Reactivity of Cis-Fused 3-(Dialkylamino)cyclobutenes in Polar and Apolar Solvents. Synthesis, X-ray Structures, and Reactions of *cis,cis*- and *cis,trans*-1,3-Cycloalkadienes

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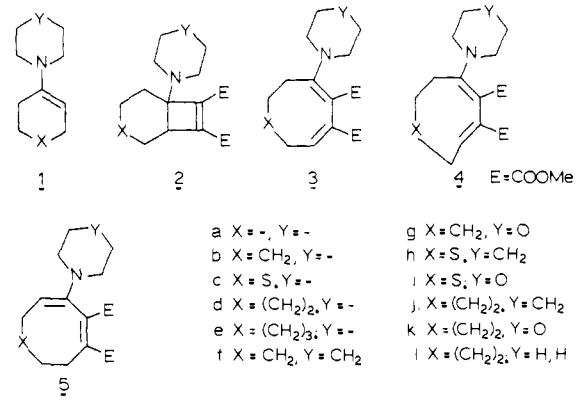
Abstract: Contrary to previous reports in the literature, the reactivity of (2 + 2) cycloadducts of enamines of cyclic ketones and DMAD in apolar solvents depends strongly on the size of the ring fused to the cyclobutene ring and on the dialkylamino group at the bridgehead position. Only the cycloadducts (**2**) of five-membered (and in some cases of six-membered) rings can be isolated. In all other cases the corresponding *cis,trans*-cycloalkadienes **4** are obtained at room temperature. The structure of **4c** was proven by a single-crystal X-ray analysis. In two cases a rapid reversible interconversion of compounds **2** and **4** in solution was observed (**2b** ⇄ **4b** and **2k** ⇄ **4k**). At higher temperatures the *cis,trans*-cycloalkadienes **4** rearrange by a thermal [1,5] hydrogen shift to give the *cis,cis*-cycloalkadienes **5** as was proven by X-ray analysis in the case of **5c**. Some compounds **5** rearrange further to the isomeric *cis,cis*-cycloalkadienes **3**. The structure of **3c** was proven by X-ray analysis. Compounds **3** have been previously reported in the literature as the reaction product in apolar solvents of the enamines and DMAD at higher temperatures. The *cis,cis*-cyclo*nona*dienes **5d**, **5j**, **5k**, and **5l** undergo further electrocyclization under these conditions in a "symmetry nonallowed" fashion to the corresponding bicyclo[5.2.0]non-8-enes **6**. The cis stereochemistry in the compounds was proven by X-ray analysis of **6b**. Under the influence of light compounds **4** rearrange to **3** by trans to cis isomerization and/or to **5** by an antarafacial [1,5] sigmatropic reaction. In polar solvent the 1-(1-pyrrolidinyl)bicyclo[*n*.2.0]alkenes **7-9** rearrange to the corresponding pyrrolizines **10-12** with a deviating pathway of the mixture of **2b** and **4b** that gives the dimer **14**, the structure of which was proven by single-crystal X-ray analysis. The conversion into pyrrolizines **15** and **16** was also observed upon reaction of the *cis,trans*-cycloalkadienes **4c** and **4d** in methanol. As a result of our work a number of structures of reaction products of enamines and DMAD reported in the literature will have to be revised.

The two-carbon ring expansion which involves the (2 + 2) cycloaddition of enamines of cyclic ketones and electron-deficient acetylenes followed by thermal rearrangement of the resulting fused cyclobutenes is an established and useful method in organic synthesis.[1,2] These ring-enlargement reactions have been successfully used in the synthesis of medium-sized heterocycles,[3-8] azulenes,[9] and several natural products including muscone,[10,11] steganone,[12] and velleral.[13,14] However, despite the widespread use and extensive coverage of this type of reaction in the literature[15-26] a number of contradictory points remain, in particular the unexplained formation of "abnormal" ring opening products[10,11,22] in several reactions. Moreover, different melting points have been reported for some reaction products[20] and several ^{1}H NMR spectroscopical data of such compounds are very unlikely[19] or not consistent in independent publications.[15,19] The reasons for the extremely facile ring opening of 3-aminocyclobutenes have been discussed in the literature. Criegee et al.[27] have attributed the fast reaction to stabilization of ionic intermediates by the amino and ester groups. With regard to the stereochemistry of the ring opening of the cis-fused 3-aminocyclobutenes it has been generally accepted[1,2,28] that the reaction occurs in a disrotatory mode which is anti-Woodward-Hoffmann.[29] According to Epiotis[30] the presence of strongly polarizing groups at the termini of the π-electron system will lower the activation energy of the "disallowed" disrotatory process. As a consequence also the disrotatory conversion of cis-fused cyclobutenes into *cis,cis*-cycloalkadienes would be a facile reaction.

We have recently found that the solvent has a remarkable effect on the reactions of dimethyl acetylenedicarboxylate (DMAD) and 1-pyrrolidinyl enamines.[31-33] Whereas in apolar solvents (2 + 2) cycloaddition takes place, in polar solvents like methanol, pyrrolizines are formed by reaction of the initially formed linear Michael adducts of enamines and DMAD. In relation with further mechanistic studies on this pyrrolizine formation we decided to study the reactivity of (2 + 2) cycloadducts of these enamines and DMAD, viz., 3-(1-pyrrolidinyl)cyclobutenes, in polar solvents.

Chart I



A number of the required 3-(1-pyrrolidinyl)cyclobutenes have been reported in the literature, mainly as unstable intermediates,

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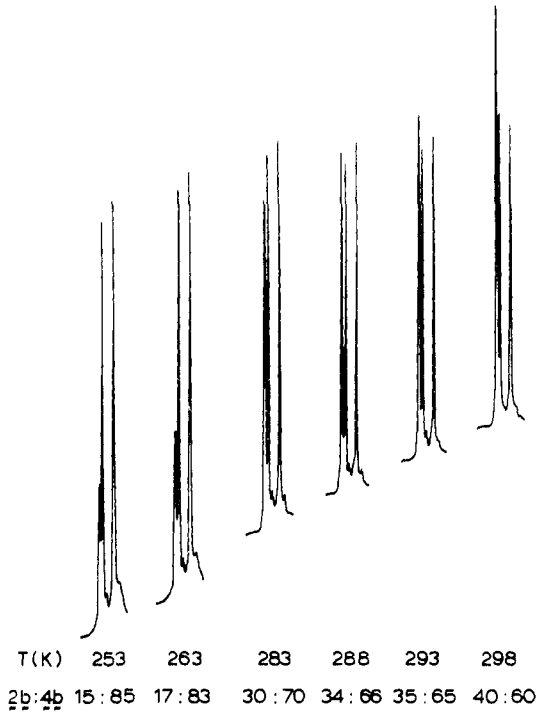

Figure 1. Part of the ^1H NMR spectrum (methoxy signals) of the equilibrium mixture of **2b** and **4b**.

in publications on ring-enlargement reactions. When these reactions were reproduced in our laboratory and the compounds isolated, several structures were found to be different from those reported. In particular the stereochemistry of the ring-opening reaction appeared to be different from generally accepted literature data. This paper deals with the results of these studies and eliminates a number of inconsistencies in the literature.

Results[34]

Reactions of Enamines and DMAD in Apolar Solvents. The (2 + 2) cycloadduct **2a** has been reported in the literature as an intermediate in the reaction of 1-(1-cyclopenten-1-yl)pyrrolidine (**1a**) and DMAD in apolar solvents but never isolated.[15-18] We have carried out the reaction under carefully controlled conditions (temperature <35 °C) and obtained **2a** (Chart I) as an unstable oil (vide infra).

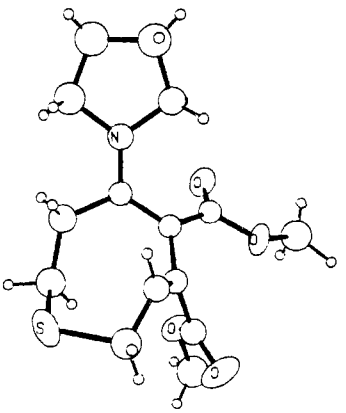

Figure 2. View of **4c**.

The synthesis of the (2 + 2) cycloadduct **2b** by reaction of 1-(1-cyclohexen-1-yl)pyrrolidine (**1b**) and DMAD has previously been described by Brannock et al.[17] In our hands reaction in diethyl ether gave a solid product (mp 80–89 °C) in a yield of 79%. However, ^1H NMR spectroscopy revealed that the product was not a single compound but a mixture of **2b** and the *cis,trans*-2,8-cyclooctadiene **4b**. The structure of **4b** was proven by NMR spectroscopy which shows in the ^1H NMR spectrum an absorption at δ 5.51 (dd) and at δ 3.75 and 3.60 (s, OCH_3) (vide infra) and in the ^{13}C NMR spectrum three singlets and one doublet corresponding to four sp^2-hybridized carbon atoms. The temperature-dependent ^1H NMR spectra of the mixture showed that **2b** and **4b** were interconverting slowly on the ^1H NMR timescale but fast on the chemical timescale at temperatures varying from 253 and 298 K (see Figure 1).

The reaction of the 4-thia analogue of **1b**, 1-(3,6-dihydro-2*H*-thiopyran-4-yl)pyrrolidine (**1c**), with DMAD gave a crystalline compound (mp 144–145 °C) in a yield of 82%. The spectroscopic data were similar to those of **4b** and single-crystal X-ray analysis finally proved the structure to be the *trans-cis*-thiocin **4c**. The molecular structure as determined by X-ray diffraction is shown in Figure 2. The unit cell contains two crystallographically independent molecules with the same conformation (vide infra). The mean torsion angles for the double bonds in the eight-membered ring are 142.5° and -27.8°, indicating the trans,cis conformation. The deviations of the torsion angles from the ideal values of 180° and 0° indicate the presence of severe strain in this molecule. A torsion angle distortion of the same order of magnitude in *trans*-cyclooctene has recently been discussed by Ermer and Mason.[35]

The reactions of 1-(1-cyclohepten-1-yl)pyrrolidine (**1d**) and 1-(1-cycloocten-1-yl)pyrrolidine (**1e**) with DMAD in diethyl ether at room temperature gave the corresponding *cis,trans*-cycloalkadienes **4d** and **4e**. Compound **4d** was isolated in a yield of 91% as a crystalline solid (mp 141.5–142.5 °C). The ^1H NMR spectrum clearly showed the cis,trans geometry of the 1,3-diene moiety; the absorption of the vinylic proton is present at δ 6.03 (dd).

The same compound has previously been described by Hirsch and Cross[20] and by Brannock et al.[17] who have assigned the cis,cis geometry, viz., **3d**. Compound **4e** (mp 102–106 °C) was obtained in a yield of 82%. This compound which exhibits in the ^1H NMR spectrum the absorption of the vinylic proton at δ 5.82 (dd) has previously[21] been assigned the *cis,cis*-cyclodecadiene structure, notwithstanding the reported absorption of the vinylic proton at δ 5.68 (CCl_4).

