2CH_3	80
15	CH_2Ph	83
16	Ph	69

[a] Reactions were run in benzene using boron trifluoride as catalyst.

Table III. Solvent and Catalyst Influence on Stereochemical Preferences in the Synthesis of 3-Phenyl-*N*-carbethoxy-2-azabicyclo[2.2.2]oct-5-ene (**14**)



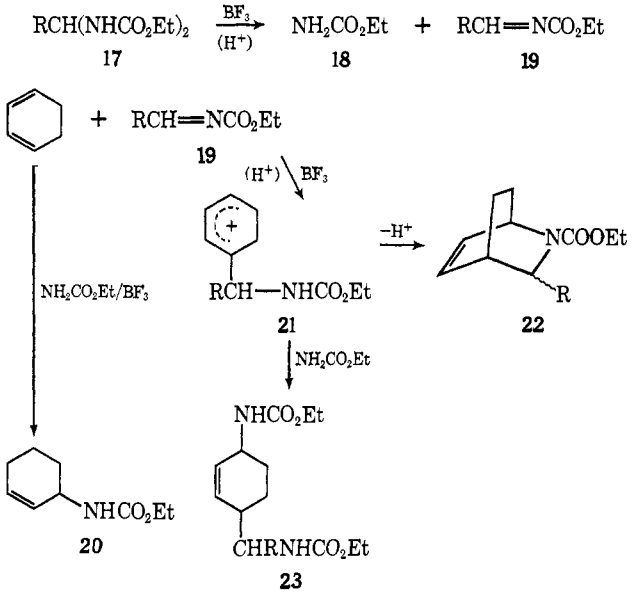
Solvent	Catalyst	Exo adduct (%)
$CHCl_3$	BF_3	87
CCl_4	BF_3	86
CH_2Cl_2	BF_3	91
C_6H_6	BF_3	80
C_6H_6	$BF_3.CuBr_2$	81
C_6H_6	H_2SO_4	84
C_6H_6	$AlCl_3$	74
C_6H_6	$SnCl_4$	73

established that under the reaction conditions neither was the formation of 3-substituted-5,6-dehydroisoquinuclidines reversible nor were the adducts epimerized at C-3. To do this the mixture of 3-acetyl isomers **8a** and **8b** which consisted of 67% *exo*-**8a** was isomerized. Sodium hydroxide–methanol or sodium hydride–tetrahydrofuran treatment followed by quenching in water yielded a new mixture containing only 38% of *exo*-**8b**. When the 67 and the 38% *exo*-phenyl mixtures of **8b** were separately refluxed overnight with an excess of 1 equiv of boron trifluoride etherate in benzene neither isomeric ratio was affected. Since the original 67% exo mixture was not regenerated from the 38% exo mixture, the exo–endo product ratio **8a**:**8b** does not result from equilibration of the acetyl group following cycloaddition, nor is the cycloaddition reversible under the original reaction conditions. The product ratios derived from the reaction of iminourethanes are subject to kinetic control and can be explained by considering transition-state interactions between imine substituents and diene.

Confrontation of Possible Mechanisms. The principal questions involved in describing the mechanism for the 1,4 addition of iminourethanes and 1,3-cyclohexadiene are (1) the nature of the imine reactive species, (2) the transition-state orientation of imine and diene, and (3) the energy profile involved in product formation. While it is not possible to determine the exact mechanism with certainty at this time, a reaction sequence in agreement with experimental observations can be proposed.

Evidence that product formation likely involves a stepwise process in which diene first adds to the carbon of an acid complexed iminourethane includes the ability of protonated iminourethanes to effect aromatic substitution of aryl ethers under the acidic reaction conditions[15a] and the isolation of side products derived from cationic intermediates[15b] in a study of products from the reaction of glyoxal bisurethane with cyclohexa-1,3-diene. As shown in Scheme II, in the presence of

Scheme II



boron trifluoride bisurethane **17** is in equilibrium with urethane **18** and iminourethane **19**. Under the acid conditions, 20–30% of the cyclohexadiene becomes protonated and reacts with urethane to form *N*-carbethoxycyclohexen-2-ylamine (**20**). The diene also can be attacked by protonated iminourethane to form a cation, **21**.[15] Cation **21** upon intramolecular collapse forms azabicyclic product **22**, isolated by distillation, and upon attack by urethane leads to **23**, isolated by silica gel chromatography. Attack of **23** on cation **21** leads to an incompletely characterized oil of *m/e* 362.

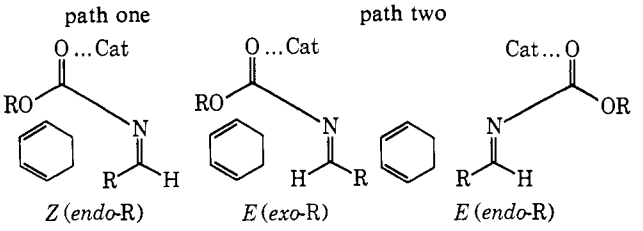
In order to explain reaction stereochemistry, a number of possible transition-state orientations for acid-complexed iminourethane **19** and diene might be considered.

Path One. A cyclic transition state might involve *cisoid*- or *transoid*-(*Z*)-iminourethane.[16] This pathway is not likely here since both bulky substituents should prefer the sterically favored endo position.[8c] Tables I–III indicate preferential formation of C-3 *exo*-phenyl adducts.

