Bicyclic Enamines. VI.[1] Homoallylic Participation in the Formation and Properties of Some Bicyclic Enamines[2,3]

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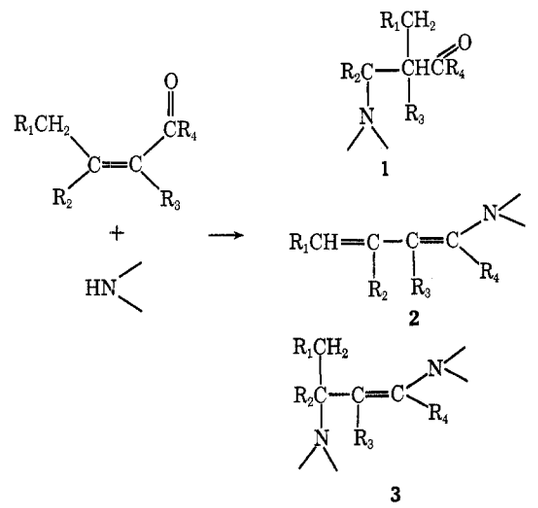
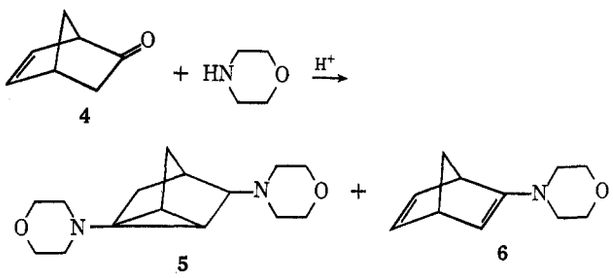
The reaction of norbornenone and morpholine without an acid catalyst results in formation of a tricycloenamine, a normal enamine, an enamine reduction product, and an amino ketone. The amino ketone is apparently formed *via* a homoenolate ion. Treatment of bicyclo[2.2.2]oct-5-en-2-one with morpholine and an acid catalyst gives the thermodynamic product, *N*-phenylmorpholine, in refluxing xylene and the kinetic product, 2-*N*-morpholinobicyclo[2.2.2]octa-2,5-diene, at room temperature.

Secondary amines react with α,β-unsaturated ketones or aldehydes in one of the following three ways: (1) nucleophilic attack of the amine on the β carbon resulting in a β-amino ketone or aldehyde such as structure **1**;[4-7] (2) a combination of nucleophilic attacks of the amine on both the β carbon and the carbonyl carbon to form a γ-aminoenamine such as structure **3** or an isomer thereof;[8,9] (3) nucleophilic attack of the amine on the carbonyl carbon alone to form dienamine such as structure **2** or an isomer thereof[10] (although many dienamines are formed *via* a γ-aminoenamine such as structure **3**).



The reaction of secondary amines with the bicyclo[2.2.1]heptyl homoallylic ketone system by pathway types 2 and 3 has been observed when it was found that the acid-catalyzed reaction between morpholine and norbornenone (**4**) produced 2,5-bis(*N*-morpholino)-tricyclo[2.2.1.$0^{2,6}$]heptane (**5**) (*via* pathway 2) and 2-*N*-morpholinobicyclo[2.2.1]hepta-2,5-diene (**6**) (probably *via* pathway 3).[5]



We have found that the reaction of norbornenone (**4**) with morpholine *without acid catalyst* gives four products which are formed by all three pathway types. These four products include tricyclic amine **5** and bicyclic enamine **6**, which were observed in the acid-catalyzed reaction mentioned above,[5] and two new products. The two new products are bicyclic amine **7** and amino ketone **8** (Scheme I).

Tricyclic amine **5** (*via* pathway 2) was identified by comparison with an authentic sample.[5] The yield of tricyclic amine **5** increases the most markedly of the four products as the reaction time is extended as seen in Table I. Enamine **6** (probably formed *via* pathway 3) was identified by its ir and nmr spectra (see Table II), gas chromatography, hydrogenation to produce the identified saturated amine **9**, and a low yield synthesis by the Diels–Alder reaction of 1,1-dimorpholinoethene (**10**)[11] with cyclopentadiene followed by elimination of morpholine. *endo*-2-*N*-Morpholinobicyclo[2.2.1]hept-5-ene (**7**) was probably produced by the reduction of enamine **6** with excess morpholine which reduction has been shown to give the endo isomer.[5,12,13] The structure of **7** was demonstrated by glc and ir comparison with an authentic sample obtained by reduction of iminium salt **11**.[12]