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We have subsequently studied the influence of the dialkylamino group of the enamine on the formation of compounds **2** and **4**, respectively. Reaction of 1-(1-cyclohexen-1-yl)piperidine (**1f**) and of 4-(1-cyclohexen-1-yl)morpholine (**1g**) with DMAD at room temperature gave the corresponding (2 + 2) cycloadducts **2f** and **2g**, both as unstable oils. The ^{1}H NMR spectra showed for both compounds the characteristic small difference in chemical shift of the methoxy absorptions and a broad multiplet at δ 3.05–3.20 for the bridgehead hydrogen atom. The ^{1}H NMR spectra of solutions of these compounds failed to show any of the corresponding *cis,trans*-cyclooctadienes **4f** and **4g** as was the case with the pyrrolidinyl derivative over a temperature range of 210–298 K. The 1-(3,6-dihydro-2*H*-thiopyran-4-yl)piperidine (**1h**) and 4-(3,6-dihydro-2*H*-thiopyran-4-yl)morpholine (**1i**) reacted smoothly with DMAD to give oils. In the case of **1h** ^{1}H NMR spectroscopy showed the presence of both **2h** [δ 3.82 and 3.80 (s, 3 H, OCH_3)] and **4h** [δ 5.40 (dd, =CH)]. Compound **1i** gave only the (2 + 2) cycloadduct **2i** [δ 3.82 and 3.81 (s, 3 H, OCH_3)]. Both products rapidly undergo further isomerization at room temperature (vide infra).

The piperidinyl, morpholinyl, and diethylamino enamines of cycloheptanone (**1j**, **1k**, and **1l**) reacted with DMAD to give the corresponding crystalline *cis,trans*-cyclononadienes **4j** (mp 137.5–139 °C), **4k** (mp 157–159.5 °C), in yields of 69 and 36%, respectively, and **4l** as an oil which isomerized upon purification (vide infra). The ^{1}H NMR and ^{13}C NMR spectra of these compounds are very similar with those of **4c** and **4d**. When the ^{1}H NMR spectrum of **4k** was recorded at 80 °C in toluene-d_8 we could also detect the signals corresponding with the bicyclic isomer **2k** [δ 3.47 (s, 6 H, OCH_3)]. The other *cis,trans*-nonadienes did not show this equilibrium of **2** and **4** in the spectra.

The experiments described so far have all been carried out under carefully controlled reaction conditions, temperatures below 35 °C, and if necessary in the dark. These precautions are necessary because both higher temperatures and in some cases (day)light render these reactions less selective. Since in the literature most reactions have been performed without protecting the reactants and reaction products from light and because most reactions have been carried out with the aim of ring enlargement at higher temperatures it is not too surprising that our results are in some cases different. Moreover, the surprising *cis,trans*-cycloalkadiene structure together with the thermal instability of various compounds **4** led us to investigate both their thermal and photochemical reactivity. In this study the thermal reactions of the "stable" (2 + 2) cycloadducts **2** are included.

Thermal Reactions of *cis,trans*-Cycloalkadienes (4) and (2 + 2) Cycloadducts (2). Upon standing at room temperature or at higher temperatures **2a** isomerized to the known *cis,cis*-2,7-cycloheptadiene **3a** (mp 136–138 °C).[15-17] This compound shows an absorption of the vinylic proton in the ^{1}H NMR spectrum at δ 6.86 (t) due to deshielding of the ester group at the adjacent carbon atom of the 1,3-diene moiety (vide infra). When the conversion of **2a** into **3a** was monitored by ^{1}H NMR spectroscopy we observed a transient absorption with low intensity at δ 5.72. This might be attributed to the vinylic proton of the *cis,trans*-cycloheptadiene derivative **4a**. Similarly the equilibrium mixture of **2b** and **4b** isomerized at room temperature to *cis,cis*-2,8-cyclooctadiene **3b**. This compound with mp 141.5–142.5 °C, which was previously described by Brannock et al.,[17] exhibits in the ^{1}H NMR spectrum a characteristic double doublet at δ 6.70.

However, when the solution of a mixture of **2b** and **4b** in deuteriochloroform was monitored at 50–55 °C by ^{1}H NMR spectroscopy, besides the signals of **3b**, a characteristic triplet absorption at δ 4.69 (J = 7.3 Hz) was observed, which was attributed to the *cis,cis*-1,3-cyclooctadiene **5b** (vide infra).

At room temperature the 1-piperidinyl and 4-morpholinyl analogues of **2b**, viz., **2f** and **2g**, both isomerize to the corresponding *cis,cis*-cyclooctadienes **3f** and **3g** which were obtained as crystalline compounds with mp 138–140 °C and 210–212 °C,[15,16] respectively. When a solution of **4c** in toluene was heated in the dark for 4 h at 100 °C the starting material completely disappeared. The solid compound (mp 169–170 °C) that was isolated in 44% yield shows an absorption in the ^{1}H NMR spectrum at δ 6.70 (dd). X-ray analysis proved the *cis,cis*-7,8-dihydro-2*H*-thiocin structure **3c** (Figure 3). In **3c** the torsion angles for the C=C—C=C part of the eight-membered ring are −3.7° (2), −51.9° (2) and −17.4° (2), respectively. These values are indicative for a *cis,cis*-1,3-diene moiety with little conjugation between the double bonds. Due to the cis,cis conformation of **3c** the torsion angles for corresponding bonds in **4c** and **3c** are different. It is interesting to note that when, starting with the S atom, the torsion angles of **3c** (Table V) are compared with those of **4c** in opposite order (i.e., clockwise instead of anticlockwise) the agreement is much better. The mean difference in torsion angles of 55° in the first case is reduced to 13° when the torsion angles in one of the compounds are taken in opposite order.

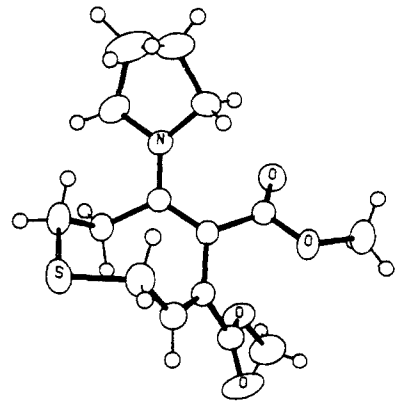
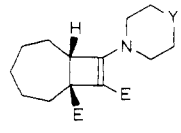


Figure 3. View of **3c**.

The reaction products of the 1-piperidinyl and 4-morpholinyl enamines **1h** and **1i** and DMAD have been obtained exclusively (**2i**) or at least predominantly (**2h**) as the (2 + 2) cycloadducts (vide supra). At room temperature (**2h**) or upon heating in toluene (**2i**), these compounds underwent isomerization to **5h**[22] and to **5i**, mp 118.5–120.5 °C, respectively. The latter compound showed the characteristic "enamine" absorption in the ^{1}H NMR spectrum at δ 5.04 (dd) as compared with the absorption of the same proton in **5h** at δ 4.99 (dd).

The reaction of the *cis,trans*-cyclononadiene **4d** in toluene at 110 °C was monitored by ^{1}H NMR spectroscopy. After 45 min **4d** was partly converted into the *cis,cis*-1,3-cyclononadiene **5d** as followed from the absorption at δ 4.35 (dd) and the ester absorptions at δ 3.80 and 3.75. After 4 h reaction time both the starting material and **5d** had almost completely been converted into a novel isomer which was isolated as an oil in a yield of 65%. This thermally and photochemically stable compound exhibited a molecular peak in the mass spectrum which was the same as in the spectrum of **5d** ($C_{17}H_{25}NO_4$). The ^{13}C NMR spectrum revealed only the presence of one olefinic bond (δ 157.5 and 94.1) that was obviously strongly polarized. In addition two significant signals were present at δ 52.2 (s) and 49.8 (d). The ^{1}H NMR spectrum revealed the absence of a vinylic proton and showed an absorption at δ 3.24 (dd). On the basis of these data we concluded that this isomer of **4d** which is formed by reaction of **5d** has the bicyclo[5.2.0]non-8-ene structure **6a**.



6a, Y = -
b, Y = CH_2
c, Y = O
d, Y = H,H

A similar reactivity was found when the *cis,trans*-cyclononadienes **4j**, **4k**, and **4l** were heated in toluene for 17–23 h. The corresponding bicyclo[5.2.0]non-8-ene **6b** was isolated in a yield of 83%. Compounds **6c** and **6d** could be obtained, but not in a pure state. All three compounds showed the characteristic absorption at δ 3.4–3.1 for the bridgehead hydrogen atom. When the reactions of **4j** and **4k** at 100 °C were monitored in the ^{1}H NMR spectrometer, we observed the formation of the corresponding *cis,cis*-cyclononadienes **5j** and **5k** and their conversion

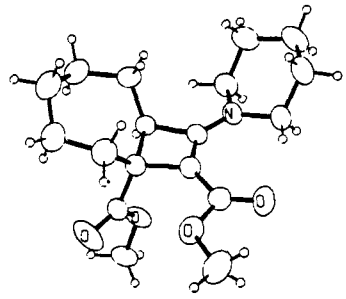


Figure 4. View of **6b**.

into **6b** and **6c**, respectively. The characteristic absorption corresponding to the "enamine" proton in **5j** and **5k** were recorded at δ 4.71 (t) and 4.76 (t), respectively. In the case of the diethylamino derivative **4l** we could isolate the corresponding *cis,cis*-1,3-cyclononadiene **5l** because upon chromatography at room temperature **4l** isomerized selectively to **5l**. Compound **5l** was obtained in a yield of 66% and could be fully characterized by ^{1}H and ^{13}C NMR spectroscopy. In an independent experiment **5l** was converted at 110 °C in toluene into **6d**.

Finally we succeeded in obtaining one of the bicyclo[5.2.0]-non-8-enes **6** as a crystalline compound. The piperidinyl derivative **6b** (mp 76.0–78.5 °C) gave single crystals that were used for an X-ray structure determination (Figure 4), which surprisingly revealed that the two rings are fused with the cis stereochemistry and provided the definite proof of the bicyclo[5.2.0]non-8-ene structure **6**.

Reaction of the *cis,trans*-1,10-cyclodecadiene **4e** in toluene at 110 °C for 40 h yielded exclusively the corresponding *cis,cis*-1,3-cyclodecadiene **5e** as followed from the "enamine" absorption in the ^{1}H NMR spectrum at δ 4.05 (dd). The conversion after 40 h was 80%.

