Stabilized Derivatives of *cis,cis,cis*-1,3,5-Cyclodecatriene. Keto–Enol Tautomerism in 2,3-Dicarbomethoxy-*cis,cis*-3,5-cyclodecadienones and *cis*-3-Cycloalkenones[1]

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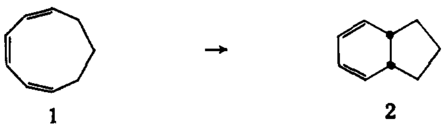
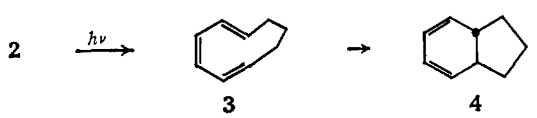
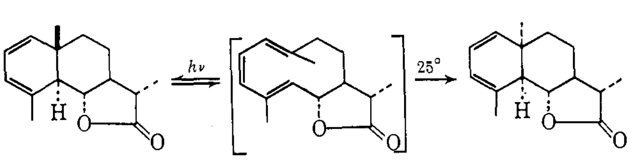
Abstract: The preparation of 1-dimethylamino-2,3-dicarbomethoxy-*cis,cis,cis*-1,3,5-cyclodecatriene and its 9-oxa analog, the first stabilized derivatives of the 1,3,5-cyclodecatriene system, is described. The geometrical configuration of these mesocyclic polyolefins has been established by a combination of chemical and spectral methods. Mild acid hydrolysis of the enamine portion of these molecules provided a synthetic entry to the 2,3-dicarbomethoxy-*cis,cis*-3,5-cyclodecadienones which, in striking contrast to earlier precedent, exist predominantly in their tautomeric enol form. Quantitative spectral measurements of the enol/keto ratio (K_e) of these keto diesters as well as of several *cis*-3-cycloalkenones (C_7–C_{10}) in a broad spectrum of solvents have been made, and a brief discussion of the probable stereochemical and steric factors which control the various K_e's is presented.

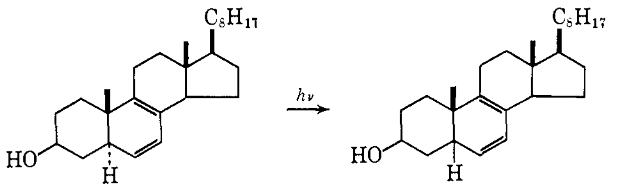
Of the many cyclic polyolefins known to date, the conjugated trienes of the medium-sized rings are certainly among the most intriguing. The recent interest to be accorded such molecules is due in part to the unusual highly stereospecific nature of their valence-bond isomerization during which the triene with its six π electrons is converted to a cyclohexadiene with four π and two σ electrons. Such rearrangements, although purely thermal in nature, occur under very mild conditions (usually at appreciable rates in the temperature range 0–50°). For example, *cis,cis,cis*-1,3,5-cyclononatriene (**1**) rearranges smoothly to *cis*-bicyclo[4.3.0]nona-2,4-diene (**2**) at 25.0° with a first-order rate constant of $(7.62 \pm 0.13) \times 10^{-6}$ sec^{-1} ($\Delta H^* = 23.0$ kcal/mole; $\Delta S^* = -4.7$ eu).[3] The *trans,cis,cis* isomer of **1** (**3**) has been prepared recently by the ultraviolet irradiation of **2**;[4] this triene (**3**) likewise rearranges by first-order kinetics,[5] but gives rise exclusively to *trans*-bicyclo[4.3.0]nona-2,4-diene (**4**).


1 **2**


3 **4**

Essentially the same observations have been noted with 1,3,5-cyclodecatriene derivatives. Thus, Corey[6] and Hortmann have shown that triene **6**, generated in a photoequilibration of **5**, undergoes complete thermal conversion to **7** within 6 hr at 25° in methanol solution. An identical mechanistic course has been *postulated*[7] for the photoconversion of isodehydrocholesterol (**8**) to its 5 epimer (**9**).[8] In both instances, the high reactivity of the intermediate conjugated cyclodecatrienes precluded their solution.


5 **6** **7**


8 **9**

The dramatic stereospecificity of the above electrocyclic reactions has been interpreted recently by Woodward and Hoffmann[9] on the basis of orbital symmetry control during the cyclization process. Such considerations predict, on the basis of extended Hückel theory, that the energetically preferred mode in proceeding from triene to diene will be disrotatory as is observed.

The present investigation was initiated to explore the possibility of preparing derivatives of 1,3,5-cyclodecatriene which would be stable to rearrangement at ambient temperatures and above, by virtue of the presence of selected stabilizing substituents. A second goal which developed during the above study was the determination of the extent to which *cis,cis*-3,5-cyclodecadienones undergo enolization and an elucidation of the probable stereochemical and steric factors which might control this equilibrium process.

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(1) This work was supported in part by the Petroleum Research Fund, administered by the American Chemical Society. The authors are indebted to the donors of this fund.

(2) Alfred P. Sloan Foundation Research Fellow.

(3) D. S. Glass, J. W. H. Watthey, and S. Winstein, *Tetrahedron Letters*, 377 (1965); J. W. H. Watthey and S. Winstein, *J. Am. Chem. Soc.*, **85**, 3715 (1963).

(4) E. Vogel, W. Grimme, and E. Dinné, *Tetrahedron Letters*, 391 (1965).

(5) Relative to **1**, **3** was observed to rearrange at a slightly faster rate with a lower ΔH^* (20.1 ± 1.0 kcal/mole). The rate process for the conversion of **3** → **4** was followed by nmr spectroscopy in the temperature range 28–40°. The entropy of activation was calculated to be −12.8 eu.[4]

(6) E. J. Corey and A. G. Hortmann, *J. Am. Chem. Soc.*, **87**, 5736 (1965).

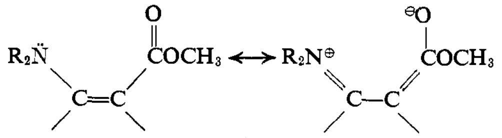
(7) P. de Mayo and S. T. Reid, *Quart Rev.* (London), **15**, 393 (1961).

(8) A. Windaus and G. Zühlsdorf, *Ann.*, **536**, 204 (1938).

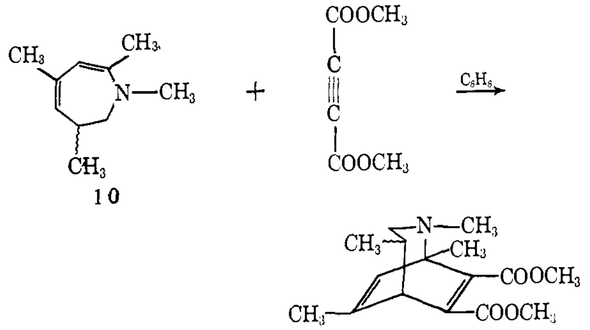
(9) R. B. Woodward and R. Hoffmann, *J. Am. Chem. Soc.*, **87**, 395 (1965).