TABLE I

REACTION OF NORBORNENONE WITH MORPHOLINE IN REFLUXING XYLENE (NO ACID CATALYST)

Time, hr	% Yield 5	6	7	8
50	4	2	1	1
114	17	2	3	1
261	23	2	3	1

The structure of *exo*-5-*N*-morpholinobicyclo[2.2.1]-

(1) For the previous article in the series, see A. G. Cook, S. B. Herscher, D. J. Schultz, and J. A. Burke, *J. Org. Chem.*, **35**, 1550 (1970).

(2) For a preliminary communication of this work, see A. G. Cook and W. M. Kosman, *Tetrahedron Lett.*, 5847 (1966).

(3) Support of this work by a grant from the Petroleum Research Fund, administered by the American Chemical Society, and by Valparaiso University research grants is gratefully acknowledged.

(4) S. I. Suminov and A. N. Kost, *Russ. Chem. Rev.*, **38**, 884 (1969).

(5) A. G. Cook, W. C. Meyer, K. E. Ungrodt, and R. H. Mueller, *J. Org. Chem.*, **31**, 14 (1966).

(6) H. Shenhav, Z. Rappoport, and S. Patai, *J. Chem. Soc. B*, 469 (1970).

(7) E. Rouvier, J. C. Giacomoni, and A. Cambon, *Bull. Soc. Chim. Fr.*, 1717 (1971).

(8) C. Mannich, K. Handke, and K. Roth, *Ber.*, **69**, 2112 (1936).

(9) For a comprehensive review of the formation and structure of enamines, see "Enamines: Synthesis, Structure, and Reactions," A. G. Cook, Ed., Marcel Dekker, Inc., New York, N. Y., 1969.

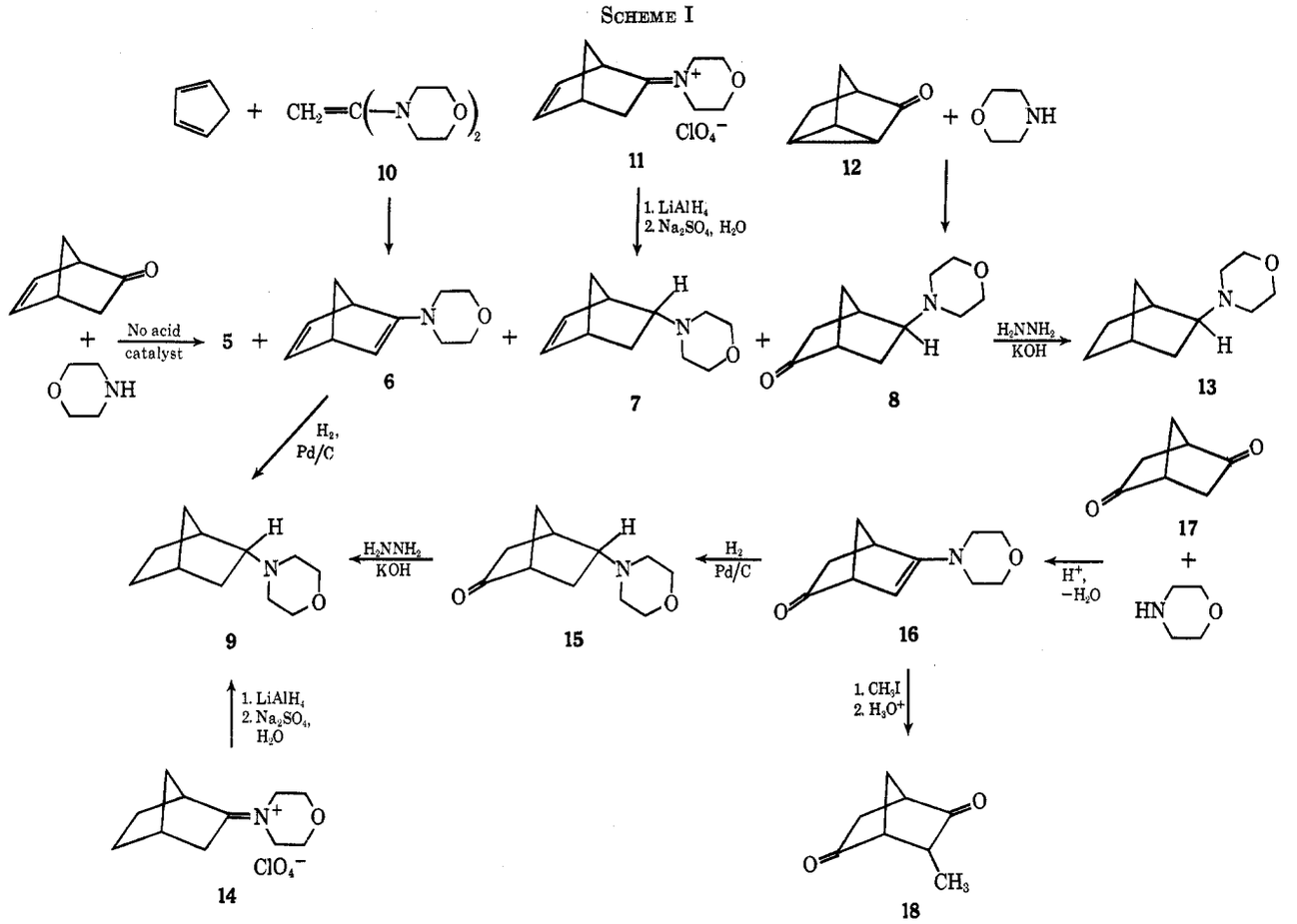
(10) G. Optiz and W. Merz, *Justus Liebigs Ann. Chem.*, **652**, 139 (1962).

