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X=Y-ZH Systems as Potential 1,3-Dipoles. Part 42.[1] Decarboxylative Three Carbon Ring Expansion of Cyclic Secondary α-Amino Acids via Azomethine Ylide Formation.

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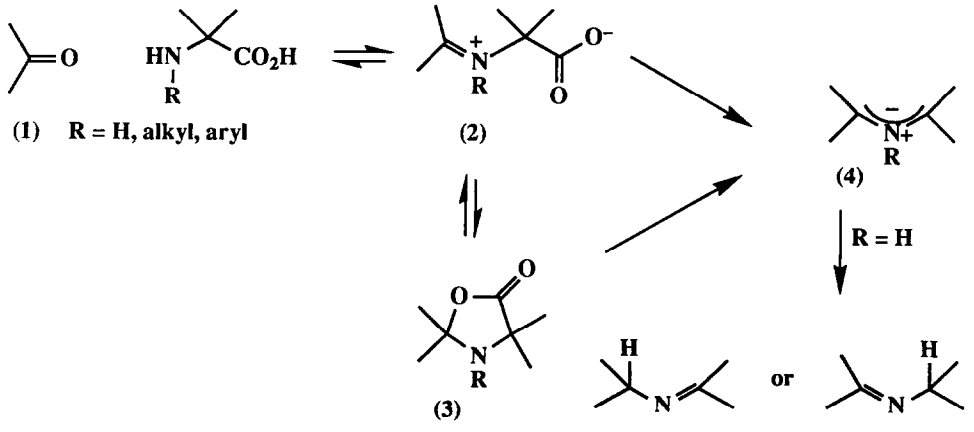
Abstract. *Cyclic 5- and 6-membered secondary α-amino acids react with formaldehyde and acetylenic dipolarophiles via azomethine ylide formation, cycloaddition and subsequent ring expansion to give 8- and 9- membered rings respectively. Ring expansion occurs by reaction of the bridgehead nitrogen of the initial bicyclic cycloadduct with a further molecule of dipolarophile to give a zwitterion which triggers the ring expansion. Dynamic p.m.r. studies show that ring inversion between pairs of mirror image conformations of the medium ring products are occurring with inversion barriers of 13-14.6 kcal/mol.*

We have shown that a wide range of *in vitro* and, by analogy, *in vivo* decarboxylations of α-amino acids (1) mediated by aldehydes and ketones proceed via intermediate azomethine ylides (Scheme 1). These decarboxylations encompass the Strecker Degradation,[1] the Ninhydrin Reaction and related processes developed for the qualitative and quantitative detection of α-amino acids,[2,3] and pyridoxal-[4] and pyruvoyl-[5] mediated enzymic processes.