Photochemical Reactions of the *cis,trans*-Cycloalkadienes (4). A number of the compounds **4** underwent conversion upon standing in daylight even in the solid state and more rapidly in solution. Since this aspect has never been mentioned in the literature on reactions of enamines with DMAD, we decided to study these photochemical reactions in more detail. Upon irradiation of the equilibrium mixture of **2b** and **4b** in benzene-d_6 for 1 h at 20 °C with a high-pressure mercury lamp we obtained with high selectivity **5b**. Compound **5b** isomerizes thermally at room temperature slowly to **3b**. The corresponding (2 + 2) cycloadducts **2f** and **2g** were not converted upon irradiation. The S analogue of **4b**, viz., **4c**, dissolved in deuteriochloroform, underwent, on standing in a quartz flask in daylight for 8 days or upon irradiation with a daylight lamp for 17 h, a selective conversion into an isomeric compound (mp 77–79 °C) which was isolated in a yield of 83%. The ^{1}H NMR spectrum showed the absorption of the "enamine" proton characteristic for structures **5**, in this case at δ 4.71 (dd), and in the ^{13}C NMR spectrum we found the corresponding "enamine" carbon atom at δ 101.4 (d). A single-crystal X-ray analysis definitely proved the structure of **5c** including the cis,cis stereochemistry of the 1,3-diene moiety (Figure 5) [C=C—C=C torsion angles: −8.4° (2), −58.8° (2), and −1.1° (2)]. The conformation of the eight-membered ring of **5c** is similar to the conformation of **3c** when torsion angles are taken in opposite order (vide supra), which takes into account the different positions of the double bonds. The main difference in torsion angles (Table V) in this case is 4°. All structures **5** (vide supra) were correlated on the basis of comparison of spectroscopic data with those of **5c**.

An independent experiment revealed that **5e** isomerized selectively to **3c** upon heating for 2 h at 100° C in toluene.

The *cis,trans*-cyclononadienes **4d**, **4j**, **4k**, and **4l** were irradiated in benzene-d_6 solution at room temperature until complete conversion. The results given in Table I show that in all cases mixtures of **5** and **3** were obtained in which **5** dominates. The structures **3** were proven by ^{1}H NMR spectroscopy [δ 6.9–6.8 (dd)] and compounds **5** were, for comparison with the intermediate products of thermal isomerization, fully characterized by ^{1}H NMR spectroscopy.

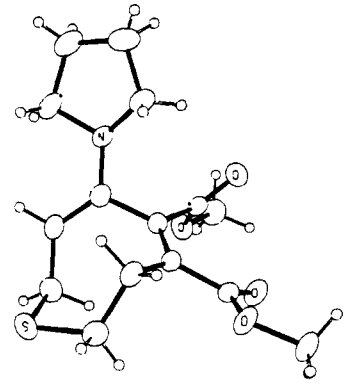


Figure 5. View of **5c**.

Table I. Irradiation of 4d,j-l

compd	time, h	ratio of 5:3[a]
4d	5.5	2:1
4j	3.5	4:1
4k	4.0	2:1
4l	10.0[b]	>10:1

[a] Ratios determined by ^{1}H NMR spectroscopy. [b] Conversion about 75%.

In a separate experiment we have excluded the possibility of a photostationary state between **3** and **5**. When the reaction mixture containing **3d** and **5d** (ratio 1:2) in toluene was heated for 20 h at 110 °C compound **5d** was converted into **6a** whereas **3d** did not react. When the mixture of **6a** and **3d** was further irradiated at room temperature no reaction occurred.

The photochemical isomerization of *cis,trans*-cyclodecadiene **4e** was a relatively slow reaction. After irradiation for 11 h only 66% of **4e** was converted into a 1:1 mixture of **5e** and **3e**. The latter compound was identified by the absorptions in the ^{1}H NMR spectrum for the vinylic hydrogen atom and the methoxy groups at δ 6.88 (dd) and δ 3.71 and 3.56 (s), respectively.

The above results clearly indicate that only a few (2 + 2) cycloadducts can be obtained as relatively "stable" compounds at room temperature when the cyclobutene ring is fused to a five- or six-membered ring. For further reaction in polar solvents, apart from **2a**, we have also prepared the 1-(1-pyrrolidinyl)bicyclo-[*n*.2.0]alkenes **7**,[22] **8**,[25] and **9**.[25] In toluene these compounds isomerize to the corresponding *cis,cis*-cycloalkadienes (type **3**) in agreement with the literature. In these cases the *cis,trans*-cycloalkadienes (type **4**) could not be detected.

Reactivity of (2 + 2) Cycloadducts 2 and 7–9 and *cis,trans*-Cycloalkadienes 4 in Methanol. The actual reason for the preparation of the (2 + 2) cycloadducts of enamines and DMAD as outlined in the introduction was the possible conversion of the (2 + 2) cycloadducts of pyrrolidinyl enamines into pyrrolizines. Consequently **7** (Chart II) was dissolved in methanol at room temperature and we observed a fast isomerization. After 2 h **7** was quantitatively converted into the thieno[2,3-*b*]pyrrolizine **10**. The structure, including the cis stereochemistry,[33] was proven by ^{1}H and ^{13}C NMR spectroscopy which showed the characteristic absorptions at δ 4.85 (dd, NCH), and 76.8 (d, NCH) and 54.4 [s, $C(E)CH_2E$], respectively, and by comparison of these data with those of a thieno[2,3-*b*]pyrrolizine, the structure of which has been ascertained by X-ray analysis.[31] A similar result was obtained with **8** which was converted into the *cis*-indeno[2,1-*b*]pyrrolizine **11** in a yield of 78%. Reaction of **9** at room temperature gave after a reaction time of 47 h only a conversion of 75% into **12** but when the reaction was performed at 65 °C for 18 h, the conversion was 95%. Because of this lower reactivity of **9** in methanol we were able to follow this conversion by ^{1}H NMR spectroscopy. After 1, 6, and 22 h we observed a singlet absorption at δ 5.95 which was assigned to the *Z* isomer of **13**.

Separate experiments of DMAD with the corresponding enamines in methanol at 25 °C gave the pyrrolizines **10**, **11**, and **12**[32] in comparable yields.

Table II. Characteristic ^1H and ^{13}C NMR Chemical Shifts of Compounds 4

	^1H NMR ($CDCl_3$)				^{13}C NMR ($CDCl_3$), δ					
compd	δ =CH (dd)	*J*, Hz	δ E (s)		C=O (s), C-3[a] (s)			=CH (d)	C-1[a] (s)	C-2[a] (s)
4b	5.51	5.1 and 12.0	3.75	3.60	169.8	165.4	162.1	139.8	134.9	96.9
4c	5.50	4.6 and 12.6	3.76	3.60	169.1	165.1	159.0	131.2	134.3	96.1
4d	6.03	3.7 and 11.5	3.74	3.57	168.9	167.0	164.6	152.9	132.7	97.3
4e	5.82	5.0 and 12.2	3.72	3.57	169.0	164.9	163.7	147.3	132.7	98.0
4h	5.40	4.5 and 12.5	3.74	3.62	*b*	*b*	*b*	*b*	*b*	*b*
4j	5.99	3.9 and 11.2	3.74	3.58	171.4	168.9	164.8	151.9	133.5	97.8
4k	6.06	3.9 and 11.2	3.75	3.59	170.5	168.6	164.9	153.1	133.1	99.1
4l	5.92	3.7 and 11.2	3.75	3.57	170.8	169.2	164.8	152.0	133.6	99.3

[a] In the case of 4c C-1, C-2, and C-3 correspond to C-4, C-5, and C-6, respectively. [b] The ^{13}C NMR spectrum of 4h could not be recorded on account of isomerization.

Table III. Crystallographic Data

	3c	4c	5c	6b	14
space group	$P2_1/c$	$P\bar{1}$	$P\bar{1}$	$P2_1/c$	$P2_1/n$
a, Å	9.704 (4)	13.600 (2)	12.028 (2)	12.358 (2)	13.718 (1)
b, Å	17.260 (8)	11.477 (2)	9.446 (1)	10.885 (1)	25.950 (1)
c, Å	10.049 (4)	10.546 (2)	7.027 (1)	13.870 (2)	8.922 (1)
α, deg	90	74.66 (2)	100.92 (1)	90	90
β, deg	108.58 (3)	78.52 (2)	100.34 (1)	110.58 (1)	102.11 (1)
γ, deg	90	79.93 (2)	96.05 (1)	90	90
Z	4	4	2	4	4
T (K)	293 (2)	293 (2)	218 (2)	293 (2)	148 (2)
λ, Å	1.5418	0.7107	1.5418	1.5418	1.5418
ω scan width, deg	1.7 + 0.8 tan ω	1.5 + 0.8 tan ω	2.0 + 0.5 tan ω	1.8 + 0.7 tan ω	2.0 + 0.5 tan ω
ω scan speed, deg s^{-1}	0.05	0.03	0.05	0.05	0.08
ω range, deg	$3 < \omega < 65$	$2 < \omega < 22.5$	$3 < \omega < 74$	$4 < \omega < 74$	$4 < \omega < 65$
no. of measured refl.	3061	4046	2594	2896	5313
no. of refl. with $I > \sigma(I)$	2806	3497	2415	2585	4369
no. of parameters refined	275	388	275	317	564
R factor, %	5.0	5.9	4.4	4.5	9.5

Table IV. Bond Distances in the Eight-Membered Rings[a]

	3c	4cA	4cB	5c	14A	14B
X1-C2	1.820 (2)	1.839 (5)	1.837 (5)	1.801 (2)	1.521 (6)	1.520 (6)
X1-C8	1.794 (3)	1.825 (5)	1.820 (4)	1.833 (3)	1.520 (6)	1.516 (7)
C2-C3	1.484 (3)	1.461 (6)	1.478 (6)	1.534 (3)	1.551 (6)	1.543 (6)
C3-C4	1.340 (3)	1.341 (5)	1.341 (5)	1.508 (3)	1.537 (5)	1.552 (5)
C4-C5	1.475 (3)	1.458 (5)	1.460 (5)	1.347 (3)	1.355 (5)	1.458 (5)
C5-C6	1.386 (2)	1.403 (5)	1.398 (5)	1.490 (3)	1.493 (5)	1.518 (6)
C6-C7	1.509 (3)	1.528 (6)	1.522 (5)	1.345 (3)	1.345 (5)	1.342 (6)
C7-C8	1.541 (3)	1.516 (6)	1.529 (6)	1.502 (3)	1.503 (6)	1.508 (7)

[a] The atom indicated X1 is S-1 in the case of 3c and 4c and C-1 for 14. Double bonds are indicated by an underscore.[74]

Table V. Torsion Angles in the Eight-Membered Rings[74]

	3c	4cA	4cB	5c	14A	14B
C8-X1-C2-C3	−82.4 (2)	32.2 (3)	35.1 (3)	53.5 (2)	60.4 (4)	−69.1 (4)
C2-X1-C8-C7	52.2 (1)	−81.0 (3)	−82.7 (3)	−85.4 (1)	−78.4 (4)	73.9 (4)
X1-C2-C3-C4	100.6 (2)	−91.2 (3)	−93.2 (3)	−89.6 (1)	−89.7 (3)	99.2 (3)
C2-C3-C4-C5	−3.7 (2)	143.0 (3)	141.9 (3)	103.4 (2)	84.5 (3)	−60.0 (3)
C3-C4-C5-C6	−51.9 (2)	−35.3 (4)	−36.0 (4)	−8.4 (2)	12.0 (4)	−44.3 (3)
C4-C5-C6-C7	−17.4 (2)	−28.4 (4)	−27.2 (4)	−58.8 (2)	−70.9 (4)	93.1 (4)
C5-C6-C7-C8	108.1 (2)	−10.0 (4)	−9.9 (4)	−1.1 (2)	−1.0 (4)	−1.6 (5)
C6-C7-C8-X1	−90.3 (2)	103.8 (3)	103.1 (3)	99.9 (2)	87.4 (4)	−80.7 (4)

The equilibrium mixture of **2b** and **4b** was also reacted in methanol at room temperature for 4 h to give a mixture of two products. The minor product could be identified as the known *cis,cis*-cyclooctadiene **3b**, but the major product, isolated in a yield of 57%, was not the expected pyrrolizine.[32] The mass spectrum of this compound pointed to a dimer of **2b**. Single-crystal X-ray analysis proved the structure of the dimer **14** (Figure 6).