(11) H. Baganz and L. Domaschke, *Chem. Ber.*, **95**, 2095 (1962).

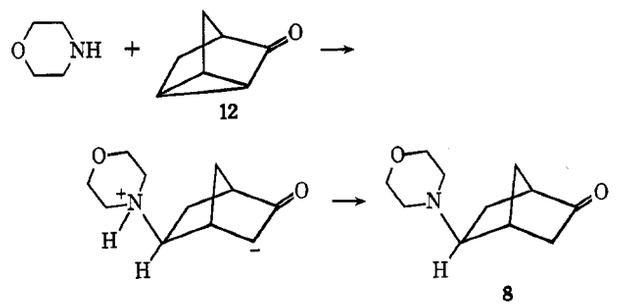
(12) A. G. Cook and C. R. Schulz, *J. Org. Chem.*, **32**, 473 (1967).

(13) The observation that morpholine is also among those secondary amines that reduce amines in the presence of an acid catalyst was first reported by E. L. Patmore and H. Chafetz, *ibid.*, **32**, 1254 (1967). Morpholine has also been observed to reduced enamines in the absence of acid catalyst when heated with the enamine over an extended period of time as reported by Stephen and Marcus (see Table II, ref *e*).

SCHEME I



heptan-2-one (**8**) (formed *via* pathway 1) was demonstrated by comparison of physical, spectral, and chromatographic properties with those of an authentic sample. The authentic sample was synthesized by treatment of tricyclo[2.2.1.$0^{2,6}$]heptan-3-one (**12**) with



morpholine.[5] The same product is obtained whether an acid catalyst is present or not. Since the presence of acid is not necessary for this reaction, it probably proceeds by a nucleophilic backside attack of morpholine on **12** to produce a carbanion followed by proton removal and addition to give amino ketone **8**. This would mean that the compound produced (**8**) is the exo isomer. Proof of its being the exo isomer was obtained by reducing amino ketone **8** by the Wolff–Kishner reduction to the corresponding amine (**13**). The gas chromatogram and ir spectrum of this amine were compared with those of an authentic sample of *endo*-2-morpholinobicyclo[2.2.1]heptane (**9**), synthesized by reduction of iminium salt **14** with lithium aluminum hydride. This type of reduction has been shown to produce the endo isomer.[12] The peaks on the gas chromatograms have different retention times under identical conditions, and the ir spectra have several distinct differences showing them to be nonidentical. The endo isomer possesses strong bands at 1180, 1030, and 798 cm^{-1} which the exo isomer does not exhibit whereas the exo isomer shows strong bands at 1010 and 865 cm^{-1} which the endo isomer does not show. Therefore amino ketone **8** and its corresponding amine **13** are indeed exo isomers. Further proof is seen by glc and ir comparison of *endo*-5-*N*-morpholinobicyclo[2.2.1]heptan-2-one (**15**) with the exo amino ketone, **8**. This comparison shows the nonidentity of amino ketones **8** and **15**. Wolff–Kishner reduction of amino ketone **15** produces endo amine **9** as additional proof of the stereochemistry of amino ketone **15**. *endo*-5-*N*-Morpholinobicyclo[2.2.1]heptan-2-one (**15**) was produced by catalytic reduction of 5-*N*-morpholinobicyclo[2.2.1]hept-5-en-2-one (**16**) (hydrogenation takes place on the less hindered exo side of the bicyclic systems), which in turn was synthesized in the usual manner[9] from diketone **17** and morpholine. The structure of enamine **16** was demonstrated by alkylation with methyl iodide followed by hydrolysis to yield 3-methylbicyclo[2.2.1]hepta-2,5-dione (**18**).