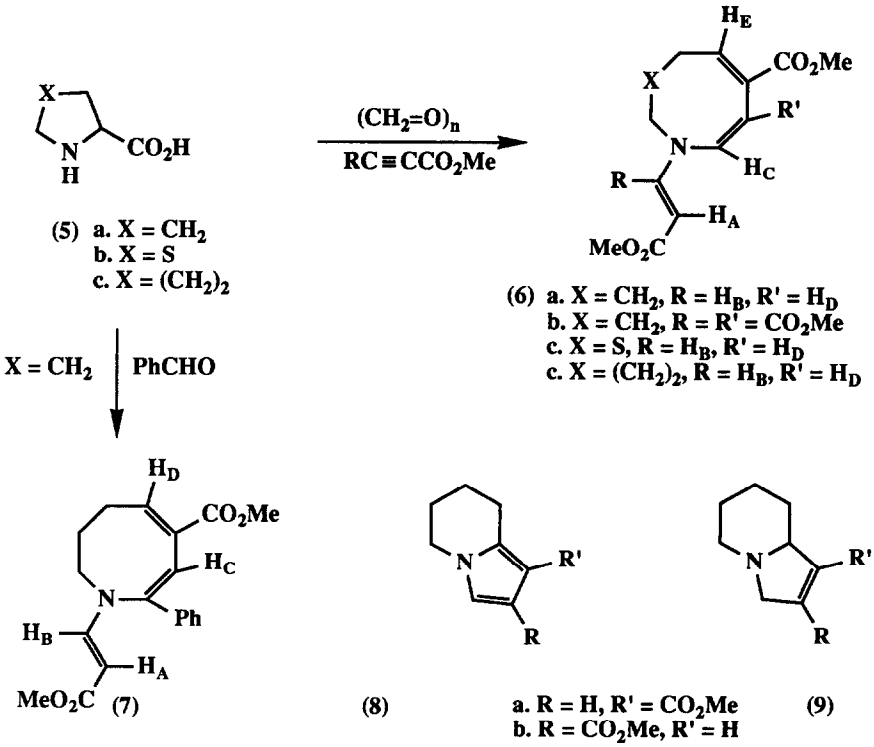


Scheme 1

Detailed studies of the effect of substrate structure on the stereochemistry of the intermediate azomethine ylides (4), as adduced from cycloadduct stereochemistry, revealed highly stereoselective formation of the 1,3-

dipoles and led us to suggest that decarboxylation probably proceeds via 1,3-dipolar cycloreversion of the oxazolidin-5-one (3) rather than direct decarboxylation of (2) (Scheme 1).[6] The reaction tolerates wide variations in carbonyl (formaldehyde, aliphatic, aromatic and heteroaromatic aldehydes and ketones) and dipolarophile components and occurs with all types of α-amino acid (primary, secondary, α, α-disubstituted, cyclic and acyclic) except tertiary amino acids. In the absence of a dipolarophile the azomethine ylide (4) undergoes 1,2-prototropy from nitrogen to carbon furnishing an imine (Scheme 1). This latter process which is important, for example, in the Ninhydrin Reaction as well as enzymic processes is dependant on the electron density at the two terminii of the 1,3-dipole. The α-amino acid→imine→azomethine ylide→ cycloadduct cascade has considerable synthetic potential especially in the intramolecular cycloaddition variant where the dipolarophile is located within the carbonyl component.[7] When cyclic secondary α-amino acids are reacted with formaldehyde (paraformaldehyde) and an excess of an acetylenic dipolarophile the initially formed cycloadducts react further to give interesting ring expanded products. Full details of these processes are now reported.[8]

The impetus for investigating this ring expansion was our observation that proline (5a) reacts over 4h with excess paraformaldehyde and methyl propiolate in toluene at 100°C to furnish the eight-membered heterocycle (6a) in excellent yield (quantitative by n.m.r.; 78% isolated). The p.m.r. spectrum ($CDCl_3$) of (6a) exhibits two AB spin-coupling systems for the protons H_A-H_D together with a triplet at δ 6.78 (H_E). Protons H_A/H_B give rise to two doublets at δ 4.93 (H_A) and 7.47 (H_B) whilst H_C and H_D resonate at δ 6.29 and 5.19 respectively.



(5) a. X = CH_2
b. X = S
c. X = $(CH_2)_2$

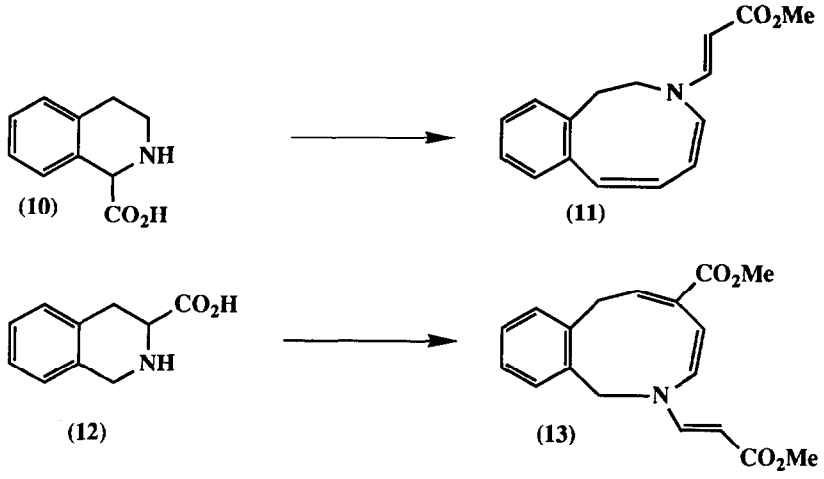
(6) a. X = CH_2, R = H_B, R' = H_D
b. X = CH_2, R = R' = CO_2Me
c. X = S, R = H_B, R' = H_D
c. X = $(CH_2)_2$, R = H_B, R' = H_D