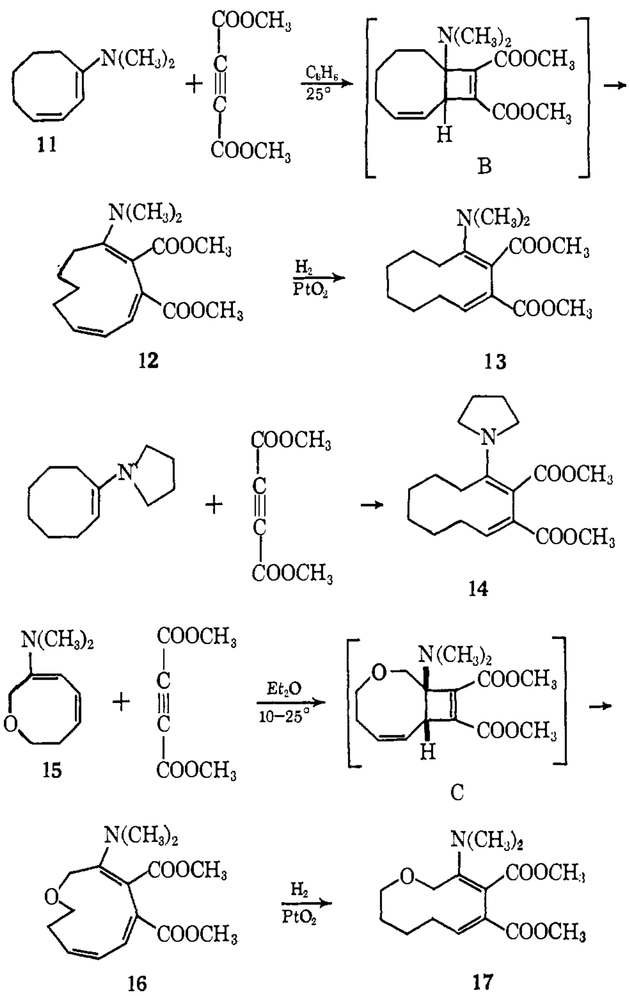
Synthesis and Discussion

Consideration of possible substituents necessary to achieve stabilization of the 1,3,5-cyclodecatriene system led to the selection of a dialkylamino group and a carbomethoxy group because of the appreciable delocalization of charge known to exist in structures such as A.[10] The selection further was dictated in part by the very limited number of available synthetic approaches. For example, in view of the novel method available for the expansion of a carbocyclic ring by two carbon atoms under mild conditions,[11-13] it was hoped that eight-membered dienamines[14] likewise might condense with dimethyl acetylenedicarboxylate to afford 1,3,5-cyclodecatriene derivatives by a sequence involving the intermediate formation of a cyclobutene adduct. Although reports of the reactions of dienamines derived from cyclic ketones with dienophiles are generally lacking, it has been established that the cyclic dienamine **10** condenses with dimethyl acetylenedicarboxylate in Diels–Alder (4 + 2π) fashion.[14] Apparently, however, this latter example is an exception to the normal enamine reaction pathway, for when 1-dimethylamino-1,3-cyclooctadiene (**11**) was treated with the same dienophile in the present study, the 1,3,5-cyclodecatriene derivative **12** was obtained readily. In agreement with structure **12**, the product exhibited pronounced ultraviolet absorption in ethanol and the requisite infrared and nmr absorptions (see Experimental Section). Further corroborative evidence for structure **12** was provided by its selective hydrogenation with platinum in ether solution to yield a dihydro derivative (**13**) identical in spectral properties with **14** which was prepared in an unequivocal manner from 1-pyrrolidinocyclooctene.



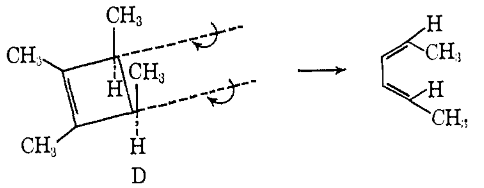
A



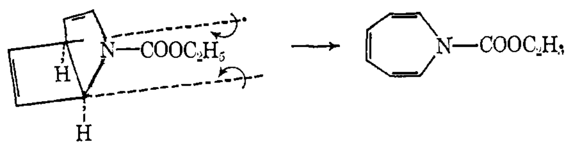


In similar fashion, treatment of **15** with dimethyl acetylenedicarboxylate afforded the heterocyclic 1,3,5-cyclodecatriene **16**.[15] This structure was established by the usual analytical and spectral data (see Experimental Section), and by partial hydrogenation to **17**. The variety of accumulated data, when taken collectively, indicated that **16** was the desired medium-ring triene.

A remaining problem was the assignment of the proper geometric configurations to the olefinic bonds in the trienes **12** and **16**. Woodward and Hoffmann[9] and Longuet-Higgins[16] have discussed the two possible modes of thermal ring opening of cyclobutene systems, namely conrotatory and disrotatory. In the conrotatory process (see D), the substituents at C_1 and C_4 move in the same sense with respect to the ring to give



D



E

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(10) A similar "push–pull" concept for purposes of stabilization recently has been applied in an independent study to the cyclobutadiene system: R. Breslow, D. Kivelevich, M. J. Mitchell, W. Fabian, and K. Wendell, *J. Am. Chem. Soc.*, 87, 5132 (1965).

(11) G. A. Berchtold and G. F. Uhlig, *J. Org. Chem.*, 28, 1459 (1963).

(12) K. C. Brannock, R. D. Burpitt, V. W. Goodlett, and J. G. Thweatt, *ibid.*, 28, 1464 (1963).

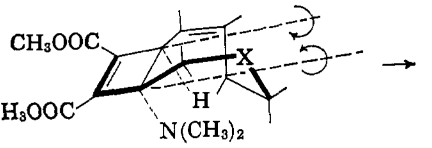
(13) A. K. Bose, G. Mina, M. S. Manhas, and E. Rzucidlo, *Tetrahedron Letters*, 1467 (1963).

(14) For a brief discussion of nomenclature pertaining to such enamines, refer to L. A. Paquette, *J. Am. Chem. Soc.*, 86, 4092 (1964), footnote 6.

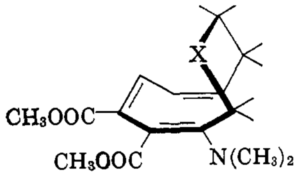
(15) Brief mention of this result has been made: L. A. Paquette, *Trans. N. Y. Acad. Sci.*, 28, 387 (1966).