Path Two. A cyclic transition state may involve (*E*)-iminourethanes. This mechanism would result in a competition for the endo position between the substituent on imine carbon and the Lewis acid com-

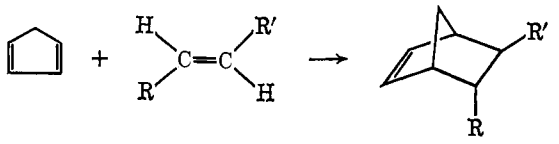
(15) Products derived from cations of *N*-ethoxycarbonylimines have also been obtained from anthracene, aryl ethers, and bicyclohepta-[2.2.1]diene. See (a) G. Krow, H. Pannella, and W. Figures, *J. Chem. Eng. Data*, 17, 116 (1972); (b) T. Sasaki, S. Eguchi, M. Sugimoto, and F. Hibi, *J. Org. Chem.*, 37, 2317 (1972).

(16) J. Jurczak and A. Zamojski, *Tetrahedron*, 28, 1505 (1972). In principle, we might consider conformers of iminocarbamate due to rotation about bonds other than the C–N single bond. An assumption that the cisoid conformation is of major importance has recently been made by the above authors for glyoxylic acid esters.



plexed urethane,[17] arbitrarily shown in the transoid conformation. In order for this to be the preferred pathway to product, several apparent conflicts must be resolved. Firstly, substituent preferences for reaction of cyclopentadiene with derivatives of *trans*-cinnamic acid, shown in Table IV, indicate aryl to be a better

Table IV. Reaction of Stereoselectivity in the Dieneophiles with Cyclopentadiene[a,b]

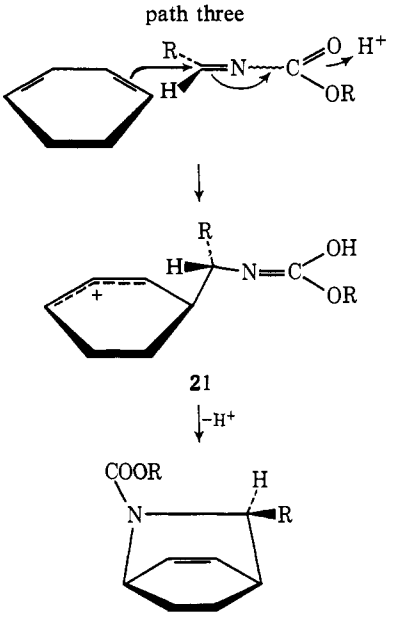


R	R′	% exo R
Ph	CH_3OCO	44[c]
p-NO_2Ph	CH_3OCO	28
Ph	HOCO	43
p-NO_2Ph	HOCO	30
p-CH_3OPh	HOCO	47
p-ClPh	HOCO	40
Ph	H_2NCO	34
p-NO_2Ph	H_2NCO	25
CH_3CO	H	19[d,f]
CH_3OCO	H	24[e,f]

[a] The data taken from Table VIII, ref 3, are kinetically derived. [b] Product ratios have been chosen using the mildest reaction conditions reported. Temperature effects on product ratios have been reported in a number of cases.[3] [c] Note, however, for the 1,1-disubstituted olefin, 2-phenylmethylacrylic acid, 60% of the *exo*-phenyl isomer is formed (ref 3, Table VIIIA). [d] J. Müller and J. Fleury, *Bull. Soc. Chim. Fr.*, 738 (1970). [e] A. C. Cope, E. Ciganek, and N. A. LeBel, *J. Amer. Chem. Soc.*, **81**, 2799 (1959). [f] W. C. Herndon and L. H. Hall, *Tetrahedron Lett.*, 3094 (1967). Extrapolation of results obtained using monosubstituted olefins to predictions of preferences for *trans* disubstituted olefins is hazardous since the transition state for endo addition in the former case most likely has the planes of the diene and olefin skewed relative to one another, while in the latter case the planes may be relatively parallel. The ratios obtained with monosubstituted olefins are here used to indicate in a qualitative way, however, substituent preferences for the endo position.

endo director than carboxylic acid derivatives. Similar stereoselectivity might be expected for reactions with cyclohexa-1,3-diene;[2c] however, for the reaction of iminourethanes, the reversal of substituent preferences might be the result of an attractive interaction between the diene and the positive charge of an endo oriented Lewis acid complexed carbonyl. Secondly, it would be expected that increasing the steric bulk of the Lewis acid might increase the tendency for the bulky, charged urethane to occupy the less hindered endo position[3,18] and thus increase the amount of *exo*-phenyl isomer (Table III). However, increasing the steric bulk of the Lewis acid results in a slight decrease of the percentage of *exo*-phenyl isomer. Thirdly, increase in the steric size of the carbamate substituent should also increase the preference of this group for the endo position and result in increasing relative amounts of *exo*-phenyl isomer.[3] The data of Table II indicate a decrease in the percentage of *exo*-phenyl isomer with increasing size of the carbamate substituent. It can be argued, however, that steric requirements of the carbamate substituents and of the Lewis acids, which are not directly bonded to the atoms of the imine bond, are negligible in the transition state. The small differences in stereoisomer ratios may not be significant considering the presence of competing pathways.