(7) (8) (9)

a. R = H, R' = CO_2Me
b. R = CO_2Me, R' = H

The coupling constant J_{AB} 13.4 Hz confirms the E-stereochemistry of the exocyclic double bond. In contrast to sharp signals for H_A - H_E and the ester methyl groups the signals for the three ring methylene groups were broad and indicative of slow conformational equilibria (see later). An analogous reaction of proline with dimethyl acetylenedicarboxylate furnished azocine (6b)(31%). The stereochemistry of the exocyclic double bond was not rigorously established but is assumed to have the E-configuration which is consistent with both the proposed mechanism (see later) and steric factors. Thus the three carbon ring expansion incorporates the aldehyde carbon atom and two carbon atoms from the dipolarophile. Replacing formaldehyde by benzaldehyde (1mol) led, upon reaction with proline and methyl propiolate, to formation of (7)(23%). The p.m.r. spectrum of (7) in addition to showing broad signals for the three ring methylene groups also exhibited a broad signal for H_C, the ring vinylic proton located between the phenyl and ester moieties.

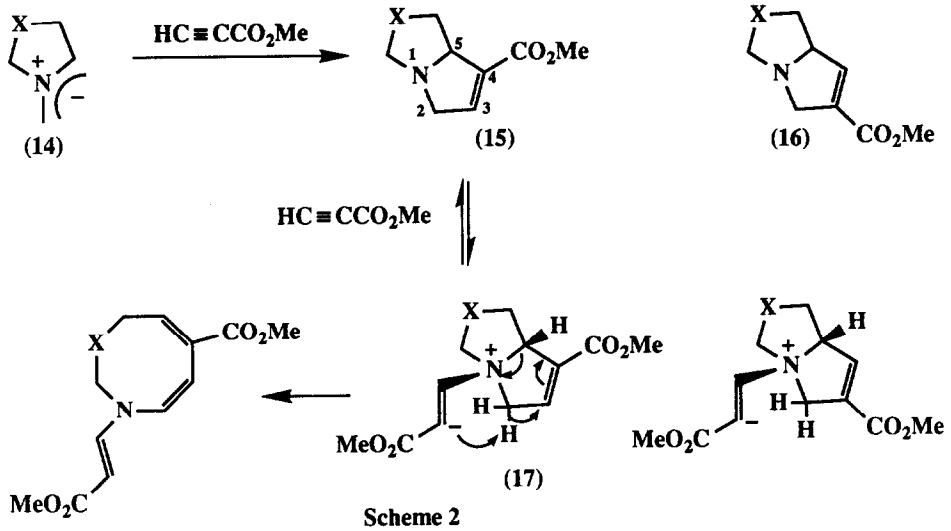
A number of other cyclic secondary α-amino acids were studied as substrates for the decarboxylative ring expansion. Typically a five-fold excess of paraformaldehyde and a two fold excess of methyl propiolate were used. Thus thiazolidine-4-carboxylic acid (5b) furnished the thiazocine (6c)(24%) together with trace amounts of two other products which were not isolated (see below). Once again the presence of broad signals in the p.m.r. spectrum of (6c) indicated fluxional behaviour. The reaction of pipecolinic acid (5c) with paraformaldehyde and methyl propiolate was conducted in the presence of 10mol% dibutyltin(IV) dichloride. This Lewis acid facilitates imine formation[9] and possibly accelerates the cycloaddition reaction by complexation with the dipolarophile. This assistance is not required for proline which is known to undergo rapid iminium ion formation.[12] In addition to the expected 9-membered ring (6d)(23%) the reaction gave rise to a 1:43 mixture (21%) of the two indolizines (8a) and (8b). Clearly (8a) and (8b) have arisen by oxidation of the initial cycloadducts (9) despite carrying out the cycloadditions under an atmosphere of nitrogen.