(16) H. C. Longuet-Higgins and E. W. Abrahamson, *J. Am. Chem. Soc.*, 87, 2045 (1965).

a *cis,trans*-diene as product. In the disrotatory example (E), the substituents move in opposite directions to afford *cis,cis*-diene. The thermal isomerization of cyclobutenes such as D is usually conrotatory.[17] However, steric factors such as the five-membered ring in E render the conrotatory process highly unfavorable and disrotatory opening is observed.[18] The influence of a fused *cis*-cyclooctene ring[19] on the rotational thermal reorganization of intermediates such as B and C was unknown. Should the fused eight-membered ring exert little strain upon the transition state of the ring opening, then a conrotatory process would be anticipated; however, models indicate a somewhat distorted extended-tube conformation for the *cis*-cyclooctene portion of B and C which imparts significant rigidity to the over-all molecular structure and suggests the likelihood that steric control might promote disrotatory ring opening. Furthermore, Dreiding models of the three possible resulting trienes demonstrated the presence of significant transannular nonbonded interactions in the *cis,trans,cis*- and *trans,cis,cis*-trienes; on the other hand, these effects are minimized in a relative sense in the *cis,cis,cis*-triene model. This diminution of steric strain in the latter structure *a priori* might be expected to be of sufficient importance to promote a disrotatory ring opening. Indeed, this latter mechanistic pathway was followed and the supporting experimental factors follow.

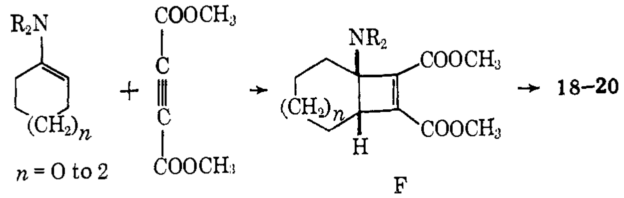


B, X = CH_2
C, X = O



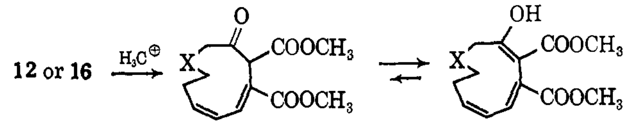
12, X = CH_2
16, X = O

The ultraviolet spectral data of Table I clearly demonstrate that the extinction coefficients of the all *cis* isomers do not parallel in magnitude those of their isomeric *cis,trans* counterparts. Most significantly, the ϵ_{max} values of **13**, **14**, and **17** are roughly comparable to those of **18–20**, the implication being that they must all be of the same geometry about the chromophore. Given the fact that **18–20** most certainly result from disrotatory ring opening of intermediate F,[20] then it follows that they are of the *cis,cis* configuration. Consequently, **13**, **14**, and **17** must contain a similar *cis,cis*-diene grouping, and since the remaining olefinic linkage in **12** and **16** must be *cis*,[19,21] then the presence of an all-*cis* configuration for these molecules is established.



F

With the elucidation of the complete structural formulas for **12** and **16**, brief mention of their stability and reactivity is warranted. Both substances are remarkably stable yellow solids which do not decompose at their melting points. They have exhibited no propensity for valence-bond isomerization under the usual laboratory conditions; preliminary attempts at photoisomerization have proven inconclusive. In methanolic hydrochloric acid, these cyclodecatrienes were readily hydrolyzed to the corresponding *cis,cis*-3,5-cyclodecadienones (**21** and **22**) which, however, exist predominantly as their enol (triene) tautomers (see following section).



21, X = CH_2
22, X = O

Studies of Keto–Enol Tautomerism. Spectra

The *cis,cis*-3,5-cyclodecadienones **21** and **22**, obtained from **12** and **16**, respectively, in the manner described above, were found, upon cursory examination, to exist almost totally in the enolic form. In view of the difficulty encountered by earlier workers in their attempts to prepare similar systems,[22,23] these observa-

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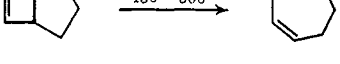
(17) For examples, *cf.* E. Vogel, *Ann.*, **615**, 14 (1958); R. Criegee and K. Noll, *ibid.*, **627**, 1 (1959).

(18) For examples, *cf.* L. A. Paquette and J. H. Barrett, *J. Am. Chem. Soc.*, **88**, 1718 (1966), and pertinent references cited in footnote 9 of the present paper.

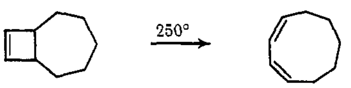
(19) The double bond at C_5–C_6 is known to be *cis* because of the unequivocal synthetic route employed in the preparation of dienamines **11** and **15**.

(20) This conclusion has been reached by making recourse to results obtained with the parent hydrocarbon systems (*vide infra*); inherent in this extrapolation is the inherently reasonable assumption that the substituents in F will not seriously affect the mode of thermal organization which, in all of these examples, occurs in a disrotatory fashion primarily because of steric factors:



O. L. Chapman, D. J. Pasto, G. W. Borden, and A. A. Griswold, *J. Am. Chem. Soc.*, **84**, 1220 (1962);

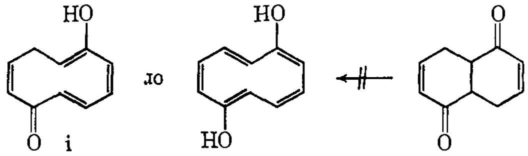
S. F. Chappell, III, and R. F. Clark, *Chem. Ind.* (London), 1198 (1962);



K. M. Shumat, P. N. Neuman, and G. J. Fonken, *J. Am. Chem. Soc.*, **87**, 3996 (1965).

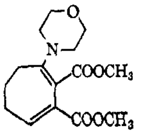
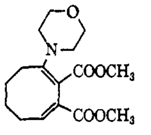
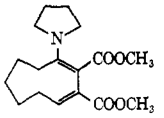
(21) It is not expected that isomerization of this bond would occur in the cycloaddition reaction.

(22) The numerous varied approaches to cyclodecapentaene are cases in point. Of especial pertinence may be cited the unsuccessful attempts of W. A. Johnson, J. D. Bass, and K. L. Williamson, *Tetrahedron*, **19**, 861 (1963), to induce i to enolize.



(23) The sesquiterpene germacrone (ii), which represents an interesting substrate for keto–enol tautomerism, has been investigated to a

Table I. Ultraviolet Absorption Data for Some Cyclic Polyolefins

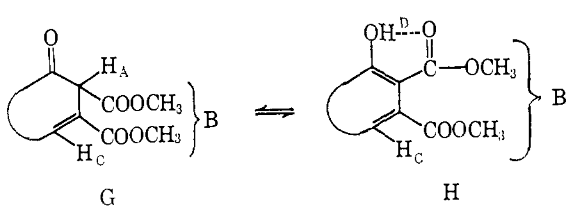
Compound	λ_{max}, mμ	ε	Solvent	Ref
1	296	4,010	Cyclohexane	*a*
3	290	2,050	Cyclohexane	*b*
cis,cis-1,3-Cyclooctadiene	228	5,600	Cyclohexane	*c*
cis,trans-1,3-Cyclooctadiene	230.5	2,600	Cyclohexane	*c*
cis,cis-1,3-Cyclononadiene	None >210	4,000 (220 mμ)	Ether	*d*
cis,trans-1,3-Cyclononadiene	218–220	7,300	Ether	*d*
cis,cis-1,3-Cyclodecadiene	None >210	3,900 (220 mμ)	Ether	*d*
cis,trans-1,3-Cyclodecadiene	218–220	7,200	Ether	*d*
13	319	13,400	Ethanol	*e*
14	315	15,200	Ethanol	*e*
17	329	12,040	Ethanol	*e*
 **18**	334	9,760	Methanol	*f*
 **19**	327	10,940	Methanol	*f*
 **20**	323	13,600	Ethanol	*e*

[a] See ref 3. [b] See ref 4. [c] A. C. Cope and C. L. Bumgardner, *J. Am. Chem. Soc.*, **78**, 2812 (1956). [d] G. J. Fonken, private communication. [e] This work. [f] See ref 11.

tions appeared interesting and were investigated in greater detail.