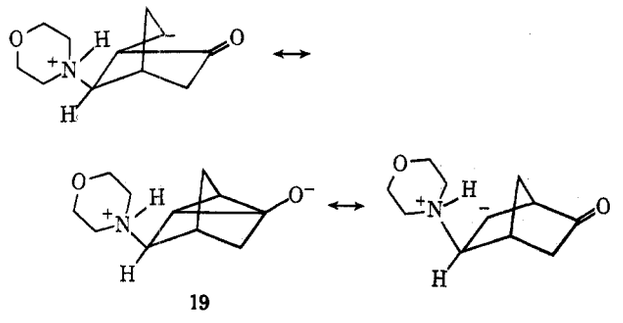
The most plausible explanation for the formation of amino ketone **8** from norbornenone (**4**) and morpholine is *via* a homoenolate ion intermediate (**19**)[14] in a Michael-type addition reaction. The ketone group must exert a homoconjugative effect on the carbon–

(14) A. Nickon, J. L. Lambert, R. O. Williams and N. H. Werstuik, *J. Amer. Chem. Soc.*, **88**, 3354 (1966), and previous articles.

TABLE II
PHYSICAL PROPERTIES OF SOME MORPHOLINE ENAMINES

Component ketone	Uv spectrum: Solvent[a]	λ_{max}, nm	ϵ	ν_{max}^{film}, cm^{-1} (>C=C<N)	Nmr, δ (HC=CN)	Synthesis[b]	Yield, %	Bp, °C (mm)	n^tD (t)	Formula	C, % Calcd	C, % Found	H, % Calcd	H, % Found
Norbornenone (4)	A	203	4680	1600 (m), 1660 (s)		c								
Norcamphor	A	None above 200		1600 (s)[d]	4.60 (d)[e]	f								
Bicyclo[2.2.1]-heptane-2,5-dione (17)	A	None above 200		1600 (s)	4.32 (d)	A	54	118 (0.4)						
Bicyclo[2.2.2]-oct-2-en-5-one (20)	E, A, C	217 and 244 (sh), none above 200, 243 (sh)	4000 and 2200, 1700	1600 (m), 1630 (s)	4.93 (m)	B	50	81–82 (0.3)	1.5288 (24)	$C_{12}H_{17}NO$	75.35	75.16	8.96	8.86
Bicyclo[2.2.2]-octan-2-one (23)	E, A	217, none above 200	5600	1620 (s)		B	71	93–94 (0.5)	1.5224 (21)	$C_{12}H_{19}NO$	74.57	74.44	9.91	9.87

[a] E, diethyl ether; A, ethanol; C, cyclohexane. [b] A, amine, ketone and acid catalyst in refluxing xylene;[9] B, amine, ketone and $TiCl_4$ at room temperature.[15] [c] See Experimental Section. [d] An incorrect assignment reported in ref 5 was first corrected by M. Mazarguil and A. Lattes, *Bull. Soc. Chim. Fr.*, 319 (1969). [e] J. F. Stephen and E. Marcus, *J. Org. Chem.*, **34**, 2535 (1969). [f] See ref 5.