Both 1,2,3,4-tetrahydroisoquinoline-1- and -3-carboxylic acids (10) and (12) react with paraformaldehyde and methyl propiolate in the presence of 10mol% dibutyltin(IV) dichloride, albeit in poor yield, to give (11)(6%) and (13)(21%) respectively.

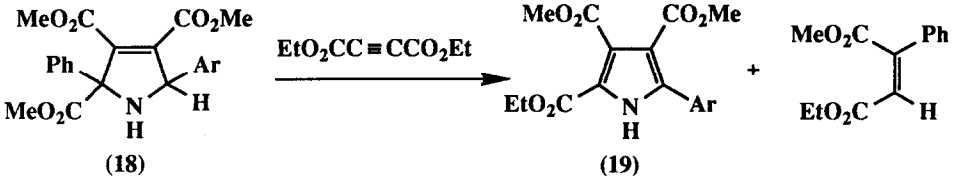
Mechanism. The proposed mechanism for the ring expansion is outlined in Scheme 2. Azomethine ylide (14) is formed via the mechanism outlined in Scheme 1. Cycloaddition of (14) with methyl propiolate can give rise to two regioisomeric cycloadducts (15) and (16). The dipole - dipolarophile frontier orbital interactions will

be very similar for both regioisomeric transition states[11] and preference for (15) in the case of proline is attributed to steric factors, with 2,3-bond formation expected to be somewhat in advance of 4,5-bond formation due to the larger terminal coefficient at the β-carbon of the propiolate. Nevertheless substantial amounts of the other regioisomer (16) are probably formed in the case of (5b,c), (10) and (12) with consequent reduction in the yield of the ring expanded products.



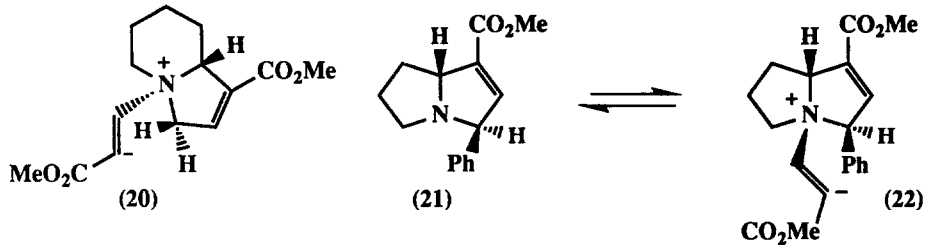
Scheme 2

Reaction of (15) and (16) with a further molecule of methyl propiolate furnishes the corresponding zwitterions, only one of which, (17), possesses sufficiently acidic protons for deprotonation and subsequent rearrangement. The rearrangement, a 6π-disrotatory electrocyclic process, requires a cis-ring fusion in (17). We have previously reported a related rearrangement in the transformation of pyrrolines (18) to pyrroles (19).[12]



The proposed intramolecular proton abstraction (17, arrows) finds further support in literature reports involving 3-(1-pyrrolidinyl)thiophenes[13] and cyclohex[b]indoles,[14] whilst formation of zwitterions related to (17) has been reported for several disparate systems.[15] A sizeable amount of product arising from oxidation of the alternative regioisomeric cycloadduct (16) was isolated from the reaction of (5c) and corresponding pyrrolic products were detected in reactions with acids (5b), (8a) and (8b). This would account, in part, for the generally poor yields of ring expanded products. The lower yields arising from the six-membered α-amino acids may reflect, in part, their greater tendency to form a trans-fused zwitterion (20), deprotonation of which should be unproductive for a disrotatory electrocyclic ring opening. Additionally for azomethine ylides arising from (5b), (10) and (12), field and mesomeric effects arising from the sulphur atom and the aryl rings may favour the unproductive cycloadduct regioisomer. The lower yield of ring expanded product (7) arising from

(5a), benzaldehyde and methyl propiolate presumably reflects a switch from intra- to inter-molecular deprotonation since the expected stereochemistry (21) of the initial cycloadduct would lead to zwitterion (22).