Path Three. Lewis acid complexed iminourethane



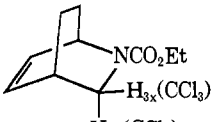
of either *Z* or *E* configuration might approach the diene system so that the larger substituent (phenyl or acetyl) on imine carbon is oriented over the diene and away from the hydrogens of the diene bridge. The nitrogen end of the imine will then be oriented away from the diene ring. This implies only slight interaction between the diene and acid complexed urethane functionality, in agreement with the slight changes observed upon changes in catalyst (Table III). Due to the presence of a charged imine it can be expected that electronic interaction of the diene with the aryl group will be of little importance in determining stereochemical preferences, and indeed the data of Table I indicate roughly 80% exo aryl isomers are obtained with both electron-withdrawing and electron-donating aryl substituents. Electrophilic attack by the diene upon the positively charged carbon can generate an intermediate cation which then either reacts with external urethane or collapses *via* an intramolecular ring closure. The intramolecular ring closure requires a bond rotation in which the substituent originally oriented over the diene in the formation of the carbon–carbon bond leading to the allylic cation **21** will occupy an exo position in the bicyclic product **22**.

Although the stepwise carbonium ion mechanism

(17) A. Fratiello and R. Schuster, *J. Org. Chem.*, 37, 2237 (1972). It can be noted that Lewis acid coordination with the carbonyl oxygen maximizes opportunity for resonance stabilization of the positive charge. Coordination at imine nitrogen by a number of sterically different Lewis acids might be expected to have a greater influence on reaction stereoselectivity than has been observed (Table III).

(18) E. F. Lutz and G. M. Bailey, *J. Amer. Chem. Soc.*, **86**, 3389 (1964). Marked increases in regioselectivity have been attributed to steric bulk of catalyst in the cycloaddition of 2-methylbutadiene and methyl vinyl ketone.

of path three apparently is in best agreement with the formation of 3-exo substitution products **22** and with product studies, path two involving some version of a cyclic transition state utilizing an (*E*) iminourethane cannot be ruled out by the data. In fact, on the basis of additional evidence, path two seems to be the likely mechanism. In a study of the boron trifluoride catalyzed cycloaddition of cyclohexa-1,3-diene with the (*Z*) imine formed from 5-methoxy-3-phenylhydantoin stereospecific formation of endo product occurred.[8c] In agreement with the cyclic process of path one, the bulkier substituents of the (*Z*) imine prefer the endo position in the transition state for cycloaddition. If path three had obtained, the stepwise process should have led to exo adduct **3**. In a second set of experiments, *N*-carbethoxytrichloromethylimine[19] was synthesized and reacted with cyclohexa-1,3-diene. Although there was negligible reaction after 1 week in refluxing benzene, addition of boron trifluoride etherate to the solution resulted in disappearance of starting imine after 24 hr to give a 3-trichloromethyl-*N*-carbethoxy-5,6-dehydroisoquinuclidine (**24**) which con-



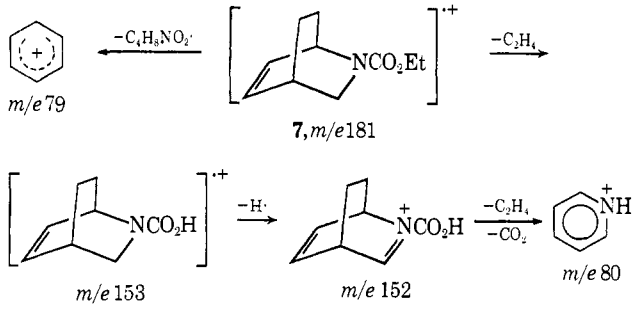
24a, *exo*-CCl_3
b, *endo*-CCl_3

tained 80% of the *endo*-trichloromethyl isomer.[20] The formation of endo product is best explained by a major contribution from path two in which the bulky trichloromethyl prefers the endo orientation. Path three should have led to a preference for *exo*-trichloromethyl adduct.

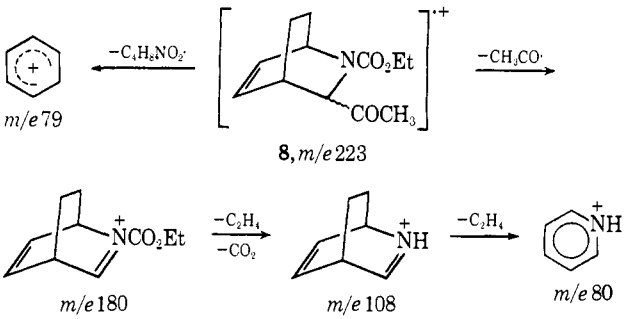
In conclusion, the stereochemical course of the present cycloadditions is likely explained as proceeding *via* stepwise cyclic transition states involving acid complexed (*E*)-iminourethanes. However, predictions based on such a model must be tempered by the recognition that allylic cations often may play an important role in determining product structure and stereochemistry.