Bond distances (Table IV) and torsion angles (Table V) clearly show the *cis*-cyclooctene of the first and the *cis,cis*-cyclooctadiene structure of the second eight-membered ring. The conformation of the cyclooctadiene ring in **14** is the same as the conformations of the rings of **3c** and **5c** which also have a *cis,cis*-1,3-diene moiety.

We found that pyrrolizines are not only formed by reaction of the (2 + 2) cycloadducts but also from several *cis,trans*-cycloalkadienes **4** which according to ^1H NMR spectroscopy do not contain the isomeric (2 + 2) cycloadducts in detectable quantities.

Compound **4c** reacted in methanol slowly at room temperature but was completely converted after reaction at 65 °C for 15 h. A mixture of the cis,cis-isomer **3c** and the *cis*-thiopyrano[3,4-*b*]pyrrolizine **15** was obtained in a ratio of 2:5. Pyrrolizine **15**

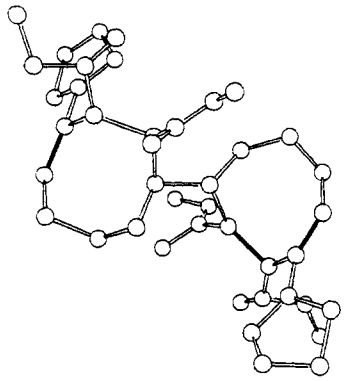
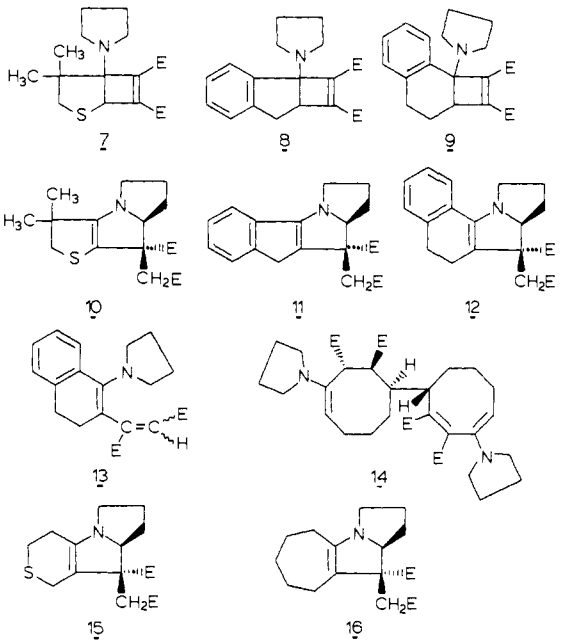


Figure 6. View of **14**. Hydrogen atoms have been omitted for clarity. Double bonds are indicated by solid lines.

Chart II



was also obtained by reaction of enamine **1c** with DMAD in methanol in a yield of 41%. The *cis,trans*-cyclononadiene **4d** was selectively converted into the corresponding pyrrolizine after reaction in methanol at 65 °C for 24 h. The cyclohepta[*b*]pyrrolizine **16** was obtained in a yield of 90% as an oil. The structures of **15** and **16** were proven by ^1H and ^{13}C NMR spectroscopy which showed the characteristic absorptions at δ 4.43 (dd) and 4.41 (dd, NCH) and δ 68.5 and 69.1 (d, NCH) and δ 57.4 and 57.6 [s, $C(E)CH_2E$], respectively.[31,32]

Discussion

Our results clearly show that the reactions of enamines and DMAD in apolar solvents are far more complicated than the existing literature would suggest. The fact that the (2 + 2) cycloadducts **7–9**, synthesized in apolar solvents, undergo a rearrangement to pyrrolizines **10–12** in methanol adds further evidence that the (2 + 2) cycloaddition of DMAD and enamines is a concerted process. This means that 1,4-dipolar intermediates, when occurring, in the (2 + 2) cycloaddition would be captured by the *intramolecular* rearrangement to pyrrolizines (vide infra).[31,32] The stereochemistry of the (2 + 2) cycloadducts that are sufficiently stable that they can be isolated has not been determined by X-ray analysis, but it has to be cis because trans-fusion of a cyclobutene ring to a five- or six-membered ring can be ruled out on the basis of the steric strain involved. In the case of larger rings we cannot isolate the compounds **2** but the corresponding bicyclic (2 + 2) cycloadducts of silyl enol ethers and ethyl propiolate all have the cis stereochemistry and according to Clark and Untch[36] attempts to react (*Z*)-((*tert*-butyldimethylsilyl)oxy)cyclododecene even failed to give the trans-fused cycloadduct whereas the *E* isomer reacted to the cis cycloadduct. Therefore we conclude that the (2 + 2) cycloaddition of enamines and DMAD occurs in a concerted fashion to give the cis cycloadducts.

The thermal valence isomerization of (hetero)cyclobutenes to 1,3-butadienes is a classical example of a stereospecific reaction. In agreement with the principle of conservation of orbital symmetry in electrocyclic reactions the ring opening occurs in a conrotatory mode.[29,37,38] For compounds in which the cyclobutene ring is cis-annulated to another ring system that possesses less than eight atoms, it is generally accepted that the ring opening must occur by way of the symmetry-forbidden disrotatory mode[21,30,39] or by homolytic[40] or heterolytic[27] pathways all having a higher activation energy. As mentioned in the introduction the facile ring opening of 3-aminocyclobutenes cis-fused to 5-, 7-, 8-, and 12-membered rings by a concerted disrotatory mode has found a theoretical basis in results of configuration interaction analysis of polarized π-systems.[30] However, our work clearly shows now that the ring opening of (2 + 2) cycloadducts **2** of DMAD and enamines occurs in the symmetry-allowed fashion. Compared with "unsubstituted" *cis*-bicyclo[*n*.2.0]alkenes[41-45] the rate of isomerization of **2** is much faster because of the presence of *both* an acceptor and a donor substituent at the cyclobutene ring that is formed. This result is in agreement with the theoretical work of Epiotis.[30] Carpenter,[46] however, predicts an increase of the rate of disrotatory ring opening of 1-substituted cyclobutenes but a decrease for the rate of conrotatory ring opening. Obviously the presence of *both* the dialkylamino and ester groups is required for a fast rate since 3-(dimethylamino)-1,2,3,4-tetramethylcyclobutene isomerizes only at 200 °C[47] and 1-cyanocyclobutene isomerizes at a lower rate than cyclobutene.[48] Also the position of the substituents is essential; if the positions of ester and dialkylamino groups are interchanged like in **6**, these compounds are thermally "stable". A comparison of the effect of the structure of the dialkylamino group on the rate of isomerization is possible in the series **2b**, **2f**, and **2g**. The (2 + 2) cycloadduct with the more effective π-electron-donating 1-pyrrolidinyl group undergoes a thermal rearrangement at room temperature whereas the analogues with a 1-piperidinyl or 4-morpholinyl substituent at the bridgehead sp^3-hybridized carbon atom are thermally stable at room temperature.[49] Similarly in the 4-thiabicyclo[4.2.0]oct-7-ene series we observed the effect of the dialkylamino group. Whereas **2e** is not even detected, **2h** is rapidly equilibrating with **4h** and **2i** is stable at room temperature. This result is in agreement with data obtained by Reiss.[50] The generally accepted statement in the literature that ring opening to give *cis,trans*-cycloalkadienes can be excluded for steric reasons when the product contains less than 10 atoms is obviously incorrect. Kirmse and Richarz[51,52]

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have recently shown that under mild conditions 5-methoxy-*cis*,-*trans*-1,3-cyclooctadiene and even *cis,cis,trans*-1,3,6-cyclooctatriene could be generated.

The conrotatory electrocyclization, e.g., **4b** to **2b**, has a precedent in the conversion of the unsubstituted *cis,trans*-1,3-cyclooctadiene into *cis*-bicyclo[4.2.0]oct-7-ene at 80 °C.[44] Bloomfield and McConaghy[43,53] have shown that at 110 °C the two compounds are in equilibrium. Our observation that the *cis,trans*-cycloalkadienes **4c** and **4d** can be trapped in methanol as the pyrrolizines **15** and **16** lends further support to equilibration of the (2 + 2) cycloadducts **2** and *cis,trans*-cycloalkadienes at room temperature. The temperature dependence of the equilibrium is shown in the cases of **2b** and **4b** (see Figure 1) and of **2k** and **4k** at 80 °C.

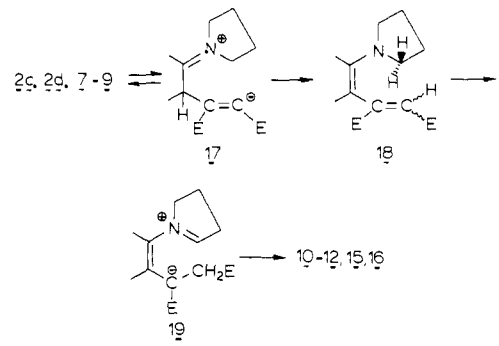
The reactivity of the *cis,trans*-cycloalkadienes **4** both thermally and photochemically makes it understandable that in the literature the *cis,trans*-cycloalkadienes have escaped isolation or detection, in particular in the case of (hetero)bicyclo[4.2.0]oct-7-ene derivatives. On the other hand the higher cis,trans isomers in this series are "stable" and mainly on the basis of analogy incorrect cis,cis structures have been published. The direct cis,trans to cis,cis isomerization is only a major reaction in the thermal rearrangement of compound **4c** although even in this case a two-step process via **5c** cannot be excluded (vide infra). In all other cases the reaction gives the isomeric cycloalkadienes **5**. This conversion can be interpreted as a concerted [1,5] sigmatropic hydrogen shift which occurs in a suprafacial mode.[54,55] The driving force for this reaction is provided by the relief of steric strain of the diene system. It is very well possible that the thermal cis,trans to cis,cis cycloalkadiene isomerization, e.g., **4c** to **3c**, may occur via two consecutive [1,5] hydrogen shifts with **5c** as an intermediate. Evidence in favor of such a mechanism is the detection of **5b** in the isomerization of the equilibrium mixture of **2b** and **4b** and the formation of **5h** on isomerization of **4h**. Besides we have observed independently the conversion of **5c** to **3c** upon reaction at 100 °C.