Dynamic N.M.R. Studies. The variable temperature proton n.m.r. spectra of the medium ring heterocycles (6a), (6c) and (13) were investigated to determine their conformational behaviour in solution. The crystal structure[8] of (6a) shows the ring as an irregular tub (Fig.1). This conformation is close in shape to the "C_1" conformation (23) proposed by Allinger[16] as one of the two minimum energy forms of cycloocta-1,3-diene. His calculations predicted a dihedral angle between the double bonds of 47° for (23) and of 57° for the other minimum energy "C_2" conformation (24). In the crystal structure of (6a) the observed dihedral angle is 41° (see Table 6 in the experimental section). Our semi-empirical calculations (AM1) agree with Allinger's results and support the "C_1" conformation as the preferred conformation for 1-azacycloocta-2,4-diene (Table 6, experimental section). The related compounds (25)[17] exist in the solid state in twist boat chair conformations, related to (24), which is one of the conformations suggested for cycloocta-1,3-diene in solution based on ^{13}C n.m.r. spectroscopy.[18] The solution behaviour of the two compounds (6a) and (6c) is therefore of considerable interest in view of the variable results obtained previously. The nine-membered ring (13), which is effectively an azacyclonona-1,3,6-triene, is also of interest as solution studies of conformational equilibria in systems of this type have not been reported to our knowledge, although the synthesis and limited spectral data of a few cyclonona-1,3-dienes have been described.[17]

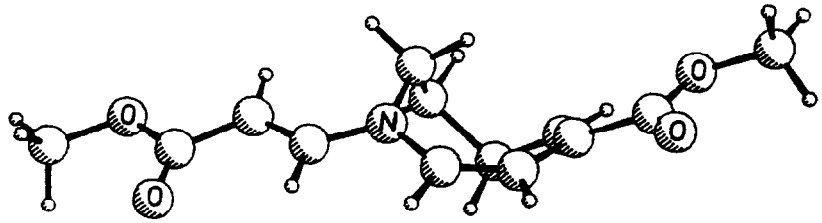
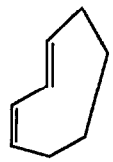
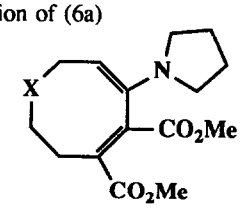


Figure 1. Crystallographic projection of (6a)



(23)

(24)



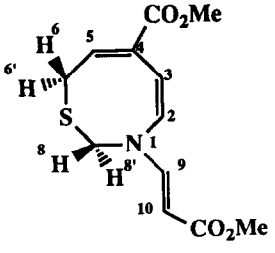
(25) X = CH_2 or S

An important feature in the crystal structure of (6a) is the planarity of the nitrogen atom, indicating an energetically favourable overlap of the nitrogen lone pair with the two adjacent π-systems.[8] This overlap results in an increase in the bond order of the exocyclic N-C bond and leads to slow rotation of the side chain at low temperatures (see below).

The p.m.r. spectra ($CDCl_3$) of all three compounds at ambient temperatures (~294°K) show evidence of slow interconversion between different conformations. Thus the protons of the ring CH_2 groups appear as broad peaks, in each case, which sharpen up on heating or cooling the solutions. The olefinic protons on the other

Table 1. Chemical Shifts and Coupling Constants ($CDCl_3$) for (6c).