Mass Spectra. Inspection of the principal ions in the high resolution mass spectra of 3-substituted-*N*-carbethoxy-5,6-dehydroisoquinuclidines **7**, **8**, and **14** (Schemes III–V) indicates the ion at *m/e* 79 to be a

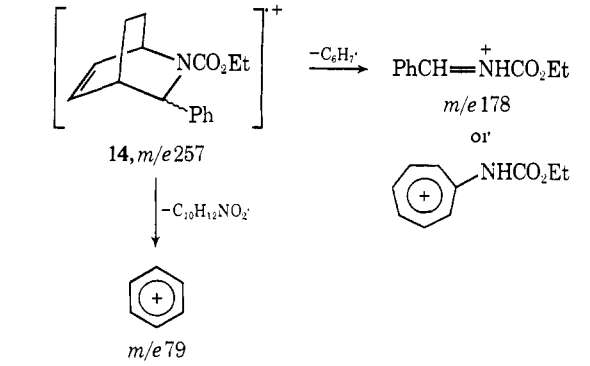
Scheme III



Scheme IV



Scheme V



common, although not dominant, feature in the fragmentation patterns. This ion is likely the cyclohexadienyl cation which can be visualized as arising from M^+ by ring opening between C-1 and nitrogen, abstraction of a hydrogen atom from C-7 by nitrogen or oxygen, and elimination of an RCHNHCOOEt radical. A marked influence of the 3-substituent on the fragmentation pattern was revealed. For **7** where R = H (Scheme III), the principal mode of fragmentation involves loss of ethylene from the urethane to form *m/e* 153 (100), followed by loss of a hydrogen atom to afford an ion at *m/e* 152 (50). Loss of ethylene from this ion in a reverse Diels–Alder reaction and loss of CO_2 give the C_5H_6N ion at *m/e* 80 (85). The fragmentation pattern for the acetyl isomer mixture **8** (Scheme IV) is characterized by loss of acetyl from the molecular ion to give an ion at *m/e* 180 (89). This ion loses ethylene from the urethane, CO_2, and ethylene in a reverse Diels–Alder reaction to again afford C_5H_6N at *m/e* 80 (100). The 3-phenyl isomer mixture **14** (Scheme V) is characterized by ring opening at nitrogen followed by loss of a C_6H_7 radical to give the parent ion at *m/e* 178 (100), which can undergo a number of additional transformations. The C_6H_8 ion at *m/e* 80 (41) might arise *via* a reverse Diels–Alder reaction, a process not observed for **7** and **8**. Similar behavior was found for 3-phenyl-*N*-carbobenzoxy-5,6-dehydroisoquinuclidine (**15**) (see Experimental Section). The remaining important ions for these compounds are indicated in the Experimental Section.

Although several derivative ions of 3-substituted-*N*-carbethoxy-5,6-dehydroisoquinuclidines formed in the mass spectrometer showed a tendency to eliminate neutral fragments *via* reverse Diels–Alder reactions, unlike a number of reported bicyclo[2.2.2]octenes,[21] the molecular ion is not characterized by this process because of competing pathways. It can be mentioned that

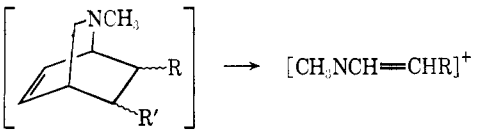
(19) H. Ulrich, B. Tucker, and A. Sayigh, *J. Org. Chem.*, **33**, 2887 (1968).

(20) Thermal and acid-catalyzed reactions of halomethylimines with dienes are to be reported elsewhere. Isomer ratios **24a**:**24b** were determined from the nmr resonances (benzene-d_6) for H_{3x} (δ 4.76, d, J = 3 Hz) and H_{3n} (δ 4.42, q, J = 3 Hz, 1.3 Hz).

(21) C. M. Cimarusti and J. Wolinsky, *J. Org. Chem.*, **36**, 1871 (1971).

a fragmentation pattern involving generation of an ion having a straight chain C-7 to C-1 to N linkage as reported[22] for 7- and 8-carbomethoxy-*N*-methyl-5,6-dehydroisoquinuclidines (**25** and **26**) was not observed (Scheme VI).

Scheme VI



25, R = CO_2CH_3; R' = H
26, R = H, R' = CO_2CH_3

Experimental Section

The nmr spectra were determined on a Varian Associates XL-100-15 spectrometer using tetramethylsilane as an internal standard. Solutions of 5–10% solute in CCl_4, $CDCl_3$, or acetone-d_6, all containing 1% tetramethylsilane, were used for nmr measurements. Chemical shift values were where necessary obtained with the aid of decoupling experiments. Vpc was performed on a Varian A-90 gas chromatograph using a 5 ft × 0.25 in. 10% XF-1150 on Chromosorb G (60–80 mesh), a 20 ft × 3/8 in. 15% SE-30 on Chromosorb W (30–60 mesh), or a 5 ft × 0.25 in. 20% DC-550 on Chromosorb W (40–50 mesh). High resolution mass spectra were obtained at Battelle Memorial Institute using an MS-902 mass spectrometer at 500 eV.[23]

Exo–endo isomer ratios at C-3 were determined by nmr examination of the olefinic region of distilled products. Fractionation of mixtures did not occur on isolation since no significant differences in exo–endo isomer ratios were observed when crude reaction mixtures were prepped and analyzed directly. The integrated area for H_5 of the minor isomer was subtracted from the area for H_5–H_6 of the major isomer + H_6 of the minor isomer. One-half of the remainder represents H_5 of the major exo isomer and this can be compared to H_5 of the minor endo isomer. In certain instances the exo–endo ratios could be checked by comparison of H_3 for the exo isomer with H_5 of the endo isomer. Reported isomer ratios obtained by repeated integration are accurate ±2%.