In all thermal reactions of the cyclononadienes **5d**, **5j**, **5k**, and **5l**, the electrocyclization to the corresponding bicyclo[5.2.0]-nonenes **6** is much faster than the isomerization to the cyclononadienes **3**. The surprising result in this reaction is the cis stereochemistry of **6** since we have proven that the intermediate dienes **5** have the cis,cis stereochemistry. This means that the cyclization occurs in a disallowed disrotatory mode. However, the X-ray structure determination of **5c** shows that not much conjugation is present in the 1,3-diene moiety (C–C length 1.490 (3) Å; torsion angle around the single bond, −58.8° (2)). It is questionable whether in such a situation a phase relation between the two termini of the π-system is a determining factor. In the other cases, viz., **5e** and **5i**, the compounds are "stable" under reaction conditions.

The photochemical isomerization of compounds **4d**, **4e**, and **4j–l** to the corresponding *cis,cis*-cycloalkadienes **3** does not proceed stepwise via **5**. We have excluded a photostationary state between **3** and **5** (vide supra) and from the thermal reactions we know that at room temperature a thermal [1,5] hydrogen shift, e.g., **5e** to **3e**, does not occur. Moreover, in the photochemical reaction the ratio of **5** to **3** is constant as a function of time. The photochemical [1,5] hydrogen shift, if concerted must be antarafacial and such a pericyclic reaction in a cyclic compound has hitherto never been reported.[56] The transition state of an antarafacial reaction is obviously possible in this case.

As described in the introduction this work was initiated by a study towards the mechanism of the formation of pyrrolizines in polar solvents by reaction of enamines with DMAD. Our results show that the assumption, made on the basis of a small difference

Scheme I



in the overall rates of reaction in polar and in apolar solvents,[32,34b] that (2 + 2) cycloadducts can be the precursors of the pyrrolizines is correct. In apolar solvents the 1,4-dipole **17** is obviously not sufficiently stabilized, but in methanol the conversion of the (2 + 2) cycloadduct into **17** is faster than the conrotatory ring opening of compounds **2c**, **2d**, **7–9**. Protonation by the solvent of **17** gives the Michael adducts **18** that subsequently undergo an antarafacial [1,6] hydrogen shift to give the dipole **19**. In methanol the stereochemistry of **19** will be as depicted (Scheme I) and electrocyclization will occur in a stereospecific symmetry-allowed disrotatory pathway to give the pyrrolizines. It also follows from our results that several of the *cis,trans*-cycloalkadienes, e.g., **4c** and **4d**, undergo this conversion in methanol to give **15** and **16**, respectively. This means that a kinetically rapid equilibrium between **4** and **2** exists in these cases although ^{1}H NMR spectroscopy does not show the presence of **2**. This result completes our mechanistic study of the pyrrolizine formation.

A deviating result is the formation of the dimer **14** by reaction in methanol of the mixture of **2b** and **4b**. We can only speculate about the mechanism but the driving force of the reaction must be provided by the highly strained double bond in **4b** and the nucleophilicity of the 1,3-dienamine moiety. The reaction differs from the dimerization of *cis,trans*-cyclooctadiene via a $[{}_\pi 2_s + {}_\pi 2_s]$ cycloaddition of two trans double bonds as was reported by Padwa.[57]

Experimental Section

Melting points were determined with a Leitz Wetzlar 1121 or a Reichert melting point apparatus and are uncorrected. ^{1}H NMR spectra ($CDCl_3$) were recorded with a Bruker WP-80 spectrometer, and ^{13}C NMR spectra ($CDCl_3$) were recorded with a Varian XL-100 spectrometer (Me_4Si as an internal standard). Mass spectra were obtained with a Varian Mat 311A spectrometer and IR spectra with a Perkin-Elmer 257 spectrophotometer. Elemental analyses were carried out by the Element Analytical Section of the Institute for Organic Chemistry TNO, Utrecht, The Netherlands, under supervision of W. J. Buis and G. J. Rotscheid.

Dimethyl acetylenedicarboxylate (DMAD) refers to Aldrich reagent and was distilled before use. The enamines **1a**,[58] **1b**,[59] **1c**,[60] **1d**,[58] **1e**,[59,61] **1f**,[62] **1g**,[63] **1j**,[64] and **1k**[65] were prepared according to the literature. The enamines **1h**,[60] **1i**,[66] and **1l**[67] were prepared according to the method of

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Carlson et al.[68] by reaction of the ketone and the appropriate amine in the presence of titanium tetrachloride in petroleum ether (bp 60–80 °C) as a solvent. All reactions were carried out under a nitrogen atmosphere.

General Procedure for the Reaction of Enamines 1a–l with DMAD in Diethyl Ether. A solution of DMAD (2.84 g, 20 mmol) in 5 mL of diethyl ether was added over a period of 10 min to a solution of **1a–l** (20 mmol) in 20 mL of diethyl ether at 25–30 °C unless otherwise stated. After the reaction was complete, the reaction was worked up as described for the individual reaction mixture. Characteristic ^1H and ^{13}C NMR data of compounds **4** are summarized in Table II.

Dimethyl 1-(1-Pyrrolidinyl)bicyclo[3.2.0]hept-6-ene-6,7-dicarboxylate (2a). After the reaction mixture was stirred for 40 min the solvent was removed under reduced pressure ($T < 35$ °C) to give **2a** as an unstable oil: ^1H NMR δ 3.79 and 3.77 (s, 3 H, OCH_3), 2.9–2.6 (m, 4 H, NCH_2).

Thermodynamic Mixture of Dimethyl 1-(1-Pyrrolidinyl)bicyclo-[4.2.0]oct-7-ene-7,8-dicarboxylate (2b) and Dimethyl 3-(1-Pyrrolidinyl)-*cis*,*trans*-2,8-cyclooctadiene-1,2-dicarboxylate (4b). The reaction mixture was stirred for 10 min after which 25 mL of pentane was added. Upon cooling of the reaction mixture to 0 °C a light-sensitive yellow solid precipitated which was filtered off and purified by trituration with pentane: yield 79%; mp 80–89 °C (diethyl ether) (lit.[17] mp 77–81 °C). The ^1H NMR spectrum showed that this product was a mixture of **2b** and **4b**, rapidly equilibrating on the chemical timescale and slowly on the ^1H NMR timescale.

2b: ^1H NMR δ 3.80 (s, 6 H, OCH_3); ^{13}C NMR δ 162.4 and 161.9 (s, C=O), 147.9 and 140.3 (s, C=C), 67.0 (s, C-1), 43.0 (d, C-6).

Dimethyl *trans*,*cis*-7,8-Dihydro-6-(1-pyrrolidinyl)-2*H*-thiocin-4,5-dicarboxylate (4c). In this case the solution of DMAD was added over 30 min to the solution of **1c** at 20 °C in the dark. The reaction mixture was stirred for 2 h. After removal of the solvent under reduced pressure, the remaining solid was triturated with methanol to give **4c** as a white crystalline compound: yield 82%; mp 144–145 °C (ethanol); IR (KBr) 1710 and 1670 (C=O) cm^{-1}; mass spectrum, *m/e* 311.121 (M^+); calcd 311.119.

Anal. Calcd for $C_{15}H_{21}NO_4S$ (M_r 311.404): C, 57.86; H, 6.80; N, 4.50. Found: C, 57.85; H, 6.83; N, 4.49.

Dimethyl 3-(1-Pyrrolidinyl)-*cis*,*trans*-2,9-cyclononadiene-1,2-dicarboxylate (4d). The reaction mixture was stirred for 30 min. Upon cooling to −35 °C crystallization occurred. The solid was filtered off and triturated with diethyl ether to give pure **4d**: yield 91%; mp 141.5–142.5 °C (ethyl acetate); IR (KBr) 1703 and 1665 (C=O), 1620 (C=C) cm^{-1}; mass spectrum, *m/e* 307.180 (M^+); calcd 307.178.

Anal. Calcd for $C_{17}H_{25}NO_4$ (M_r 307.394): C, 66.43; H, 8.20; N, 4.56. Found: C, 66.44; H, 8.27; N, 4.52.

Dimethyl 3-(1-Pyrrolidinyl)-*cis*,*trans*-2,10-cyclodecadiene-1,2-dicarboxylate (4e). The reaction mixture was stirred for 1 h. Upon cooling to −50 °C crystallization occurred. The solid was filtered off and triturated with diethyl ether to afford pure **4e**: yield 82%; mp 102–106 °C (diethyl ether); IR (KBr) 1715 and 1675 (C=O), 1623 (C=C) cm^{-1}; mass spectrum, *m/e* 321.1965 (M^+); calcd 321.194.

Anal. Calcd for $C_{18}H_{27}NO_4$ (M_r 321.421): C, 67.26; H, 8.47; N, 4.36. Found: C, 67.31; H, 8.44; N, 4.33.

Dimethyl 1-(1-Piperidinyl)bicyclo[4.2.0]oct-7-ene-7,8-dicarboxylate (2f). The reaction mixture was stirred for 1 h. The solvent was removed under reduced pressure ($T < 35$ °C) to give **2f** as an unstable oil which could not be purified: ^1H NMR δ 3.80 and 3.78 (s, 3 H, OCH_3), 3.2–3.05 (m, 1 H, =CCH), 2.7–2.4 (m, 4 H, NCH_2).

Dimethyl 1-(4-Morpholinyl)bicyclo[4.2.0]oct-7-ene-7,8-dicarboxylate (2g). Under the same conditions as described for **2f**, **2g** was also obtained as an unstable oil: ^1H NMR δ 3.80 and 3.79 (s, 3 H, OCH_3), 3.2–3.05 (m, 1 H, =CCH), 3.9–3.6 (m, 8 H, OCH_2 and NCH_2).

Thermodynamic Mixture of Dimethyl 1-(1-Piperidinyl)-4-thiabicyclo-[4.2.0]oct-7-ene-7,8-dicarboxylate (2h) and Dimethyl *trans*,*cis*-7,8-Dihydro-6-(1-piperidinyl)-2*H*-thiocin-4,5-dicarboxylate (4h). In this case the reaction was performed at 5 °C. After stirring for 2 h at that temperature, the solvent was removed under reduced pressure ($T < 25$ °C) to give an unstable mixture of **2h** and **4h**.

2h: ^1H NMR δ 3.82 and 3.80 (s, 3 H, OCH_3).

Dimethyl 1-(4-Morpholinyl)-4-thiabicyclo[4.2.0]oct-7-ene-7,8-dicarboxylate (2i). After stirring for 2 h the solvent was removed under reduced pressure ($T < 35$ °C) to give **2i** as an oil: ^1H NMR δ 3.82 and 3.81 (s, 3 H, OCH_3), 3.9–3.55 (m, 4 H, OCH_2), 3.5–2.2 (m, other CH_2); mass spectrum, *m/e* 327.111 (M^+); calcd for $C_{15}H_{21}NO_5S$, 327.114.

Dimethyl 3-(1-Piperidinyl)-*cis*,*trans*-2,9-cyclononadiene-1,2-dicarboxylate (4j). The reaction mixture was stirred for 3 h. Upon cooling to −40 °C, **4j** crystallized from the reaction mixture and was filtered off: yield 69%; mp 137.5–139 °C (methanol); IR (KBr) 1700 and 1660 (C=O), 1600 (C=C) cm^{-1}; mass spectrum, *m/e* 321.192 (M^+); calcd 321.194.