H	320°K(δ)	243°K(δ)	Coupling Constants (Hz) at 243° K	
2	6.25	6.29	J_{23}	10.0[a]
3	5.13	5.10	J_{56}	8.0
5	6.70	6.75	$J_{56'}$	10.0
6		3.29	$J_{66'}$	12.0
	3.39			
6'		3.47	$J_{88'}$	15.0
8		4.12	J_{910}	14.0
	4.48			
8'		4.75	a. ± 0.5Hz	
9	7.44	7.51	b. or vice versa	
10	5.12	5.08		
11 (OMe)	3.73[b]	3.72		
12 (OMe)	3.82[b]	3.82		



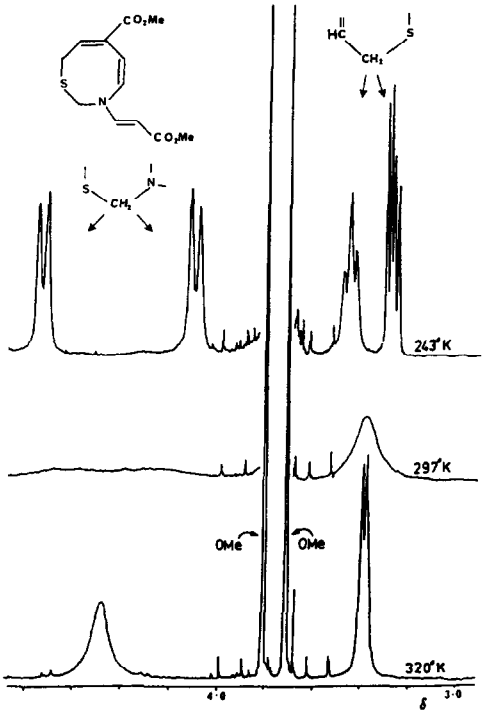


Figure 2. 400MHz PMR Spectra ($CDCl_3$) of (6c)

hand appear as sharp multiplets at all temperatures. This indicates that for all three compounds, the ring

inversions taking place are between pairs of mirror image conformations in which the olefinic protons are in identical environments. The only variation is the interchange of the two protons in each methylene group between pseudo-axial and pseudo-equatorial conformations, which results in different chemical shifts.

In (6c) the SCH_2N methylene group splits into an AB quartet (J15.0Hz) as expected at low temperature, and the $C\underline{H}_2CH$= methylene protons appear as the AB portion of an ABX spin system (J_{AB}12.0Hz, J_{AX}10.0Hz, J_{BX}8.0Hz). The corresponding $CH_2C\underline{H}$ olefinic multiplet changes, as expected, from a sharp triplet (J9Hz) at room temperature to a double doublet (J8 and 10Hz) at low temperature. In Fig.2 these changes are shown for a $CDCl_3$ solution at 243°K, while chemical shifts and coupling constants are recorded in Table 1. From the coalescence of the proton multiplets of the two methylene groups, the energy barrier,$\Delta G^{\ddagger}$, was calculated as 14.6 $\pm$ 0.5 kcal/mol using the Eyring equation.[19] No evidence was seen in the spectra of (6c) of rotational isomerism of the olefinic side chain.