The following bisurethanes have been previously reported: methylene,-[10d] benzaldehyde-,[10d] *o*-tolualdehyde[10b], and methylglyoxal bisurethane.[10b] Also, dicarbobenzoxybenzylidenediamine[24] has been described. The following 3-substituted-*N*-carbethoxy-5,6-dehydroisoquinuclidines have been previously reported: hydrogen,[10d] phenyl,[10d] acetyl,[10b] and *o*-tolyl.[10b]

General Procedure for the Synthesis of Bisurethanes.[10b] Urethane (1 mol), aldehyde (0.5 mol), and boron trifluoride etherate (5 ml) in benzene (500 ml) were refluxed with a water separator until the water was removed. Upon cooling the mixture, the bisurethanes solidified.

General Procedure for the Synthesis of 3-Substituted-*N*-carbalkoxy-2-azabicyclo[2.2.2]oct-5-enes. A solution of cyclohexa-1,3-diene (12.5 g, 0.125 mol) in 100 ml of dry benzene was added dropwise over 30 min to a stirred refluxing solution of alkylidene biscarbamate (0.125 mol) and 5 g of boron trifluoride etherate in 200 ml of dry benzene, chloroform, methylene chloride, or carbon tetrachloride. After 2–24 hr reflux the reaction was cooled, washed with water, aqueous sodium carbonate, dilute HCl, and water, and dried over magnesium sulfate. If large amounts of unreacted bisurethane appeared to be present, the oil was diluted ten to one with *n*-heptane, and solid material was filtered. Solvent was removed *in vacuo* and the product was isolated by distillation, column chromatography, or vpc.

***N*-Carbethoxy-2-azabicyclo[2.2.2]oct-5-ene (7).** Nmr ($CDCl_3$) analysis of the previously reported[10d] but incompletely characterized 5,6-dehydroisoquinuclidine **7** indicated absorptions at δ 6.32 (11-Hz peak width at half-height, H_5, H_6), 5.67 (broad, H_1), 4.06 (CH_2O), 3.26 (dd, J = 10.5, 2.2 Hz, H_{3x}), 3.04 (dt, J = 10.5, 2.2, 2.2 Hz, H_{3n}), 2.70 (broad, H_4), 1.20 (CH_3), 1.15 (complex, H_{8a}), 2.0–1.15 (broad); mass spectrum (500 eV) *m/e* (rel intensity) 181 (29), 153 (100), 152 (50), 124 (67), 108 (18), 93 (34), 81 (14), 80 (85, C_5H_6N), 79 (18, C_6H_7).

3-Acetyl-*N*-carbethoxy-2-azabicyclo[2.2.2]oct-5-ene (8). Nmr (CCl_4) analysis of the previously synthesized but incompletely characterized[10b] 3-acetyl isomer indicated for the 3-*exo*-acetyl isomer **8a** δ 6.44 (multiplet, 11-Hz peak width at half-height, H_5,H_6) 4.74 (H_1), 4.04 (OCH_2), 3.68 (q, J = 2.8, 1.5 Hz, H_3), 2.92 (H_4), 2.10 (CH_3CO), 1.25 (H_{8a}), 2.0–1.1 (broad). For the 3-*endo*-acetyl isomer **8b** resonances appeared at δ 6.54 (H_6), 6.20 (H_5), 4.74 (H_1), 4.04 (OCH_2), 3.86 (H_3), 3.02 (H_4), 1.88 (CH_3CO), 2.0–1.1 (broad). Nmr integration of the olefinic regions enabled a determination of 67% preference for the 3-*exo*-acetyl isomer **8a**. Mass spectrum of the isomeric mixture (500 eV) showed *m/e* (rel intensity) 223 (0), molecular ion, 189 (89), 152 (78), 135 (11), 108 (15), 93 (12), 81 (6), 80 (100), C_5H_6N), 79 (33).

An analysis of a crude reaction mixture (0.1 mol of each reactant) by silica gel chromatography indicated in addition to **8** and *N*-carbethoxycyclohexen-2-yl-1-amine (**20**),[10b] which eluted with 50% ether–heptane, a later fraction eluted with ether which afforded 2.1 g (8%) of a viscous oil containing a small amount of unreacted acetyl bisurethane and 1-[*N*-carbethoxy-4-amino-2-cyclohexenyl]-1-*N*-carbethoxyaminoacetone: nmr ($CDCl_3$) δ 5.9–5.4, 4.4–3.9, 2.65–2.0, 2.20 (CH_3CO), 2.0–1.0; mass spectrum (500 eV) *m/e* (rel intensity) 313 (15), 224 (28), 180 (100), 152 (67), 144 (35), 135 (63), 108 (18), 80 (40), 43 (53).

Isomerization of the Exo–Endo Mixture 3-Acetyl-*N*-carbethoxy-2-azabicyclo[2.2.2]oct-5-ene (8). The mixture of 3-acetyl isomers **8** (500 mg) which consisted of 67% *exo*-acetyl isomer was refluxed for 5 hr in methanol (50 ml) with two sodium hydroxide pellets. Upon cooling the mixture, dilute HCl was added to neutrality. Ether extraction afforded recovered adduct (370 mg) which was 63% *endo*-acetyl isomer.