Anal. Calcd for $C_{18}H_{27}NO_4$ (M_r 321.421): C, 67.26; H, 8.47; N, 4.36. Found: C, 67.43; H, 8.40; N, 4.33.

Dimethyl 3-(4-Morpholinyl)-*cis*,*trans*-2,9-cyclononadiene-1,2-dicarboxylate (4k). This compound was prepared similarly as **4j** in a yield of 36%: mp 157–159.5 °C (diethyl ether); IR (KBr) 1701 and 1662 (C=O), 1611 (C=C) cm^{-1}; mass spectrum, *m/e* 323.170 (M^+); calcd 323.173.

Anal. Calcd for $C_{17}H_{25}NO_5$ (M_r 323.394): C, 63.14; H, 7.79; N, 4.33. Found: C, 62.96; H, 7.85; N, 4.27.

Dimethyl 3-(Diethylamino)-*cis*,*trans*-2,9-cyclononadiene-1,2-dicarboxylate (4l). After stirring for 2 h the solvent was removed under reduced pressure to give **4l** as an oil which was not further purified: IR (KBr) 1715 and 1670 (C=O), 1616 (C=C) cm^{-1}; mass spectrum, *m/e* 309.193 (M^+); calcd for $C_{17}H_{27}NO_4$, 309.194.

Dimethyl 3-(1-Pyrrolidinyl)-*cis*,*cis*-2,7-cycloheptadiene-1,2-dicarboxylate (3a). Compound **3a** crystallized slowly from the crude reaction mixture of **1a** and DMAD (see synthesis **2a**) in a yield of 30%: mp 136–138 °C (ethanol) (lit.[15] mp 145–146 °C, lit.[16] 135–138 °C, lit.[17] 147–148 °C); ^1H NMR δ 6.86 (t, J = 7.5 Hz, 1 H, =CH), 3.72 and 3.59 (s, 3 H, OCH_3), 3.5–3.2 (m, 4 H, NCH_2), 2.45–1.65 (m, 10 H, CH_2); ^{13}C NMR δ 168.8 and 166.3 (s, C=O), 161.3 (s, C-3), 136.7 (s, C-1), 136.0 (d, C-7), 94.9 (s, C-2), 51.7 (t, NCH_2).

Dimethyl 3-(1-Pyrrolidinyl)-*cis*,*cis*-2,8-cyclooctadiene-1,2-dicarboxylate (3b). A solution of the crude reaction mixture of **1b** and DMAD in acetonitrile was stirred for 16 h at room temperature. Subsequently the solvent was removed under reduced pressure. The partly crystalline residue was triturated with ethanol and pure **3b** was obtained in a yield of 21%: mp 141.5–142.5 °C (ethanol) (lit.[17] mp 141–142 °C); ^1H NMR δ 6.70 (dd, J = 7.2 and 9.6 Hz, 1 H, =CH), 3.71 and 3.59 (s, 3 H, OCH_3), 3.8–3.5 and 3.25–2.9 (m, 2 H, NCH_2); ^{13}C NMR δ 169.7 and 166.4 (s, C=O), 159.5 (s, C-3), 138.3 (d, C-8), 133.7 (s, C-1), 94.0 (s, C-2), 51.7 and 50.7 (q, OCH_3), 51.3 (t, NCH_2).

Dimethyl *cis*,*cis*-7,8-Dihydro-6-(1-pyrrolidinyl)-2*H*-thiocin-4,5-dicarboxylate (3c). A solution of **4c** (0.55 g, 1.8 mmol) in 20 mL of toluene was heated at 100 °C for 4 h in the dark. After removal of the solvent under reduced pressure, addition of diethyl ether to the residue gave a solid from which pure **3c** was obtained by trituration with diisopropyl ether: yield 44%; mp 169–170 °C (toluene); IR (KBr) 1710 and 1680 (C=O), 1610 (C=C) cm^{-1}; ^1H NMR δ 6.70 (dd, J = 6.7 and 11.0 Hz, 1 H, =CH), 3.74 and 3.61 (s, 3 H, OCH_3), 3.8–1.7 (m, 14 H, CH_2); ^{13}C NMR δ 169.1 and 166.2 (s, C=O), 155.8 (s, C-6), 133.5 (d, C-3), 132.4 (s, C-4), 94.4 (s, C-5), 52.0 and 51.0 (q, OCH_3), 51.4 (t, NCH_2); mass spectrum, *m/e* 311.120 (M^+); calcd 311.119.

Anal. Calcd for $C_{15}H_{21}NO_4S$ (M_r 311.404): C, 57.86; H, 6.80; N, 4.50. Found: C, 57.80; H, 6.76; N, 4.54.

Compound **3c** was also obtained by heating a solution of **5c** in toluene at 100 °C for 2 h.

Dimethyl 3-(1-Piperidinyl)-*cis*,*cis*-2,8-cyclooctadiene-1,2-dicarboxylate (3f). After the crude reaction mixture of **1f** and DMAD (see synthesis **2f**) stood for 24 h at room temperature, petroleum ether (bp 60–80 °C) was added to give a solid from which **2f** was isolated by trituration with petroleum ether (bp 60–80 °C) in a yield of 43%: mp 138–140 °C (diethyl ether); IR (KBr) 1710 and 1680 (C=O), 1612 (C=C) cm^{-1}; ^1H NMR δ 6.65 (dd, J = 7.3 and 9.5 Hz, 1 H, =CH), 3.71 and 3.62 (s, 3 H, OCH_3), 3.6–1.0 (m, 18 H, CH_2); ^{13}C NMR δ 169.4 and 167.1 (s, C=O), 164.1 (s, C-3), 138.1 (d, C-8), 133.7 (s, C-1), 97.4 (s, C-2), 51.7 (t, NCH_2), 51.7 and 50.9 (q, OCH_3); mass spectrum, *m/e* 307.178 (M^+); calcd 307.178.

Anal. Calcd for $C_{17}H_{25}NO_4$ (M_r 307.394): C, 66.43; H, 8.20; N, 4.56. Found: C, 66.36; H, 8.09; N, 4.48.

Dimethyl 3-(4-Morpholinyl)-*cis*,*cis*-2,8-cyclooctadiene-1,2-dicarboxylate (3g). After a solution of the crude reaction mixture of **1g** and DMAD (see synthesis **2g**) in diethyl ether stood for 24 h at room temperature, ethyl acetate was added to give **3g** as a pure solid in a yield of 93%: mp 210–212 °C (chloroform/acetone, 1:1) (lit.[15] mp 210–211 °C, lit.[16] mp 210–212 °C); ^1H NMR δ 6.72 (dd, J = 7.3 and 9.5 Hz, 1 H, =CH), 3.71 and 3.63 (s, 3 H, OCH_3), 3.8–1.0 (m, 14 H, CH_2); ^{13}C NMR δ 169.0 and 167.0 (s, C=O), 162.9 (s, C-3), 139.0 (d, C-8), 133.5 (s, C-1), 98.4 (s, C-2), 66.8 (t, OCH_2), 51.8 and 51.0 (q, OCH_3), 51.0 (t, NCH_2).

Dimethyl *cis*,*cis*-3,8-Dihydro-6-(1-pyrrolidinyl)-2*H*-thiocin-4,5-dicarboxylate (5c). A solution of **4c** (0.50 g, 1.6 mmol) in 12.5 mL of deuteriochloroform was stirred at room temperature for 8 days in a quartz flask. The solvent was removed under reduced pressure. Addition of pentane to the resulting oil gave a solid from which pure **5c** was obtained by trituration with pentane: yield 83%; mp 77–79 °C (diisopropyl ether; yellow); IR (KBr) 1720 (C=O) cm^{-1}; ^1H NMR δ 4.71 (dd,

(68) Carlson, R.; Nilsson, A.; Strömqvist, M. *Acta Chem. Scand., Ser. B* **1983**, *37*, 7–13.

J = 7.3 and 9.5 Hz, 1 H, =CH), 3.80 and 3.77 (s, 3 H, OCH_3), 3.4–2.4 (m, 10 H, CH_2), 2.1–1.7 (m, 4 H, NCH_2CH_2); ^{13}C NMR δ 167.9 and 167.4 (s, C=O), 141.3 (s, C-6), 137.6 and 134.0 (s, C-4 and C-5), 101.4 (d, C-7), 52.5 (q, OCH_3), 48.8 (t, NCH_2); mass spectrum, m/e 311.122 (M^+); calcd 311.119.

Anal. Calcd for $C_{15}H_{21}NO_4S$ (M_r 311.404): C, 57.86; H, 6.80; N, 4.50. Found: C, 57.91; H, 6.99; N, 4.34.

The same compound was obtained upon irradiation of **4c** with a 75-W daylight lamp for 17 h.

Dimethyl 3-(1-Pyrrolidinyl)-*cis*,*cis*-1,3-cyclodecadiene-1,2-dicarboxylate (5e). A solution of **4e** (0.51 g, 1.6 mmol) in 10 mL of toluene was heated at 110 °C for 40 h. The solvent was removed under reduced pressure. The resulting oil, which could not be crystallized or purified by chromatography because of decomposition, consisted for >80% of **5e**: ^1H NMR δ 4.05 (dd, J = 5.7 and 10.6 Hz, 1 H, =CH), 3.79 and 3.74 (s, 3 H, OCH_3), 3.2–2.9 (m, 4 H, NCH_2); ^{13}C NMR δ 168.9 and 166.6 (s, C=O), 147.3 (s, C-3), 144.7 and 139.6 (s, C-1 and C-2), 99.0 (d, C-4), 47.9 (t, NCH_2); mass spectrum, m/e 321.189 (M^+); calcd for $C_{18}H_{27}NO_4$, 321.194).

Dimethyl *cis*,*cis*-3,8-Dihydro-6-(1-piperidinyl)-2*H*-thiocin-4,5-dicarboxylate (5h).[22] Upon standing of a ^1H NMR sample of a mixture of **2h** and **4h** at room temperature for 2 days, quantitative isomerization had taken place to **5h**: ^1H NMR δ 4.99 (dd, J = 7.3 and 9.8 Hz, 1 H, =CH), 3.78 (s, 6 H, OCH_3), 3.7–2.2 (m, 10 H, NCH_2, SCH_2, and $=CCH_2$), 1.8–1.4 (m, 6 H, other CH_2).

Dimethyl *cis*,*cis*-3,8-Dihydro-6-(4-morpholinyl)-2*H*-thiocin-4,5-dicarboxylate (5i). A solution of crude **2i**, prepared by reaction of **1i** and DMAD, in 20 mL of toluene was heated at 110 °C for 2 h. After removal of the solvent under reduced pressure the crude reaction mixture was purified by column chromatography (silica gel, chloroform/ethyl acetate, 1:1) to afford **5i** as a solid: yield 31% (calculated on **1i**); mp 118.5–120.5 °C (diisopropyl ether); IR (NaCl) 1718 (C=O) and 1615 (C=C) cm^{-1}; ^1H NMR δ 5.04 (dd, J = 7.2 and 9.9 Hz, 1 H, =CH), 3.80 (s, 6 H, OCH_3), 3.85–3.6 (m, 4 H, OCH_2), 3.55–2.1 (m, 10 H, other CH_2's); ^{13}C NMR δ 168.2 and 166.5 (s, C=O), 145.0 (s, C-6), 137.5 and 135.0 (s, C-4 and C-5), 107.9 (d, C-7), 66.7 (t, OCH_2), 52.6 and 52.5 (q, OCH_3), 49.6 (t, NCH_2); mass spectrum, m/e 327.111 (M^+); calcd 327.114.