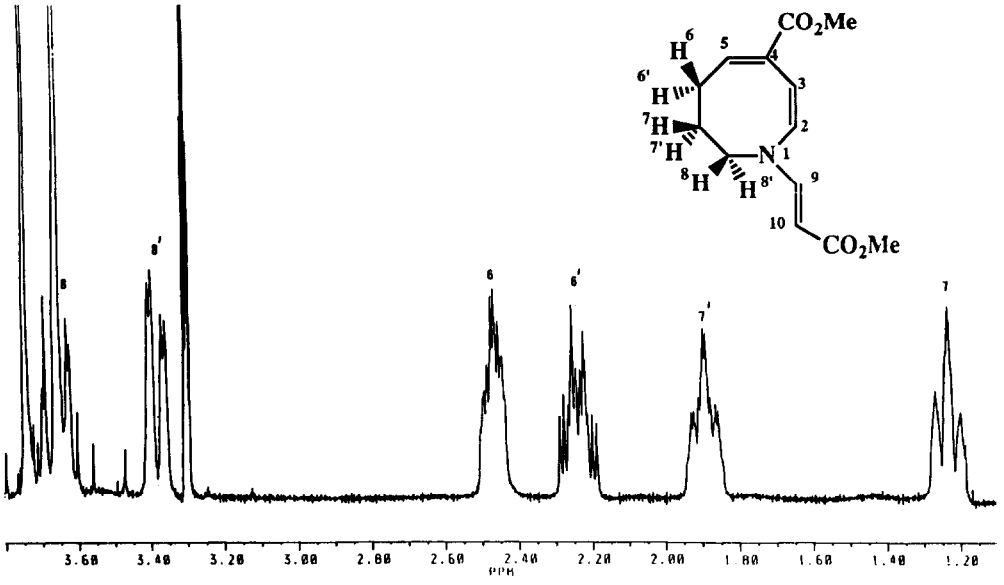


Figure 3. 400MHz PMR Spectrum (CD_3OD) of (6a) at 233°K

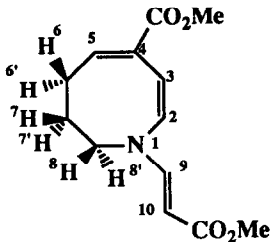
Similar dynamic effects are apparent in the spectra of (6a). The olefinic protons appear as sharp doublets or triplets at all temperatures whereas the methylene protons appear as broad featureless bands at ambient temperature. At 233°K, however, the three adjacent methylene groups appear as six separate sharp multiplets (Fig.3), from which the coupling constants for the -$CH_2CH_2CH_2CH$= fragment could be determined (Table 2). At low temperature (233°K) a small amount (~6%) of another conformer is visible in the ^1H spectrum. This may well be due to slow rotational isomerism about the side chain N-C bond. The planarity of the nitrogen atom apparent in the crystal structure[8] indicates that the nitrogen lone pair of electrons provides partial double bond character to the N-C bond. An alternative, but perhaps less likely explanation for the minor conformer, could be the presence of a low concentration of the twist boat chair conformation (24).[17,18] It is difficult to rule out the latter explanation without further experiments.

The approximate energy barrier to interconversion of the major conformation of (6a) was measured by

the coalescence method, giving values for $\Delta G^{\ddagger}$ of 13.0 ± 0.5 kcal/mol. The barriers for (6c) and (6a) are somewhat higher than those measured fro cycloocta-1,3-diene[18] (7.1 and 9.1 kcal/mol). It was not possible to measure the energy barrier for interconversion of the minor conformer.

Table 2. Chemical Shifts and Coupling Constants (CD_3OD) for (6a).[a]

H	233°K(δ)	273°K(δ)	Coupling Constants (Hz) at 233°K	
2	6.51	6.45	J_{23}	10.4
3	5.16	5.17	J_{56}	7.9
5	6.80	6.78	$J_{56'}$	9.8
6	2.48		$J_{66'}$	14.0
6'	2.24	Broad	J_{67}	~3.0
7	1.23	featureless	$J_{67'}$	2.3
7'	1.89	peaks at	$J_{6'7}$	12.4
8	3.66	273°K	$J_{6'7'}$	4.8
8'	3.38		$J_{77'}$	13.5
9	7.63	7.60	J_{78}	3.1
10	5.00	5.00	$J_{78'}$	3.9
11(OMe)	3.66[b]	3.67	$J_{7'8}$	13.2
12(OMe)	3.74[b]	3.75	$J_{7'8'}$	<1.5
			$J_{88'}$	14.5
			J_{910}	13.4



a. Minor isomer (~6%) peaks resolved at 233°K : δ6.43(2-H), 5.33(3-H), 6.83(5-H) and 7.26(9-H).
b. or vice versa.

The low temperature behaviour of (13) is similar to that of the eight-membered rings, in that the major rate process appears to be between mirror image conformational isomers, with each methylene group appearing as an AB quartet at low temperatures.