When the 3-acetyl isomer (500 mg) was stirred in tetrahydrofuran for 30 min with 1 equiv of sodium hydride (57% in mineral oil), and recovered by adding dropwise to stirred ice-cold dilute HCl, the isomeric mixture was enriched with the *endo*-acetyl isomer (62% endo).

The mixture of 3-acetyl isomers (370 mg) containing 63% of the endo-acetyl isomer was refluxed overnight in dry benzene containing boron trifluoride etherate. No change in the isomeric ratio was observed. The original mixture of 3-acetyl isomers containing 67% of the *exo*-acetyl isomer, which was formed using boron trifluoride etherate in refluxing dry benzene, was unchanged on further treatment.

3-Phenyl-*N*-carbomethoxy-2-azabicyclo[2.2.2]oct-5-ene (9). Reaction of methyl benzalbiscarbamate (**27**) (4.7 g, 0.02 mol) and 1,3-cyclohexadiene (1.5 g, 0.02 mol) afforded upon work-up and distillation 1.1 g (23%) of product: bp 145–148° (0.5 mm), ir (CCl_4) 1695 cm^{-1}, and 0.4 g of methyl benzylcarbamate,[25] identical with a sample prepared from benzylamine and methyl chloroformate. The product was purified by chromatography (5 ft × 0.25 in., 10% XF1150, 60–80 Chromosorb W, 185°). The nmr (acetone-d_6) indicated for the 3-*exo*-phenyl isomer **9a** δ 7.25 (Ph), 6.50 (H_5, H_6), 4.88 (H_1), 4.38 (H_3), 3.44 (OCH_3), 2.74 (H_4), 0.92 (H_{8a}), 2.1–1.2 (multiplets). The 3-*endo*-phenyl isomer **9b** had peaks at δ 7.25 (Ph), 6.56 (H_6), 5.88 (H_5), 4.88 (H_1), 4.70 (H_3), 3.44 (OCH_3), 2.90 (H_4), 2.1–1.2 (multiplets). Nmr integration of the olefinic region indicated 82% of the 3-*exo*-phenyl isomer **9a**.

Anal. Calcd for $C_{15}H_{17}O_2N$: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.97; H, 7.00; N, 5.93.

3-*p*-Nitrophenyl-*N*-carbethoxy-2-azabicyclo[2.2.2]oct-5-ene (10). Reaction of *p*-nitrobenzaldehyde bisurethane (**28**) (6.4 g, 0.02 mol) and cyclohexa-1,3-diene (1.5 g, 0.02 mol) as described above afforded upon work-up 4.35 g (71%) of an oil: bp 155–160° (0.01 mm on bulb to bulb distillation), which was purified by vpc (20 ft × 3/8 in. 15% SE-30, 30–60 Chromosorb W, 260°, flow rate (FR) 120 ml/min, R_T 12 min). Upon chromatography on silica gel with 80% ether–20% heptane as eluent the endo isomer **10b** eluted first although incomplete separation resulted. The nmr ($CDCl_3$) of the *exo*-*p*-nitrophenyl isomer **10a** showed δ 8.18 (d), 7.46 (d) (Ph), 6.54 (H_5,H_6), 4.96 (H_1), 4.68 (H_3), 4.04 (OCH_2), 2.78 (H_4), 2.0–0.8 (envelope). The endo isomer **10b** showed δ 8.18 (d), 7.46 (d) (Ph), 6.44 (H_6), 5.94 (H_5), 4.96 (H_1) 4.82 (H_3), 4.04 (OCH_2), 2.90 (H_4 shoulder), 2.0–0.8 (envelope). Nmr analysis using olefinic absorptions indicated 80% 3-*exo*-*p*-nitrophenyl isomer **10a**.

(22) R. A. Wiley, B. A. Faraj, and A. Jantz, *J. Med. Chem.*, **15**, 374 (1972).

(23) No significant differences between mass spectral results at 500 and 70 eV have been noted.

(24) A. E. Martell and R. M. Herbst, *J. Org. Chem.*, **6**, 878 (1941).

(25) R. Weerman and W. Jongkees, *Recl. Trav. Chim. Pays-Bas*, **25**, 238 (1906).

Anal. Calcd for $C_{15}H_{17}N_2O_4$: C, 63.58; H, 5.96; N, 9.27. Found: C, 63.65; H, 5.96; N, 8.99.

3-*p*-Tolyl-*N*-carbethoxy-2-azabicyclo[2.2.2]oct-5-ene (11). Reaction of *p*-tolualdehyde bisurethane (**29**) (5.6 g, 0.02 mol) and cyclohexa-1,3-diene (1.5 g, 0.02 mol) as described above afforded 3.3 g (61%) of an oil which was purified by vpc (5 ft × 0.25 in. 10% XF-1150 60–80 Chromosorb W, 200°, FR 150 ml/min, R_T 7.5 min). The nmr (acetone-d_6) of the *exo*-*p*-tolyl isomer **11a** indicated δ 7.10 (Ph), 6.49 (H_5,H_6), 4.88 (H_1), 4.31 (H_3), 3.90 (OCH_2), 2.70 (H_4), 2.28 (CH_3), 2.0–0.8 (envelope). The *endo*-*p*-tolyl isomer **11b** showed δ 7.10 (Ph), 6.49 (H_6), 5.90 (H_5), 4.88 (H_1), 4.67 (H_3), 3.90 (OCH_2), 2.86 (H_4 shoulder), 2.28 (CH_3), 2.0–0.8 (envelope). Nmr analysis using olefinic absorptions indicated 85% 3-*exo*-*p*-tolyl isomer **11a**.