For purposes of comparison, several 2,3-dicarbomethoxy-*cis*-3-cycloalkenones of medium-ring size, namely **23–27**, structures in which the additional olefinic bond of **21** and **22** was absent, were desired. These β-keto esters were prepared conveniently by the mild acid hydrolysis of the corresponding enamine derivatives and were obtained crystalline except in the case of **26**. Whereas compounds **21–24** and **27** crystallized in the enol form, **25** solidified with some reluctance and then as the keto tautomer. On the other hand, **26** was obtained only as a viscous colorless oil which consisted of an equilibrium mixture of the two tautomeric forms. These conclusions were derived from spectral evidence (see below).

The characteristic infrared absorption bands found for this group of compounds are summarized in Table II. The band assignments are patterned after, and confirm, those derived from a number of earlier studies.[24] Specifically, the 1590–1610-cm^{-1} absorption has been assigned to the diene or triene stretching vibrations, the 1655–1660-cm^{-1} band to the enol chelate, and the absorption in the 1720–1725-cm^{-1} range to the carbonyl stretching vibrations of the unsaturated ester carbonyl groups. In those examples which displayed a significant concentration of keto tautomer, an additional band was observed at 1765 cm^{-1}; this high frequency absorption has been attributed to the saturated ester carbonyl group present in the keto form (G). The ketone carbonyl absorption which is likewise present in such tautomers is believed



G H

to fall under the absorption attributed earlier to the unsaturated carbomethoxy functions (1720–1725 cm^{-1}). This assignment appears reasonable in view of the recorded carbonyl stretching frequency for mesocyclic ketones[25] when allowance is made for the expected ketone frequency shifts in the medium ring β-keto diester ($\Delta\nu \approx$ 8–9 cm^{-1}).[24] The general change in

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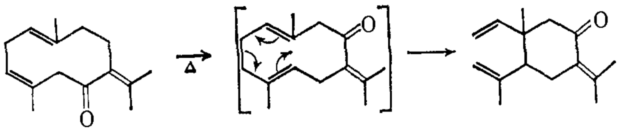
considerable extent but unfortunately no comments regarding its enol content are available. However, a small amount of enol tautomer perhaps is suggested by its published infrared spectrum; G. Ohloff,



ii

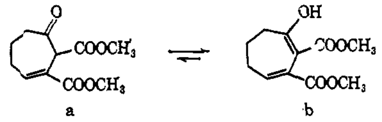
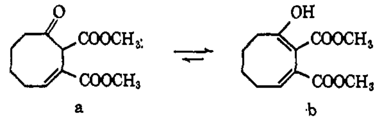
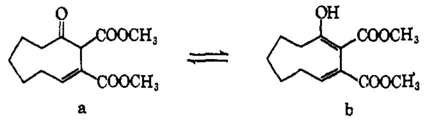
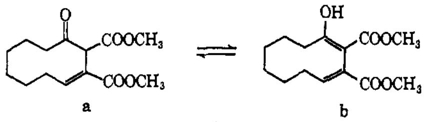
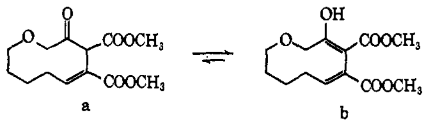
H. Farnow, W. Philipp, and G. Schade, *Ann.*, **625**, 206 (1959), and references cited therein.

When attempts were made to vacuum distil germacrone above 165°, the indicated rearrangement was elucidated (not observed with **21** or **22**): I. Ognjanov, D. Ivanov, V. Herout, M. Horak, J. Pliva, and F. Sorm, *Collection Czech. Chem. Commun.*, **23**, 2033 (1958); V. Herout and M. Suchy, *ibid.*, **23**, 2169 (1958); M. Suchy and F. Sorm, *ibid.*, **23**, 2175 (1958).

(24) S. J. Rhoads, J. C. Gilbert, A. W. Decora, T. R. Garland, R. J. Spangler, and M. J. Urbigkeit, *Tetrahedron*, **19**, 1625 (1963), and references cited therein.

(25) C. N. Rao, "Chemical Applications of Infrared Spectroscopy," Academic Press Inc., New York, N. Y., 1963, p 214.

Table II. Infrared Absorptions of Some 2,3-Dicarbomethoxy-*cis,cis*-3,5-cyclodecadienones and *cis*-3-Cycloalkenones

	ν, cm^{-1}			
Compound	Diene	Enol chelate	Ketone and unsatd ester carbonyls	Satd ester carbonyl
 **23**	1606 (m)	1660 (s)	1725 (s)	. . .
 **24**	1610 (m)	1655 (s)	1725 (s)	. . .
 **25**	. . . 1606 (w)^a	. . . 1655 (w)	1725 (s) 1720 (s)	1765 (m) 1765 (m)
 **26**	1606 (m)	1655 (m)	1725 (s)	1765 (m)
 **27**	1610 (m)	1665 (s)	1725 (s)	. . .
 **21**	1590 (s)	1655 (s)	1725 (s)	. . .
 **22**	1610 (m)	1660 (s)	1725 (s)	. . .

^{a} This set of values was obtained after an equilibration period of 4 days at room temperature.

contour of this band in such cases also supports this conclusion.

Table III summarizes the ultraviolet spectra of the keto diesters which were measured in cyclohexane, ethanol, and acetonitrile. The region of maximum absorption is quite solvent sensitive and is decreased markedly with increasing solvent polarity. Such evidence is in accord with the expected high enol content in hydrocarbon solvents with increasing ketonization as the polarity of the medium is enhanced. Because the absorption characteristics of enols are known to be almost totally independent of the particular medium employed,[26] and since the assumption can be made that the apparent extinction coefficients in cyclohexane are representative of the extinction coefficient of the enol tautomer,[27] equilibrium constants (K_e) for the more polar solvents may be calculated, and these values are shown in Table III.