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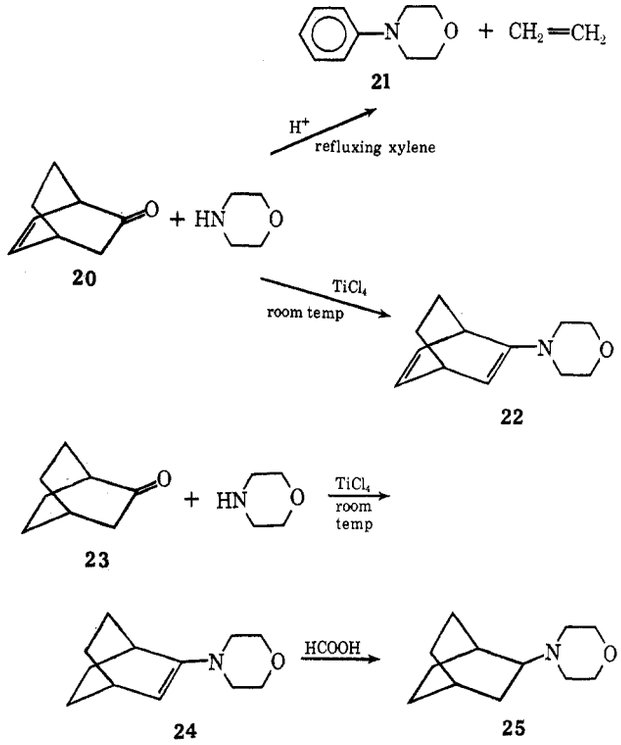
carbon double bond since neither norbornene nor nobornadiene react with morpholine under these conditions.[5] Michael addition reactions involving secondary amines and α,β-unsaturated carbonyl compounds have been reported before[4-7], but this is the first example of such a reaction involving the homoenolate ion.

An extension of this study into the bicyclo[2.2.2]-octyl system was carried out to determine the generality of these reactions. Homoallylic participation in the bicyclo[2.2.2]octyl system has been shown to be important in solvolysis reactions.[15] Treatment of bicyclo[2.2.2]oct-5-en-2-one (**20**) with morpholine in the presence of an acid catalyst in refluxing xylene results in the loss of a mole of ethylene along with the expected mole of water producing *N*-phenylmorpholine (**21**) in a 78% yield. Using titanium tetrachloride catalyst in benzene at room temperature, according to the method of White and Weingarten,[16a] with ketone **20** and morpholine gives the kinetically controlled product,[16b] 2-*N*-morpholinobicyclo[2.2.2]octa-2,5-diene (**22**), in a 50% yield. No sign of homoallylic products, such as were discovered in the bicyclo[2.2.1]-heptyl system, was found. Bicyclo[2.2.2]octan-2-one (**23**) is readily converted to 2-*N*-morpholinobicyclo[2.2.2]oct-2-ene (**24**) in a 71% yield by the same method. Enamine **24** is readily reduced to 2-*N*-morpholinebicyclo[2.2.2]octane (**25**) with 98–100% formic acid.

Listed in Table II are the physical properties and elemental analyses of those enamines reported for the first time.



21 20 22 23 24 25

Experimental Section

The instruments used in this work were the Beckman DK-2A recording spectrophotometer, the JEOL C-60HL high resolution nmr spectrometer, the Perkin-Elmer Model 137 and the Beckman IR-20A ir spectrometers, and the Hewlett-Packard Model 7620A research chromatograph. The elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

Starting Bicyclic Ketones.—Bicyclo[2.2.1]hept-2-en-5-one (**4**) and bicyclo[2.2.2]oct-2-en-5-one (**20**) were made by the method of Freeman, *et al.*[17] Bicyclo[2.2.2]octan-2-one (**23**) was synthesized using the method of Krieger.[18] The synthesis of bicyclo[2.2.1]heptane-2,5-dione (**17**) was carried out according to the method described by Meinwald, *et al.*[19]

(15) J. B. Lambert and A. G. Holcomb, *J. Amer. Chem. Soc.*, **93**, 3952 (1971).

(16) (a) W. A. White and H. Weingarten, *J. Org. Chem.*, **32**, 213 (1967); (b) D. Pocar, R. Stradi, and G. Bianchetti, *Gazz. Chim. Ital.*, **100**, 1135 (1970).

(17) P. K. Freeman, D. M. Balls, and D. J. Brown, *J. Org. Chem.*, **33**, 2211 (1968).

(18) H. Krieger, *Suom. Kemistilehti B.*, **35**, 180 (1962).