Anal. Calcd for $C_{17}H_{21}O_2N$: C, 75.38; H, 7.75; N, 5.17. Found: C, 75.35; H, 7.98; N, 5.41.

3-*o*-Tolyl-*N*-carbethoxy-2-azabicyclo[2.2.2]oct-5-ene (12). Nmr (acetone-d_6) analysis of the known but incompletely characterized[10b] 3-*o*-tolyl isomer indicated for the 3-*exo*-isomer **12a** δ 7.10 (Ph), 6.52 (H_5,H_6), 4.91 (H_1), 4.56 (H_3), 3.91 (OCH_2), 2.72 (H_4), 2.36 (CH_3), 2.0–0.8 (br). The 3-endo **12b** isomer showed δ 7.10 (Ph), 6.52 (H_6), 5.92 (H_5), 4.91 (H_1), 4.86 (H_3), 3.91 (OCH_2), 2.84 (H_4Sh), 2.36 (CH_3), 2.0–0.8 (br). Nmr integration analysis of the olefinic region indicated 83% of the 3-*exo*-*o*-tolyl isomer **12a**.

3-(3,4-Dimethoxyphenyl)-*N*-carbethoxy-2-azabicyclo[2.2.2]oct-5-ene (13). Reaction of 3,4-dimethoxybenzaldehyde bisurethane (**30**) (6.4 g, 0.02 mol) and cyclohexa-1,3-diene (1.5 g, 0.02 mol) afforded 4.05 g (64%) of viscous oil which was purified by vpc (20 ft × 3/8 in. 15% SE-30 30–60 Chromosorb W, 260°, FR 120 ml/min, R_T 11 min). The nmr (acetone-d_6) of the *exo*-3,4-dimethoxyphenyl isomer **13a** indicated δ 6.82 (Ph), 6.48 (H_5, H_6), 4.86 (H_1), 4.52 (H_3), 3.94 (OCH_2), 3.76 (OMe), 2.80 (H_4), 2.0–0.8 (envelope). The *endo*-3,4-dimethoxyphenyl isomer **13b** showed δ 6.82 (Ph), 6.48 (H_6), 5.94 (H_5), 4.86 (H_1), 4.61 (H_3), 3.94 (OCH_2), 3.76 (OMe), 3.72 (OMe), 2.72 (H_4), 2.0–0.8 (envelope). Nmr analysis of the olefinic region indicated 79% 3-*exo*-2,4-dimethoxyphenyl isomer **13a**.

Anal. Calcd for $C_{17}H_{22}NO_4$: C, 68.14; H, 7.26; N, 4.42. Found: C, 67.88; H, 7.27; N, 4.40.

3-Phenyl-*N*-carbethoxy-2-azabicyclo[2.2.2]oct-5-ene (14). Nmr ($DCCl_3$) analysis of the previously synthesized but incompletely characterized[10d] 3-phenyl isomer indicated for the 3-*exo*-phenyl isomer **14a** δ 7.21 (Ph), 6.46 (H_5H_6), 4.92 (H_1), 4.40 (dd, J = 2.5, 1.2 Hz, H_3), 4.00 (OCH_2), 2.66 (H_4), 2.0–0.8 (envelope). Resonances appeared for the 3-*endo*-phenyl isomer **14b**, δ 7.21 and 7.15 (Ph), 6.46 (H_6), 5.90 (H_5), 4.92 (H_1), 4.64 (d, J = 2.5 Hz, H_3), 4.00 (OCH_2), 2.80 (H_4), 2.0–0.8 (br). Nmr analysis of the olefinic region indicated 80% 3-*exo* phenyl isomer **14a**. The mass spectrum (500 eV) of the isomeric mixture showed *m/e* (rel intensity) 257 (18), 178 (100), 152 (35), 106 (30), 80 (22, C_5H_6N), 80 (41, C_6H_8), 79 (23).

Replacement of benzene as solvent resulted in 30–40% yields of **14** with the following exo stereoselectivities: 87% (chloroform), 86% (CCl_4), 91% (CH_2Cl_2). Replacement of BF_3 as catalyst in benzene solution afforded the following yields and stereoselectivities: $AlCl_3$ (5%, 74% exo), H_2SO_4 (10–15%, 84% exo), BF_3–$CuBr_2$ (60%, 81% exo), $SnCl_4$ (30%, 73% exo).