The nmr spectra of the tautomeric pairs were examined in solvents of widely differing dielectric constant,[28] in order to maximize alterations in the equilibrium induced by such polarity changes or by preferential hydrogen bonding between solvent molecules and one or the other of the tautomers (the internally hydrogen-bonded enol molecule is less polar than the keto species). The results are listed in Table IV. Of the spectroscopic data presented heretofore, the nmr data are the most informative because a quantitative rather than a qualitative measure of the keto–enol equilibrium

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[26] G. S. Hammond, W. G. Borduin, and G. A. Guter, *J. Am. Chem. Soc.*, 81, 4682 (1959).

[27] Such a conclusion, however, does not seem justified in the case of 25 and 26 because their combined spectral data (Tables II–IV) suggest that a high concentration of enol is never attained with these compounds even in nonpolar media. Although the derived K_e values are at best qualitative in these examples, they are useful to indicate the relative increase in keto tautomer (or, conversely, the relative decrease in enol content) when passing to solvents of increasing polarity.

[28] For some values, see J. Hine, "Physical-Organic Chemistry," 2nd ed, McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 39.

Table III. Ultraviolet Absorption Data of Some 2,3-Dicarbomethoxy-*cis,cis*-3,5-cyclodecadienones and *cis*-3-Cycloalkenones

Compd	Solvent	λ_{max}, mμ	ϵ'[a]	K_e[b]
23	Cyclohexane	261	9,100	. . .
	Ethanol	259	8,720	23.0
		210	10,150	
	Acetonitrile	262	6,550	2.6
24	Cyclohexane	256	10,520	. . .
	Ethanol	257	10,380	70.5
		213	11,300	
	Acetonitrile	258	7,720	2.7
25[c]	Cyclohexane	254[d]	6,500	. . .
	Ethanol	255	3,500	1.2
		Ca. 230	5,900	
	Acetonitrile	255	2,770	0.74
26	Cyclohexane	255[d]	5,330	. . .
	Ethanol	256	5,130	26.0
		Ca. 225	7,500	
	Acetonitrile	263	2,480	0.87
		245	1,650	
27	Cyclohexane	253	9,700	. . .
	Ethanol	238	9,700	. . .
	Acetonitrile	255	6,000	1.6
21	Cyclohexane	254	11,900	. . .
	Ethanol	265[e]	9,370	3.7
	Acetonitrile	264[f]	6,950	1.4
22	Cyclohexane	248[d]	15,500	. . .
	Ethanol	248[g]	14,000	9.4
	Acetonitrile	248[h]	12,400	4.0

[a] ϵ' = apparent extinction coefficient. [b] K_e = apparent enol/keto ratio. [c] After 12 hr at room temperature, **25** (still predominantly as **25a**) displayed the following spectral properties: $\lambda_{max}^{cyclohexane}$ 239 mμ (5640); λ_{max}^{EtOH} 231 (6120) and 253 sh mμ (3820). [d] Considerable fine structure was in evidence in these spectra. [e] Also a shoulder at 290 mμ (5350). [f] Also a shoulder at 290 mμ (3500). [g] Also a shoulder at 272 mμ (10,300). [h] Also a shoulder at 268 mμ (9300).

Table IV. Chemical Shift Values (δ units) and Enol Contents of Some 2,3-Dicarbomethoxy-*cis,cis*-3,5-cyclodecadienones and *cis*-3-Cycloalkenones

Compd	Solvent	Proton				%
		A[a]	B[b]	C	D	enol
23	CCl_4	. . .	3.64, 3.68	6.95	12.51	100[c]
	$CDCl_3$	. . .	3.72	7.08	12.60	100
	Acetone-d_6	4.71	3.65, 3.69	7.02	12.55	95
	Benzene	. . .	3.47, 3.57	7.02	12.98	100
	DMSO-d_6	4.72	3.69	7.04	12.49	90
24	CCl_4	. . .	3.64, 3.68	6.80	12.57	100
	$CDCl_3$	. . .	3.70	6.93	12.68	100
	Acetone-d_6	. . .	3.66, 3.70	6.90	12.66	100
	Benzene	. . .	3.46, 3.57	6.91	13.04	100
	DMSO-d_6	. . .	3.69	6.90	12.60	100
25	CCl_4	4.64	3.69, 3.79	6.20	12.48	46
	$CDCl_3$	4.77	3.73, 3.82	6.28	12.52	31
	Acetone-d_6	4.73	3.70, 3.80	6.30	12.61	30
	Benzene	4.86	3.54	6.10	12.91	42
	DMSO-d_6	4.74	3.69, 3.78	6.28	12.52	22
26	CCl_4	4.59	3.67, 3.78	6.18	12.33	57
	$CDCl_3$	4.73	3.74, 3.83	6.30	12.45	41
	Acetone-d_6	4.69	3.68, 3.79	6.28	12.46	39
	Benzene	4.81	3.51, 3.53	6.08	12.85	57
	DMSO-d_6	4.75	3.70, 3.80	6.33	12.43	36
27	CCl_4	. . .	3.66, 3.72	6.22	12.32	100
	$CDCl_3$	4.55	3.74, 3.75	6.30	12.40	92
	Acetone-d_6	4.58	3.67, 3.73	6.31	12.47	85
	Benzene	4.58	3.44, 3.51	6.18	12.82	95
21	CCl_4	. . .	3.66, 3.71	*d*	12.81	100
	$CDCl_3$	. . .	3.73	*d*	12.87	100
	Acetone-d_6	4.67	3.67, 3.74	*d*	12.91	66
	Benzene	. . .	3.42, 3.46	*d*	13.24	100
	DMSO-d_6	4.72	3.69	*d*	12.53	43
22	CCl_4	. . .	3.63, 3.72	*d*	12.29	100
	$CDCl_3$	. . .	3.73, 3.77	*d*	12.40	100
	Acetone-d_6	. . .	3.66, 3.76	*d*	12.45	100
	Benzene	. . .	3.46, 3.51	*d*	12.76	100
	DMSO-d_6	4.79	3.63, 3.72	*d*	12.23	94

[a] For proton designations, see structures G and H. [b] Where only one value is given, the resonance peaks of the two methyl groups overlap. [c] Berchtold and Uhlig[11] have claimed that **23** exists in the enol form to the extent of approximately 60–70%; this value was obtained by integration of absorption peaks at δ 12.54 and 5.73 (solvent unspecified). We have concluded that the absorption at δ 5.73 was perhaps an impurity in the sample of these workers. [d] The complexity of the resonance signals did not allow a specific assignment for H_C in the presence of the two additional vinyl protons.

is provided.[29] All solutions were 2.5 *M* in substrate and were allowed to equilibrate at room temperature for 4 days.[30] The signal at δ 4.6–4.8 was assigned to the keto α-proton (absent in those systems which were totally enolic) and the absorption in the δ 12.4–13.0 region, which showed considerable variation in chemical shift, to the enol OH proton. The per cent enol content was determined by integration of the areas of these two absorptions. A representative set of spectra is shown in Figure 1; the *cis*-3-cyclononenone derivative **25** was selected as the example because it displayed the greatest change with time of all the systems studied. The absorptions with chemical shifts of δ 3.7–3.8 can be assigned readily to the protons of the carbomethoxy group. The remaining δ 6.1–7.0 signal which varied greatly in splitting and general line shape was attributed to the vinyl proton (H_C); in addition to the fact that this proton would be expected to resonate at lower magnetic field, the spin–spin coupling of the H_C absorption should reflect certain first-order and long-range coupling phenomena which would be dependent upon the keto–enol ratio, and such is observed.