(19) J. Meinwald, J. K. Crandall, and P. G. Gassman, *Tetrahedron*, **18**, 815 (1962).

Reaction of Norbornenone with Morpholine (No Acid Catalyst.)—A stirred solution of 10.8 g (0.1 mol) of norbornenone, 8.7 g (0.1 mol) of morpholine, and 150 ml of xylene was refluxed under a nitrogen atmosphere for 114 hr. Water was removed during this time by means of a Dean-Stark trap. At the end of this time the solvent and excess starting materials were removed and the residual oil was fractionally distilled. The product distribution is 0.19 g (1%) of *exo*-**5**-*N*-**morpholinobicyclo[2.2.1]heptan-2-one** (**8**) (identified by glc and ir spectral comparison with an authentic sample[5]), 0.54 g (3%) of *endo*-**2**-*N*-**morpholinobicyclo[2.2.1]hept-5-ene** (**7**) (identified by glc and ir spectral comparison with an authentic sample, see below), 0.55 g of **2**-*N*-**morpholinobicyclo[2.2.1]hepta-2,5-diene** (**6**) (identified by hydrogenation to a known saturated amine, ir spectra, and independent synthesis, see below), and 4.45 g (17%) of **2,5-bis(***N***-morpholino)tricyclo[2.2.1.0^{2,6}]heptane** (**5**) (identified by comparison with an authentic sample[5]). See Table I for comparison of yields for different reaction times. The balance of the reactants were recovered as unreacted starting materials.

exo-**2**-*N*-**Morpholinobicyclo[2.2.1]heptane** (**13**).—A solution of 18.4 g (0.094 mol) of *exo*-5-*N*-morpholinobicyclo[2.2.1]heptan-2-one (**8**),[5] 135 ml of diethylene glycol, 34 g of potassium hydroxide, and 24 ml of 85% hydrazine hydrate was stirred at 60–120° for 6 hr and at 220° for 3 hr. Then ~1.5 l. of steam distillate was obtained and extracted with ether, the combined extracts were dried over anhydrous magnesium sulfate and filtered, and the solvent was removed and distilled. A total of 5.6 g (37%) of colorless product was obtained, bp 80° (0.6 mm), n^{27}D 1.4972.

Anal. Calcd for $C_{11}H_{19}NO$: C, 72.88; H, 10.56. Found: C, 73.03; H, 10.57.

endo-**2**-*N*-**Morpholinobicyclo[2.2.1]heptane** (**9**).—A stirred slurry of 5.1 g (0.018 mol) of the perchlorate salt of 2-*N*-morpholinobicyclo[2.2.1]hept-2-ene (**14**), 3.8 g (0.1 mol) of lithium aluminum hydride and 500 ml of ether was refluxed for 21 hr. The reaction mixture was treated with an aqueous saturated sodium sulfate solution and filtered, the solvent was removed, and residual oil was distilled. A total of 2.3 g (71%) of colorless liquid product was obtained, bp 76° (0.65 mm), n^{26}D 1.4953.

Anal. Calcd for $C_{11}H_{19}NO$: C, 72.88; H, 10.56. Found: C, 72.95; H, 10.60.

endo-**5**-*N*-**Morpholinobicyclo[2.2.1]heptan-2-one** (**15**).—A solution of 5.34 g (0.03 mol) of 5-*N*-morpholinobicyclo[2.2.1]hept-5-en-2-one (**16**)[20] and 75 ml of ethyl acetate was hydrogenated using 10% palladium-on-carbon catalyst and 40-psi pressure. After filtration and solvent removal, the residual liquid was distilled to give 3.6 g (66%) of a colorless product, bp 111° (0.35 mm).

Anal. Calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78. Found: C, 67.37; H, 8.99.

A Wolff–Kishner reduction was run on this product by a procedure identical with that used to reduce amino ketone **8**. *endo*-2-*N*-Morpholinobicyclo[2.2.1]heptane (**9**) was the product obtained in a 30% yield.