3-Phenyl-*N*-carbobenzoxy-2-azabicyclo[2.2.2]oct-5-ene (15). Reaction of dicarbobenzoxybenzylidenediamine (4.35 g, 0.01 mol) and cyclohexa-1,3-diene (1.50 g, 0.02 mol) as described above afforded 1.8 g (50%) of an oil which was purified by vpc (5 ft × 0.25 in. 20% DC-550 on 45–60 Chromosorb W, 270°, FR 175 ml/min, R_T 14 min). Prepped material could be crystallized from *n*-heptane and had mp 92.5–94°. The exo–endo isomeric ratio was not appreciably affected by recrystallization from *n*-heptane. The nmr (acetone-d_6) of the *exo*-phenyl isomer **15a** indicated δ 7.25, 7.16, 6.79 (Ph), 6.50 (H_5,H_6), 4.96 ($PhCH_2$ and H_1), 4.64 (H_3), 2.72 (H_4), 2.0–0.8 (broad envelope). The *endo*-phenyl isomer **15b** indicated δ 7.25, 7.16, 6.79 (Ph), 6.50 (H_6), 5.90 (H_5), 4.96 ($PhCH_2$ and H_1), 4.75 (H_3), 2.88 (H_4 shoulder), 2.0–0.8 (envelope). Comparison of the integrated areas of H_3 for the exo isomer and H_5 for the endo isomer indicated 83% of the exo isomer **15a**. The mass spectrum (500 eV) of the isomeric mixture showed *m/e* (rel intensity) 320 (2), 319 (1), 291 (3), 240 (27), 228 (7), 196 (5, $C_{14}H_{14}N$), 156 (6, $C_{11}H_{10}N$), 132 (6), 91 (100), 80 (18), 79 (9).

Anal. Calcd for $C_{21}H_{21}NO_2$: C, 79.00; H, 6.58; N, 4.39. Found: C, 79.08; H, 6.86; N, 4.67.

3-Phenyl-*N*-carbophenoxy-2-azabicyclo[2.2.2]oct-5-ene (16). Reaction of phenyl benzalbiscarbamate (**31**) (3.1 g, 0.008 mol) and 1,3-cyclohexadiene (1.5 g, 0.02 mol) as described above afforded after work-up 0.90 g (37%) of an oil which was purified by vpc (5 ft × 0.25 in. 20% DC-550 on 45–60 Chromosorb W, 260°, FR 150 ml/min, R_T 27 min). Prepped material crystallized from 4:1 *n*-heptane–$CHCl_3$ had mp 133–135°. The nmr (acetone-d_6) of the *exo*-phenyl isomer **16a** indicated δ 7.42–6.62 (Ph), 6.54 (H_6, H_5), 4.94 (H_1), 4.60 (H_3), 2.78 (H_4), 2.25–1.12 (envelope). The *endo*-phenyl isomer **16b** showed δ 7.42–6.62 (Ph), 6.54 (H_6), 5.94 (H_5), 4.94 (H_1), 4.84 (H_3), 2.92 (H_4), 0.98 (H_{8a}), 2.25–1.12 (envelope). From the integrated areas of H_1 + H_3 for both isomers and H_5 for the endo isomer, 69% of the exo isomer **16a** was formed initially. Crystallization afforded a mixture containing 58% of the exo isomer **16a**.

Anal. Calcd for $C_{20}H_{19}NO_2$: C, 78.68; H, 6.23; N, 4.59. Found: C, 78.36; H, 6.16; N, 4.72.

Methyl Benzalbiscarbamate (27). Reaction of benzaldehyde (8.9 g, 0.084 mol) and methyl carbamate (12.6 g, 0.017 mol) afforded 15 g (75%) of white solid, mp 174–176° (EtOH), ir (CCl_4) 1705 cm^{-1}.

Anal. Calcd for $C_{11}H_{14}N_2O_4$: C, 55.45; H, 5.92; N, 11.76. Found: C, 55.38; H, 6.05; N, 11.74

***p*-Nitrobenzaldehyde Bisurethane (28).** Reaction of *p*-nitrobenzaldehyde (10 g, 0.067 mol) and urethane (10.6 g, 0.13 mol) afforded 17.8 g (86%) of white solid, mp 206–207° (tetrahydrofuran), ir (CCl_4) 1705 cm^{-1}.

Anal. Calcd for $C_{13}H_{17}O_6N_3$: C, 50.16; H, 5.50; N, 13.50. Found: C, 50.39; H, 5.51; N, 13.51.

***p*-Tolualdehyde Bisurethane (29).** Reaction of *p*-tolualdehyde (25 g, 0.21 mol) and urethane (35 g, 0.4 mol) as above afforded 36 g (68%) of white solid, mp 194–195° (EtOH), ir (CCl_4) 1705 cm^{-1}.

Anal. Calcd for $C_{14}H_{20}O_4N_2$: C, 59.99; H, 7.19; N, 9.99. Found: C, 60.03; H, 7.09; N, 10.04.

3,4-Dimethoxybenzaldehyde Bisurethane (30). Reaction of 3,4-dimethoxybenzaldehyde (25 g, 0.15 mol) and urethane (24 g, 0.3 mol) afforded 44 g (90%) of white solid, mp 180–181° (EtOH), ir (CCl_4) 1705 cm^{-1}.

Anal. Calcd for $C_{15}H_{22}O_6N_2$: C, 55.21; H, 6.79; N, 8.58. Found: C, 55.40; H, 6.78; H, 8.59.

Phenyl Benzalbiscarbamate (31). Reaction of benzaldehyde (9.7 g, 0.09 mol) and phenyl carbamate (25 g, 0.09 mol) as above afforded 18.6 g (57%) of white solid, mp 190–192° (acetone).

Anal. Calcd for $C_{21}H_{18}N_2O_4$: C, 69.61; H, 4.97; N, 7.73. Found: C, 69.48; H, 5.05; N, 7.81.

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