Chemical shifts of the various proton groups in benzene solution were generally at higher magnetic field, except for the hydroxyl proton of the enol tautomer which was shifted to lower field. This effect, perhaps attributable to ring current effects arising from solute–solvent complexes, has been observed previously for a number of solvents.[29e,31]

Conclusions

The data of Tables III and IV clearly show that the keto–enol equilibria vary markedly with structure. Whereas the seven- and eight-membered *cis*-3-cycloalkenones (**23** and **24**, respectively) are almost totally enolic throughout a broad spectrum of solvent polarity, the nine- (**25**) and ten-membered (**26**) congeners display marked decreases in the degree of enolization. A further interesting change occurs when an additional ole-

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(29) In recent years, direct measurement of the degree of enolization of a number of keto–enol pairs has been made; *cf.*, for example, (a) J. A. Pople, W. G. Schneider, and H. S. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, Chapter 17, and references cited therein; (b) E. W. Garbisch, *J. Am. Chem. Soc.*, **85**, 1696 (1963); 87, 505 (1965); (c) J. L. Burdett and M. T. Rogers, *ibid.*, 86, 2105 (1964); (d) S. Forsen, F. Merenyi, and M. Nilsson, *Acta Chem. Scand.*, 18, 1208 (1964); (e) M. T. Rogers and J. L. Burdett, *Can. J. Chem.*, 43, 1516 (1965); (f) S. J. Rhoads, *J. Org. Chem.*, 31, 171 (1966); (g) G. Allen and R. A. Dwek, *J. Chem. Soc.*, 161 (1966).

(30) Random samples were examined again after standing for an additional week, but no further changes in K_e were noted. Similarly, after selected samples were heated on a steam bath for varying periods of time, no further changes in enol content was noted.

(31) (a) G. V. Hatton and R. E. Richards, *Mol. Phys.*, **3**, 253 (1960); (b) W. G. Schneider, *J. Phys. Chem.*, **66**, 2653 (1962); (c) L. LaPlanche and M. T. Rogers, *J. Am. Chem. Soc.*, **85**, 3728 (1963); **86**, 337 (1964).

finic bond is placed in the ten-membered ring as seen by the increased enol content of **21** when compared to **26**. An additional new factor is observed when one of the ring methylene groups is replaced by an ether oxygen atom; that such a modification results in an enhanced enol content is evident when **22** and **27** are compared with their carbocyclic analogs.

An understanding of the fundamental origin of these equilibrium differences demands that the conformations of the molecules under investigation be known with some degree of accuracy. This requirement is most formidable where medium-sized rings are concerned. Cyclic systems of eight to ten members are known to be quite flexible and to be subject to rapid low-energy conformational interconversions;[32] the problem is complicated further by the fact that the introduction of double bonds into such rings drastically changes their geometry and implants some elements of rigidity.[33] In addition, substitution of an oxygen atom for a tetrahedral carbon atom has been claimed to exert a negligible conformational influence on the ring,[33b] although the removal of some nonbonded interactions which accompanies such a change might be expected to relieve *I* strain[34] and transannular steric compression. This latter effect is reflected quantitatively in the high enol contents of **22** and **27**.

As a guide to the probable conformational composition of the tautomers in the above series, recourse was made to Dreiding models. However, variation of the percentage composition could not be foretold from a careful study of these models, and indeed an explanation of the trend appears to be subtle. As the ring size increases, nonbonded interactions and torsional strains are seen to increase regularly, and such effects probably are reflected in the observed decrease in enol content[35] (reversed by the introduction of an ether oxygen atom).

It is quite likely that the conjugated double bonds in these molecules cannot attain coplanarity for reasons of steric compression. The increase in $\epsilon_{\max}$ (see Table III) when going from the seven- (**23**) to the eight-membered (**24**) rings, both of which are 100% enolic in nonpolar solvents, suggests that in the somewhat more flexible larger ring a greater degree of coplanarity can be achieved. Unfortunately, this extrapolation cannot be carried to the next larger rings because of the high keto content in these systems even in cyclohexane solution. However, significant $\epsilon_{\max}$ increases are observed when **21** and **26** are compared to their oxygen analogs **22** and **27**, respectively. Such enhanced absorption can be rationalized on the basis of strain minimization accompanying the replacement of a CH_2 group by O which permits a higher (but still incomplete) degree of coplanarity to the conjugated system.

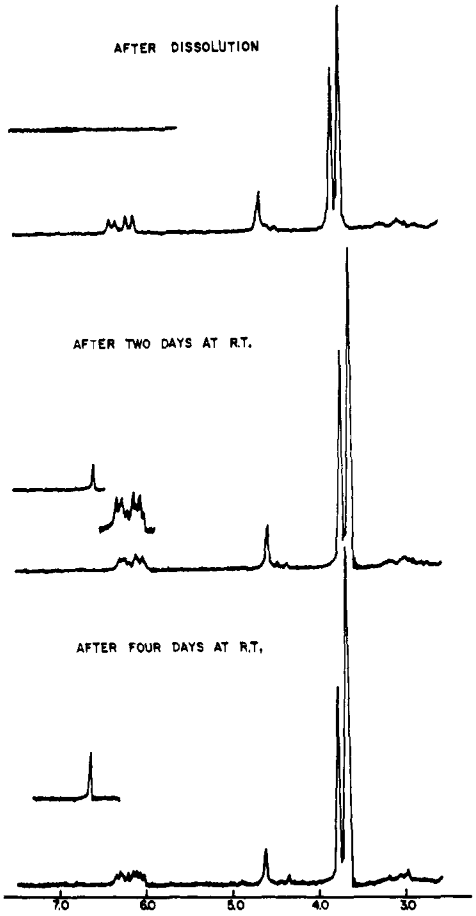

Figure 1. Partial nmr spectra of 2,3-dicarbomethoxy-3-*cis*-cyclononenone (**25**) at 60 Mc in 2.5 *M* carbon tetrachloride solution after various periods of equilibration at room temperature.

Finally, the sizeable increase of enol tautomer when an additional double bond is introduced into the ten-membered cycle (*i.e.*, **26** as compared to **21**) may be explained by a substantial change in conformational composition during which a number of steric compressions, which formerly were prohibitive to enol formation, are relieved.