3-Methylbicyclo[2.2.1]heptane-2,5-dione (**18**).—A stirred mixture of 2.43 g (0.013 mol) of 5-*N*-morpholinobicyclo[2.2.1]-hept-5-en-2-one (**16**)[20] and 226 g of methyl iodide was refluxed for 16 hr. The cooled solution was filtered, the solid residue as refluxed with dilute hydrochloric acid for 1.5 hr and extracted with ether, the combined extracts were dried over anhydrous magnesium sulfate and filtered, and solvent was removed. A total of 0.6 g (33%) of colorless liquid product was obtained, bp 124° (15 mm). It solidified on standing, mp 35–36.5°.

Anal. Calcd for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 69.71; H, 7.32.

Reaction of 1,1-Dimorpholinoethene with Cyclopentadiene.—A mixture of 3.3 g (0.05 mol) of freshly distilled cyclopentadiene, 9.9 g (0.05 mol) of 1,1-dimorpholinoethene[11] and a trace of hydroquinone was heated in a reaction bomb at 120–130° for 7 hr. At the end of this time the bomb was cooled, and a total of 0.22 g (3%) of 2-*N*-morpholinobicyclo[2.2.1]hepta-2,5-diene (**6**) was found. It was identified by ir and glc with an authentic sample.

endo-**2**-*N*-**Morpholinobicyclo[2.2.1]hept-5-ene** (**7**).—A stirred mixture of 6.0 g (0.055 mol) of norbornenone (**4**), 10.3 g (0.055 mol) of morpholine perchlorate, and 100 ml of xylene was refluxed under nitrogen for 2 hr, and water was removed with a Dean-Stark trap. The solvent was decanted, and 120 ml of ether and 3.8 g (0.1 mol) of lithium aluminum hydride was added. The stirred reaction mixture was refluxed for 17 hr, after which it was treated with a saturated solution of sodium sulfate. The mixture was filtered, the solvent was removed, and the residual oil was distilled. A total of 3.83 g (39%) of product was obtained as a colorless liquid, bp 62° (0.15 mm), n^{23}D 1.5057, nmr δ 5.90 (2 H, m, HC=CH), $\lambda_{max}^{cyclohexane}$ 203 nm (ϵ 5700).

Anal. Calcd for $C_{11}H_{17}NO$: C, 73.71; H, 9.56. Found: C, 73.85; H, 9.64.

Registry No.—**7**, 34201-83-7; **9**, 20238-39-5; **13**, 34217-00-0; **15**, 34217-01-1; **16**, 34219-66-4; **18**, 34219-67-5; **22**, 34219-68-6; **24**, 34219-69-7.

(20) See Table II for synthetic method and physical properties.

Distal Effects in E2 Eliminations. Elimination of Hydrogen Chloride from Epimeric 8-Trichloromethyldibenzobicyclo[3.2.1]octadienes[1]

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A series of C-4 substituted epimeric 8-trichloromethyldibenzobicyclo[3.2.1]octadienes were synthesized and their rates of elimination with lithium chloride in dimethylacetamide (DMA) measured. The substituents at C-4 have a marked effect on the rates for loss of hydrogen chloride from the *anti*-8-trichloromethyl epimers but have no apparent effect on the rates for the syn epimers. The k_{syn}/k_{anti} ranged from 48 to 2300 depending upon the substituent at C-4. This large ratio could be accounted for in terms of steric hindrance to approach by base to the C-8 hydrogen atom from the syn direction.

A great deal of data have been amassed on the variables associated with 1,2-elimination reactions.[2] Most of these data are concerned with how the nature of these reactions vary with changes either at the site of the leaving group (α and β positions) or in the base system employed. Little effort has been made to study what effect groups removed from the reaction sites (α and β) would have on the course of E2 eliminations. In particular, we wished to study the effect in β eliminations of groups removed from the reaction site in a sterically constrained system.

(1) (a) Taken in part from the M.S. thesis of J. P. Govoni, University of Maryland, 1970. (b) Presented in part at the 6th Middle Atlantic Regional Meeting of the American Chemical Society, Baltimore, Md., Feb 1971.

(2) (a) D. V. Banthorpe, "Elimination Reactions," Elsevier, Amsterdam, 1963; (b) J. F. Bunnett, *Angew. Chem., Int. Ed. Engl.*, **1**, 225 (1962); (c) R. F. Hudson, *Chimia (Aarau)*, **16**, 173 (1962); (d) D. J. McLennan, *Quart. Rev. (London)*, **21**, 490 (1967); (e) J. F. Bunnett, *Surv. Progr. Chem.*, **5**, 53 (1969).