Anal. Calcd for $C_{15}H_{21}NO_5S$ (M_r 327.404): C, 55.03; H, 6.47; N, 4.28. Found: C, 54.84; H, 6.38; N, 4.21.

Dimethyl 3-(Diethylamino)-*cis*,*cis*-1,3-cyclononadiene-1,2-dicarboxylate (5l). Column chromatography (silica gel, ethyl acetate) of the crude **4l**, prepared by reaction of **1l** and DMAD, gave pure **5l**: yield 66% (calculated on **1l**); oil; IR (KBr) 1725 (C=O) and 1616 (C=C) cm^{-1}; ^1H NMR δ 4.54 (t, J = 8.3 Hz, 1 H, =CH), 3.78 and 3.73 (s, 3 H, OCH_3), 2.93 (q, J = 7.0 Hz, 4 H, NCH_2), 1.00 (t, J = 7.0 Hz, 6 H, NCH_2CH_3); ^{13}C NMR δ 168.6 and 167.7 (s, C=O), 141.9, 141.3 and 135.7 (s, C-1, C-2 and C-3), 105.1 (d, C-4), 52.1 (q, OCH_3), 42.7 (t, NCH_2); mass spectrum, m/e 309.192 (M^+); calcd for $C_{17}H_{27}NO_4$, 309.194.

General Procedure for the Thermal Isomerization of 4d,j–l. Preparation of 6a–d. A solution of **4d,j–l** (20 mmol) in 30 mL of toluene was refluxed for 4 h, 23 h, 17 h, and 22 h, respectively. The solvent was removed under reduced pressure and the residue separated by column chromatography.

Dimethyl 8-(1-Pyrrolidinyl)bicyclo[5.2.0]non-8-ene-1,9-dicarboxylate (6a). Purification by chromatography (silica gel, ethyl acetate) afforded pure **6a**: yield 70%; oil; IR (KBr) 1725 and 1690 (C=O), 1625 (C=C) cm^{-1}; ^1H NMR δ 3.9–3.35 (m, 4 H, NCH_2), 3.67 and 3.57 (s, 3 H, OCH_3), 3.24 (dd, J = 4.6 and 8.1 Hz, 1 H, CH); ^{13}C NMR δ 177.0 and 163.2 (s, C=O), 157.5 (s, C-8), 94.1 (s, C-9), 52.2 (s, C-1), 51.7 (q, OCH_3), 49.8 (d, C-7); mass spectrum, m/e 307.177 (M^+); calcd for $C_{17}H_{25}NO_4$, 307.178.

Dimethyl 8-(1-Piperidinyl)bicyclo[5.2.0]non-8-ene-1,9-dicarboxylate (6b). Purification by chromatography (silica gel, chloroform/ethyl acetate, 3:2) gave pure **6b** as a solid: yield 83%; mp 76–78.5 °C (diisopropyl ether, −20 °C); IR (NaCl) 1723 and 1679 (C=O), 1610 (C=C) cm^{-1}; ^1H NMR δ 3.8–3.4 (m, 4 H, NCH_2), 3.66 and 3.56 (s, 3 H, OCH_3), 3.3–3.1 (m, 1 H, CH); ^{13}C NMR δ 177.5 and 163.7 (s, C=O), 159.5 (s, C-8), 94.4 (s, C-9), 51.8 (s, C-1), 51.6 and 50.0 (q, OCH_3), 49.3 (t, NCH_2), 48.9 (d, C-7); mass spectrum, m/e 321.192 (M^+); calcd 321.194.

Anal. Calcd for $C_{18}H_{27}NO_4$ (M_r 321.421): C, 67.26; H, 8.47; N, 4.36. Found: C, 67.03; H, 8.25; N, 4.19.

Dimethyl 8-(4-Morpholinyl)bicyclo[5.2.0]non-8-ene-1,9-dicarboxylate (6c). Separation of the crude reaction mixture by chromatography (silica gel, dichloromethane/ethyl acetate, 5:1) afforded still impure **6c** which could not be crystallized: yield 58%; oil; IR (NaCl) 1721 and 1680 (C=O), 1608 (C=C) cm^{-1}; ^1H NMR δ 3.9–3.5 (m, 8 H, NCH_2 and OCH_2), 3.71 and 3.67 (s, 3 H, OCH_3), 3.27 (dd, J = 3.7 and 6.1 Hz, 1 H, CH); ^{13}C NMR δ 176.8 and 163.3 (s, C=O), 158.8 (s, C-8), 95.6 (s, C-9), 66.8 (t, OCH_2), 51.4 (s, C-1); mass spectrum, m/e 323.170 (M^+); calcd for $C_{17}H_{25}NO_5$, 323.173.

Dimethyl 8-(Diethylamino)bicyclo[5.2.0]non-8-ene-1,9-dicarboxylate (6d). Separation of the crude reaction mixture by chromatography (silica gel, chloroform/ethyl acetate, 4:1) gave still impure **6d** which could not be crystallized: yield 45%; oil; IR (NaCl) 1725 and 1679 (C=O), 1609 (C=C) cm^{-1}; ^1H NMR δ 3.9–3.4 (m, 4 H, NCH_2), 3.66 and 3.57 (s, 3 H, OCH_3), 3.3–3.1 (m, 1 H, CH), 1.17 (t, J = 7.1 Hz, 6 H, CH_3); ^{13}C NMR δ 177.4 and 163.2 (s, C=O), 159.2 (s, C-8), 94.2 (s, C-9), 43.7 (t, NCH_2); mass spectrum, m/e 309.192 (M^+); calcd for $C_{17}H_{27}NO_4$, 309.194.

General Procedure for the Photochemical Reactions. A solution of the compound (or mixture of compounds) (60 mg) in 0.5 mL of benzene-d_6 was irradiated in a quartz ^1H NMR tube with a Hanau high-pressure mercury lamp. After completion of the reaction the solvent was removed under reduced pressure and of the residue another ^1H NMR spectrum was recorded in $CDCl_3$ as a solvent.

Irradiation of the Mixture of 2b and 4b. Formation of Dimethyl 3-(1-Pyrrolidinyl)-*cis*,*cis*-1,3-cyclooctadiene-1,2-dicarboxylate (5b). After irradiation for 1 h the mixture was quantitatively converted into **5b**: ^1H NMR δ 4.69 (t, J = 7.3 Hz, 1 H, =CH), 3.79 and 3.76 (s, 3 H, OCH_3); ^{13}C NMR δ 168.7 and 168.0 (s, C=O), 141.2, 139.5 and 134.0 (s, C-1, C-2 and C-3), 105.3 (d, C-4), 52.2 (q, OCH_3), 48.6 (t, NCH_2).

Upon standing **5b** isomerized to **3b**.

Irradiation of 4d, 4j, 4k, and 4l. Formation of Mixtures of Dimethyl 3-(1-Pyrrolidinyl)-, 3-(1-Piperidinyl)-, 3-(4-Morpholinyl)-, 3-(Diethylamino)-*cis*,*cis*-2,9-cyclononadiene-1,2-dicarboxylate (3d,j–l) and -1,3-cyclononadiene-1,2-dicarboxylate (5d,j–l). Irradiation yielded mixtures of compounds **3** and **5**. Reaction times and product ratios are summarized in Table I.

3d: ^1H NMR δ 6.83 (dd, J = 7.6 and 8.5 Hz, 1 H, =CH), 3.72 and 3.75 (s, 3 H, OCH_3).

5d: ^1H NMR δ 4.35 (dd, J = 6.6 and 10.0 Hz, 1 H, =CH), 3.80 and 3.75 (s, 3 H, OCH_3).

3j: ^1H NMR δ 6.87 (dd, J = 7.0 and 9.6 Hz, 1 H, =CH), 3.71 and 3.59 (s, 3 H, OCH_3).

5j: ^1H NMR δ 4.71 (t, J = 8.4 Hz, 1 H, =CH), 3.77 and 3.75 (s, 3 H, OCH_3).

3k: ^1H NMR δ 6.86 (dd, J = 6.9 and 9.7 Hz, 1 H, =CH), 3.71 and 3.60 (s, 3 H, OCH_3).

5k: ^1H NMR δ 4.76 (t, J = 8.4 Hz, 1 H, =CH), 3.78 and 3.76 (s, 3 H, OCH_3).

Irradiation of 4e. Formation of a Mixture of Dimethyl 3-(1-Pyrrolidinyl)-*cis*,*cis*-2,10-cyclodecadiene-1,2-dicarboxylate (3e) and Compound 5e. Irradiation for 11 h afforded a conversion of 66% into a 1:1 mixture of **3e** and **5e** (for the ^1H NMR spectrum of **5e** see above).

3e: ^1H NMR δ 6.88 (dd, J = 4.9 and 12.0 Hz, =CH), 3.71 and 3.56 (s, 3 H, OCH_3).

Methyl *cis*-2,3,6,7,7a,8-Hexahydro-8-(methoxycarbonyl)-3,3-dimethyl-5*H*-thieno[2,3-*b*]pyrrolizine-8-acetate (10).

From 7. A solution of 7[22] (0.50 g, 1.5 mmol) in 11 mL of methanol was stirred for 2 h at room temperature. The solvent was removed under reduced pressure to afford **10** as an oil: yield 90%.

From the Enamine and DMAD. A solution of DMAD (1.42 g, 10 mmol) in 2.5 mL of methanol was added dropwise to a solution of 2,3-dihydro-3,3-dimethyl-4-(1-pyrrolidinyl)thiophene[69] (1.83 g, 10 mmol) in 30 mL of methanol at −5 °C. The solution was stirred overnight at room temperature. The solvent was removed under reduced pressure to give **10** as an oil: yield 90%; IR (KBr) 1725 and 1690 (C=O) cm^{-1}; ^1H NMR δ 4.85 (dd, J = 6.6 and 9.3 Hz, 1 H, NCH), 3.75 and 3.66 (s, 3 H, OCH_3), 3.23 and 2.67 (AB q, J = 17.6 Hz, 2 H, CH_2E), 1.24 and 1.16 (s, 3 H, CH_3); ^{13}C NMR δ 173.3 and 171.6 (s, C=O), 155.2 (s, C-3a), 113.3 (s, C-8a), 76.8 (d, C-7a), 54.4 (s, C-8), 37.5 (t, CH_2E); mass spectrum, m/e 325.132 (M^+); calcd for $C_{16}H_{23}NO_4S$, 325.135.