Experimental Section[36]

1-Dimethylamino-1,3-cyclooctadiene (11).[37] A solution of 40.0 g (0.143 mole) of N-methylgranatenine methiodide[38,39] in water was passed through a column of Amberlite IRA-400 (in its basic form). The alkaline eluate was collected, and the water was removed under reduced pressure. The remaining oil was distilled at 100–120° (30 mm). The distillate was dissolved in ether and dried over magnesium sulfate to remove the remaining water. The ether was evaporated and the product redistilled to give 19.1 g (88%) of α-desdimethylgranatenine, bp 80–85° (15–20 mm), n^{24}D 1.4980 [lit.[38] bp 80° (12 mm), n^{25}D 1.4988].

This diene was pyrolyzed at 160–170° (140 mm) to induce a 1,5-dienyl hydrogen shift and give rise to 1-dimethylamino-1,3-cyclooctadiene (**11**).[40] This dienamine was obtained in 90% yield

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[32] (a) J. B. Hendrickson, *J. Am. Chem. Soc.*, **86**, 4854 (1964); (b) K. B. Wiberg, *ibid.*, **87**, 1070 (1965).

[33] (a) J. Sicher, *Progr. Stereochem.*, 3, 202 (1962); (b) J. Dale, *J. Chem. Soc.*, 93 (1963).

[34] H. C. Brown and M. Gerstein, *J. Am. Chem. Soc.*, **72**, 2926 (1950); H. C. Brown, *J. Chem. Soc.*, 1248 (1956).

[35] This statement implies that the rigidity imposed by the *cis,cis*-dienoid or *cis,cis,cis*-trienoid components of the enols causes such molecules to be more sensitive to nonbonded steric interactions than their keto tautomers which are more flexible (because the sp^2-hybridized keto carbon spreads one of the C–C–C bond angles, etc.). Dreiding models bear out the validity of this conclusion.

[36] Melting points and boiling points are uncorrected. The microanalyses were determined by the Scandinavian Microanalytical Laboratory, Herlev, Denmark.

[37] G. Merling, *Chem. Ber.*, 24, 3123 (1891); R. Willstätter and E. Waser, *ibid.*, **44**, 3423 (1911); R. Willstätter and M. Heidelberger, *ibid.*, **46**, 517 (1913); for a brief discussion of this early work, see R. F. Manske and H. L. Holmes, "The Alkaloids," Vol. I, Academic Press, Inc., New York, N. Y., 1949, p 285.

[38] A. C. Cope and C. G. Overberger, *J. Am. Chem. Soc.*, **70**, 1433 (1948).

[39] It is a pleasure to acknowledge the assistance of Mr. William Hanners in the preparation of this methiodide.

[40] For a related rearrangement, refer to A. C. Cope and A. A. D'Addieco, *J. Am. Chem. Soc.*, **73**, 3419 (1951).

and was purified by redistillation, bp 100–101° (16 mm), n^{27}D 1.5260, ν^{neat} 1604 cm^{-1}.

1-Dimethylamino-2,3-dicarbomethoxy-*cis,cis,cis*-1,3,5-cyclodecatriene (12). A solution of 7.2 g (0.048 mole) of dienamine **11** in 150 ml of anhydrous benzene was cooled to a thick slurry in a Dry Ice–acetone bath. To this frozen mixture was added a cold solution of 6.8 g (0.048 mole) of dimethyl acetylenedicarboxylate in 50 ml of the same solvent. This mixture was allowed to warm to room temperature and to stand for 45 hr.[41] The benzene was evaporated under reduced pressure, and the remaining brown solid was washed with ether to afford 6.9 (49.3%) of yellow powder. Recrystallization of this solid from acetone gave pure **12** as yellow crystals: mp 130–132°; ν^{Nujol} 1620 (w), 1670 (s), and 1735 (s) cm^{-1}; $\lambda_{\max}^{\text{EtOH}}$ 250 (ϵ 11,600), 267 (10,700), 320 (10,900), and 356 mμ (8750). Its nmr spectrum (in DMSO-d_6) displayed peaks at δ 2.97 (s, N(CH_3)$_2$), 3.49 and 3.66 (s, COOCH_3), 5.5–6.8 (3 H, vinyl protons) and 8 protons in a broad upfield absorption band (allylic and methylene protons).

Anal. Calcd for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.90; N, 4.78. Found: C, 65.43; H, 8.02; N, 4.62.

Selective Reduction of 12. 1-Dimethylamino-2,3-dicarbomethoxy-*cis,cis*-1,3-cyclooctadiene (13). A solution of 0.60 g (2.0 mmoles) of **12** in 20 ml of ether was hydrogenated at atmospheric pressure over Adams catalyst. After the consumption of 1 mole of hydrogen, the hydrogenation was stopped. The catalyst was removed by filtration, and the filtrate was evaporated under reduced pressure to give 280 mg (49%) of a white solid and a yellow viscous oil (nonreduced and over reduced materials). Recrystallization of the solid from ether afforded pure white crystals of **13**: mp 106.5 108°; ν^{CCl_4} 1540 (s), 1695 (s), and 1740 (s) cm^{-1}. Its nmr spectrum (in CCl_4) displayed peaks at δ 2.97 (s, N(CH_3)$_2$), 3.42 and 3.60 (s, COOCH_3), and 5.63 (q, J = 12.5 and 4.5 cps, vinyl proton).

Anal. Calcd for $C_{16}H_{25}NO_4$: C, 65.06; H, 8.53; N, 4.74. Found: C, 65.21; H, 8.43; N, 4.67.

1-Dimethylamino-2,3-dicarbomethoxy-9-oxa-*cis,cis,cis*-1,3,5-cyclodecatriene (16). To a solution of 3.2 g (0.021 mole) of 1-dimethylamino-7-oxa-1,3-cyclooctadiene (**15**)[42,43] in 50 ml of anhydrous ether was added 2.96 g (0.021 mole) of dimethyl acetylenedicarboxylate over 10 min keeping the temperature below 10°. The solution was allowed to stand for 30 min at room temperature and then was cooled in an ice bath. The crystals thus obtained were recrystallized from acetone to give 3.15 g (51%) of yellow crystals, mp 145–146°. Further recrystallization of this solid from acetone or ethanol–hexane afforded bright yellow crystals of **16**: mp 147–148°; ν^{Nujol} 1620 (w), 1680 (s), and 1735 (s) cm^{-1}; $\lambda_{\max}^{\text{EtOH}}$ 257 (11,200), 270 (11,900), 326 (10,200), and 356 mμ (9300). Its nmr spectrum (in DMSO-d_6) displayed peaks at *ca.* δ 2.25 (complex multiplet, allyl protons), 3.00 (s, N(CH_3)$_2$), *ca.* 3.30 (m, H-8), 3.48 and 3.64 (s, COOCH_3), *ca.* 4.42 (m, H-10), and 5.7–7.1 (m, vinyl protons).

Anal. Calcd for $C_{15}H_{21}NO_4$: C, 61.00; H, 7.17; N, 4.74. Found: C, 60.89; H, 7.22; N, 4.76.

Selective Reduction of 16. 1-Dimethylamino-2,3-dicarbomethoxy-9-oxa-*cis,cis*-1,3-cyclooctadiene (17). A solution of 3.15 g (0.011 mole) of **16** in 60 ml of ethyl acetate was hydrogenated over Adams catalyst at atmospheric pressure. The consumption of 1 equiv of hydrogen required 30 min, at which point the hydrogenation was stopped. The catalyst was removed by filtration; the filtrate was evaporated under reduced pressure, and the residual viscous oil was crystallized from acetone. There was isolated 1.94 g (61%) of white crystals, mp 127.5–128.5°. Further recrystallization of this material from acetone gave pure **17**: mp 128–129°; ν^{Nujol} 1610 (w), 1675 (s), and 1710 (s) cm^{-1}. In the nmr (CCl_4 solution), the compound gave evidence of absorption at *ca.* δ 1.50 (broad lines, H-6 and H-7), *ca.* 2.50 (broad lines, allyl protons), 3.60 (overlapping), and 3.70 (s, COOCH_3), 3.95 (s, H-10), and *ca.* 5.96 (quadruplet, J = 11.5 and 5.0 cps, vinyl proton).

Anal. Calcd for $C_{15}H_{23}NO_5$: C, 60.59; H, 7.80; N, 4.71. Found: C, 60.52; H, 7.79; N, 4.67.

2,3-Dicarbomethoxy-*cis,cis*-3,5-cyclodecadienone (21). To a solution of 2.35 g (8.0 mmoles) of **12** in 12 ml of methanol was added 3 ml of concentrated hydrochloric acid and the solution was heated to reflux on a steam bath. Water (12 ml) was added and the solution was heated on a steam bath for 10 min. The solution was allowed to cool and crystallization was induced by stratching. The crystalline product (1.0 g, 47%) was collected and recrystallized from ether to give pure white crystals of **21**, mp 90–92.5°.

Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81. Found: C, 63.22; H, 6.80.

2,3-Dicarbomethoxy-9-oxa-*cis,cis*-3,5-cyclodecadienone (22). A solution of 0.35 g (1.2 mmoles) of **16** in 3 ml of methanol and 1 ml of concentrated hydrochloric acid was hydrolyzed as above. The resulting oil was recrystallized from methanol to give 250 mg (78.5%) of **22** as white crystals, mp 70–71°.

Anal. Calcd for $C_{13}H_{16}O_6$: C, 58.20; H, 6.01. Found: C, 57.66; H, 5.93.

2,3-Dicarbomethoxy-9-oxa-*cis*-3-cyclodecenone (27). The hydrolysis of 1.00 g (3.7 mmoles) of **17** by the method described above yielded 780 mg (78%) of **27**, mp 90–92° (from ether).

Anal. Calcd for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71. Found: C, 57.73; H, 6.75.

2,3-Dicarbomethoxy-3-*cis*-cycloheptenone (23). This product was prepared in two steps by the method of Berchtold and Uhlig,[11] and was obtained as white crystals from aqueous methanol, mp 61–62° (lit. 63.5–64.0°,[11] 55–57°[12]).

2,3-Dicarbomethoxy-3-*cis*-cyclooctenone (24). This product was prepared in two steps by the method of Berchtold and Uhlig,[11] and was obtained as white crystals from aqueous methanol, mp 74–75° (lit. 75.4–76.3°,[11] 74–75°[12]).

2,3-Dicarbomethoxy-3-*cis*-cyclononenone (25). Hydrolysis of 8.0 g (26.0 mmoles) of 1-(N-pyrrolidino)-2,3-dicarbomethoxy-*cis,cis*-1,3-cyclononadiene, prepared in 76.5% yield by the method of Brannock, *et al.*,[12] mp 139–141° (lit.[12] 109.5–110.5°), according to the above procedure afforded 2.4 g (36%) of **25** as white crystals from ether, mp 76–77.5°

Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.40; H, 7.14. Found: C, 61.47; H, 7.14.

1-(N-Pyrrolidino)-2,3-dicarbomethoxy-*cis,cis*-1,3-cyclodecadiene (14). This substance was prepared in the same manner as its lower homologs. From 29 g (0.16 mole) of 1-pyrrolidinocyclooctene,[44] there was obtained 27.5 g (53%) of white crystals: mp 104–105° (from ether); ν^{CCl_4} 1540 (s), 1695 (s), and 1740 (s) cm^{-1}. Its nmr spectrum (in CCl_4) displayed peaks at δ 3.42 and 3.60 (COOCH_3) and 5.68 (q, J = 12.5 and 4.5 cps, vinyl proton).

Anal. Calcd for $C_{18}H_{27}NO_4$: C, 67.26; H, 8.47; N, 4.36. Found: C, 67.20; H, 8.46; N, 4.30.

2,3-Dicarbomethoxy-3-*cis*-cyclodecenone (26). The hydrolysis of 4.0 g (12.4 mmoles) of **14** by the method described above yielded 2.3 g (70%) of a clear oil which could not be made to crystallize, but which was submitted to two molecular distillations prior to analysis (see text for further discussion).

Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51. Found: C, 63.25; H. 7.60.

Infrared Spectra. All spectra were determined on freshly prepared (unless otherwise noted) 10% solutions in carbon tetrachloride with a Perkin-Elmer Model 237 infrared spectrometer using sodium chloride optics.

Ultraviolet Spectra. Absorptivity measurements were made in matched 1-cm quartz cells with a Cary Model 14 recording spectrophotometer in which the cell compartment was maintained at 27 ± 2°. The spectra were obtained on dilute solutions which had been equilibrated at room temperature for 3 days before measurement.

Nmr Spectra. Proton magnetic resonance spectra were obtained on 2.5 *M* solutions which had been allowed to equilibrate at room temperature for periods of 2 and 4 days and were recorded with a Varian A-60 spectrometer. Chemical shift and equilibrium constant measurements have been made at 35 ± 2°. Chemical shift values are reported in δ units from internal tetramethylsilane (δ = 0) to within ±0.02 ppm. Equilibrium constants were calculated from the integrated intensities of keto and enol proton signals; the areas of the resonance peaks were hand-integrated repeatedly

$$K_e = \frac{[\text{enol}]}{[\text{keto}]}$$

with a planimeter, and the percentages are accurate to within ±2%.

Acknowledgment. The authors wish to thank the Elanco Products Co. and the Benzol Products Co. for the generous gifts of chlorodimethyl acetal and benzyl alcohol, respectively, which materials were employed in the synthesis of **15**.

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(41) We have experienced that failure to mix these two reagents when extreme cold resulted in a vigorously exothermic reaction which afforded, upon work-up, a nondescript black tar.

(42) L. A. Paquette and R. W. Begland, *J. Am. Chem. Soc.*, **87**, 3784 (1965).

(43) Full details of the preparation of **15** will appear in a forthcoming publication.

(44) M. E. Kuehne, *J. Am. Chem. Soc.*, **81**, 5400 (1959).