Methyl *cis*-1,2,3,3a,4,5-Hexahydro-4-(methoxycarbonyl)indeno[2,1-*b*]pyrrolizine-4-acetate (11). From 8. A solution of **8**[25] (0.50 g, 1.5 mmol) in 20 mL of methanol was stirred for 2 h at room temperature. The solvent was removed under reduced pressure. The resulting oil solidified upon the addition of a few drops of ethanol. Purification by trituration with diisopropyl ether gave pure **11** in 78% yield.

From the Enamine and DMAD. A solution of DMAD (0.30 g, 2.1 mmol) in 3 mL of methanol was added to a solution of 1-(1*H*-inden-3-yl)pyrrolidine[70] (0.37 g, 2 mmol) in 7 mL of methanol at 0–5 °C. The

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solution was stirred overnight at room temperature. The solvent was removed under reduced pressure to give **11** as an impure oil which could not be crystallized or purified on silica gel or basic alumina on account of decomposition.

11: mp 114–115 °C (methanol, −20 °C); IR (KBr) 1740 (C=O) and 1630 (C=C) cm^{-1}; ^1H NMR δ 7.4–7.1 (m, 4 H, Ar H), 4.91 (dd, J = 6 and 9 Hz, 1 H, NCH), 3.72 and 3.70 (s, 3 H, OCH_3), 3.6–3.2 (m, 2 H, NCH_2), 3.34 and 2.78 (AB q, J = 17.3 Hz, 2 H, CH_2E), 3.15 (s, 2 H, CH_2C=); ^{13}C NMR δ 174.3 and 171.8 (s, C=O), 157.5 (s, C-9b), 148.1 (s), 136.1 (s), 126.0 (d), 124.9 (d), 124.6 (d) and 118.4 (d) (Ar C), 121.4 (s, C-4a), 77.9 (d, NCH), 54.8 (s, C-4), 52.5 and 51.8 (q, OCH_3), 49.5 (t, NCH_2), 37.8 (t, CH_2E); mass spectrum, m/e 327.147 (M^+); calcd 327.147.

Anal. Calcd for $C_{19}H_{21}NO_4$ (M_r 327.384): C, 69.71; H, 6.47; N, 4.28. Found: C, 69.95; H, 6.57; N, 4.19.

Isomerization of 9 in Methanol. A solution of **9**[25] (0.68 g, 2 mmol) in 25 mL of methanol was stirred at room temperature. After 1 h, 6 h, and 22 h an aliquot was taken and the solvent was removed under reduced pressure. ^1H NMR spectroscopy revealed, besides absorptions of starting material and pyrrolizine **12**,[32] the presence of a signal at δ 5.95 (s) which was assigned to (*Z*)-**13**. After a reaction time of 47 h the conversion into **12** was about 75%. Performing the reaction at 65 °C for 18 h the conversion of **9** into **12** was >95%.

Dimethyl 8-[2,3-Bis(methoxycarbonyl)-4-(1-pyrrolidinyl)-4-cyclooctene-1-yl]-3-(1-pyrrolidinyl)-1,3-cyclooctadiene-1,2-dicarboxylate (14). A solution of the equilibrium mixture of **2b** and **4b** (2.01 g, 6.5 mmol) in 40 mL of methanol was stirred for 5 h at room temperature in the dark. After removal of the solvent under reduced pressure, the remaining solid was triturated with methanol to give **14** as a yellow crystalline compound: yield 57%; mp 164–167 °C (methanol); IR (KBr) 1720 (C=O) and 1615 (C=C) cm^{-1}; ^1H NMR δ 4.62 and 4.52 (t, J = 7.8 Hz, 1 H, NC=CH), 4.33 (d, J = 12.2 Hz, 1 H, ECHC=), 3.74, 3.72 and 3.68 (s, 12 H, OCH_3), 3.34 (dd, J = 3.7 and 12.2 Hz, 1 H, ECH); ^{13}C NMR δ 174.4 and 174.2 (s, HCC=O), 167.5 and 167.2 (s, =CC=O), 142.0 and 141.3 (s, C-3 and C-4), 140.1 and 135.9 (s, C-1 and C-2), 103.8 (d, C-5), 52.2, 51.8 and 51.4 (q, OCH_3), 48.8 and 48.4 (t, NCH_2); mass spectrum, m/e 586.321 (M^+); calcd 586.325.

Anal. Calcd for $C_{32}H_{46}N_2O_8$ (M_r 586.734): C, 65.51; H, 7.90; N, 4.77. Found: C, 65.76; H, 7.96; N, 4.75.

The ^1H NMR spectrum of the crude reaction mixture showed also the presence of about 30% of compound **3b**.

Methyl *cis*-4,6,7,8,8a,9-Hexahydro-9-(methoxycarbonyl)-1*H*,3*H*-thiopyrano[3,4-*b*]pyrrolizine-9-acetate (15).

From 4c. A solution of **4c** (0.55 g, 1.8 mmol) in 20 mL of methanol was heated at 65 °C for 15 h. After removal of the solvent under reduced pressure the ^1H NMR spectrum of the crude reaction mixture showed the presence of a 2:5 mixture of **3c** and **15** which was not separated further.

From 1c and DMAD. A solution of DMAD (2.84 g, 20 mmol) in 5 mL of methanol was added dropwise to a solution of **1c** (3.39 g, 20 mmol) in 25 mL of methanol at 0–5 °C in the dark. Subsequently the reaction mixture was heated at 65 °C for 15 h. The solvent was removed under reduced pressure. From the resulting oil, pure **15** was obtained by crystallization from methanol: yield 41%; mp 109–110 °C (methanol); IR (KBr) 1730 and 1715 (C=O), 1660 (C=C) cm^{-1}; ^1H NMR δ 4.43 (dd, J = 6.0 and 9.9 Hz, 1 H, NCH), 3.74 and 3.67 (s, 3 H, OCH_3), 3.32 and 2.51 (AB q, J = 17.3 Hz, 2 H, CH_2E); ^{13}C NMR δ 173.7 and 172.0 (s, C=O), 147.3 (s, C-4a), 104.1 (s, C-9a), 68.5 (d, C-8a), 57.4 (s, C-9), 52.4 and 51.8 (q, OCH_3), 48.3 (t, NCH_2), 36.8 (t, CH_2E); mass spectrum, m/e 311.120 (M^+); calcd 311.119.

Anal. Calcd for $C_{15}H_{21}NO_4S$ (M_r 311.404): C, 57.86; H, 6.80; N, 4.50. Found: C, 57.77; H, 6.80; N, 4.49.

Methyl *cis*-1,2,3,5,6,7,8,9,10,10a-Decahydro-10-(methoxycarbonyl)-cyclohepta[*b*]pyrrolizine-10-acetate (16). A solution of **4d** (1.23 g, 4 mmol) in 20 mL of methanol was heated at 65 °C for 24 h. The solvent was removed under reduced pressure. The resulting oil, which could not be crystallized consisted for > 90% of **16**: ^1H NMR δ 4.41 (dd, J = 6.0 and 10.1 Hz, 1 H, NCH), 3.72 and 3.66 (s, 3 H, OCH_3), 3.29 and 2.40 (AB q, J = 16.7 Hz, 2 H, CH_2E); ^{13}C NMR δ 174.7 and 172.4 (s, C=O), 151.3 (s, C-4a), 111.5 (s, C-9a), 69.1 (d, C-10a), 57.6 (s, C-10), 52.1 and 51.8 (q, OCH_3), 49.6 (t, NCH_2).

X-ray Diffraction. Intensities were measured on a 4-circle single crystal diffractometer (Philips PW 1100), using graphite monochromated radiation. Details on data collection, cell constants, and other crystallographic data are given in Table III. During data collection three reference reflexions were measured every hour. A correction for decrease in intensity, based on the intensities of the reference reflexions was performed.

The structures were solved by direct methods[71] and refined by full-matrix least squares.[72] Hydrogen atoms were located in difference Fourier syntheses. The weight for each reflexion in the refinement was chosen as $w = (S + 0.01|F_o|)^{-2}$, where S is the standard deviation of the observed structure factor ($|F_o|$) due to counting statistics. Parameters refined were scale factor, isotropic extinction parameter, positional parameters of all atoms, anisotropic thermal parameters for the heavy atoms, and isotropic thermal parameters for the hydrogen atoms. In the case of **4c** the carbon and nitrogen atoms have been refined with isotropic thermal parameters. The drawings of the crystal structures have been made by ORTEP.[73] Bond distances and torsion angles in the eight-membered rings are given in Tables IV and V, respectively.

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Registry No. 1a, 7148-07-4; **1b**, 1125-99-1; **1c**, 3417-64-9; **1d**, 14092-11-6; **1e**, 942-81-4; **1f**, 2981-10-4; **1g**, 670-80-4; **1h**, 3417-63-8; **1i**, 55436-25-4; **1j**, 19353-04-9; **1k**, 7182-08-3; **1l**, 34969-50-1; **2a**, 88477-06-9; **2b**, 3603-83-6; **2f**, 88477-07-0; **2g**, 88477-08-1; **2h**, 88477-09-2; **2i**, 88477-11-6; **3a**, 88477-14-9; **3b**, 83585-94-8; **3c**, 83585-91-5; **3d**, 88477-26-3; **3e**, 14833-86-4; **3f**, 88477-15-0; **3g**, 88477-16-1; **3j**, 88477-28-5; **3k**, 88477-30-9; **4b**, 83585-93-7; **4c**, 83585-90-4; **4d**, 42205-54-9; **4e**, 42205-55-0; **4h**, 88477-10-5; **4j**, 88477-12-7; **4k**, 88495-98-1; **4l**, 88477-13-8; **5b**, 88477-25-2; **5c**, 83585-92-6; **5d**, 88477-27-4; **5e**, 88477-17-2; **5h**, 88477-18-3; **5l**, 88477-19-4; **5j**, 88477-29-6; **5k**, 88477-31-0; **5l**, 88477-20-7; **6a**, 88477-21-8; **6b**, 88477-22-9; **6c**, 88477-23-0; **6d**, 88477-24-1; 7, 50542-20-6; **8**, 82483-71-4; **9**, 82497-42-5; **10**, 88477-32-1; **11**, 88477-33-2; **12**, 85923-93-9; (*Z*)-**13**, 82483-77-0; **14**, 88477-34-3; **15**, 88477-35-4; **16**, 88477-36-5; DMAD, 762-42-5; 2,3-dihydro-3,3-dimethyl-4-(1-pyrrolidinyl)thiophene, 1076-05-7; 1-(1*H*-inden-3-yl)pyrrolidine, 31554-37-7.

Supplementary Material Available: Tables of atomic coordinates, thermal parameters, bond distances, and bond angles including all atoms (51 pages). Ordering information is given on any current masthead page.

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(74) Atom numbering is done in the same way for the structures with eight-membered rings (**3c**, **4c**, **5c**, **14**). The numbering is such that the first ester group is at C-4, the second at C-5 and the pyrrolidine group at C-6. In the case of **4c** there are two independent molecules in the unit cell indicated as **4cA** and **4cB**. Molecule **14** contains two eight-membered rings, the atoms of which have been listed separately (**14A**, **14B**).