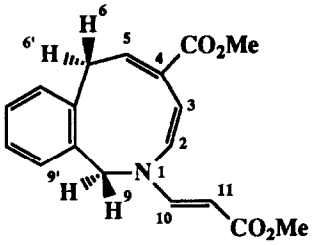
Again at the lowest temperatures used (233°K) the presence of a minor conformer (13%) is seen in the p.m.r. spectrum. In particular new multiplets are observed for H_2,H_3 and the methylene protons 9 and 9' (see Table 3). This suggests perhaps that, as with (6a), the minor conformation is probably due to rotational isomerism about the exocyclic N-C bond. The chemical shifts and coupling constants for the major conformers are recorded in Table 3. The barrier to inversion between the major conformers is difficult to estimate from the complex spectra, but appears to be $\geqslant$ 14.5 kcal/mol.

The X-ray crystal structure of (13)[21] shows it adopts a similar conformation, in the solid state, to that observed for the eight-membered ring (6a). Thus a projection of (13) (Fig. 4) can be superimposed almost exactly upon the eight-membered counterpart (6a, Fig. 1), by matching the endocyclic N-C=C moiety of the two compounds. Trans geometry of the exocyclic double bond is again observed, while the torsion angle between the two ring double bonds is 47.2°.

The structural similarity between (6c) and (6a) and the similar ^1H spectral behaviour are a good indicator of conformational similarity. In (6a) the conformation can be defined more rigorously using the vicinal coupling constants of the $CH_2.CH_2.CH_2.CH$ = fragment. In Table 4, the observed ^3J values are compared with those expected using the torsion angles from the crystal structure of (6a)[8] and a simple Karplus $\cos^2\emptyset$ relationship, without correction for electronegativity.[20] The agreement, except as expected for the proton trans to the ring nitrogen is so close that any other conformation can be immediately excluded. Thus the irregular tub structure (23), the C_1 conformation of Allinger, is present in solution as well as in the crystal, but inverting slowly at room temperature with its mirror image form (Fig. 5). It seems a reasonable assumption that (6c) is similarly flipping between two irregular tub conformations as the spectral features are similar to those for compound (6a).

Table 3. Chemical Shifts and Coupling Constants ($CDCl_3$) for (13).

H	273°Kδ	233°Kδ	Coupling Constants (Hz) at 233°K	
2	6.61	6.67		
3	5.46	5.38	J_{23}	10.0
5	6.78	6.80	J_{56}	6.0
6		3.23	$J_{56'}$	13.0
6'	v. broad	3.98	$J_{66'}$	13.0
9	bands	5.09	$J_{99'}$	15.0
9'		4.04	$J_{10\,11}$	14.0
10	7.47	7.61		
11	4.95	4.87		
12(OMe)	3.62	3.62		
13(OMe)	3.78	3.78		
Ph	7.1-7.3	7.1-7.3		



Minor conformer (13%) resolved at 233°K : δ6.56(2-H), 5.66(3-H) and 4.24(9-H). The other proton signals were not well defined.

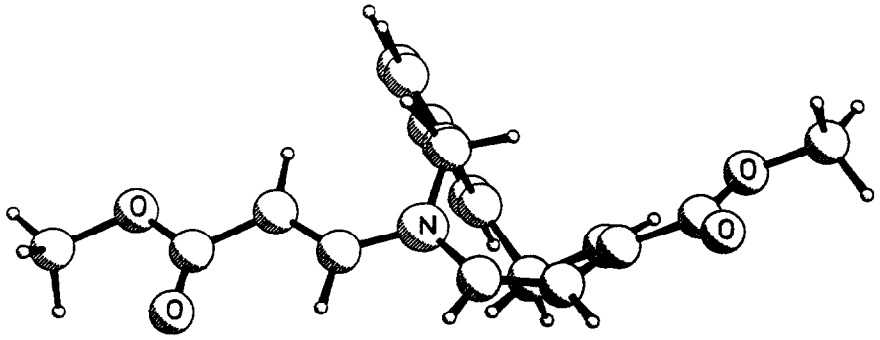


Figure 4. Crystallographic Projection of (13).

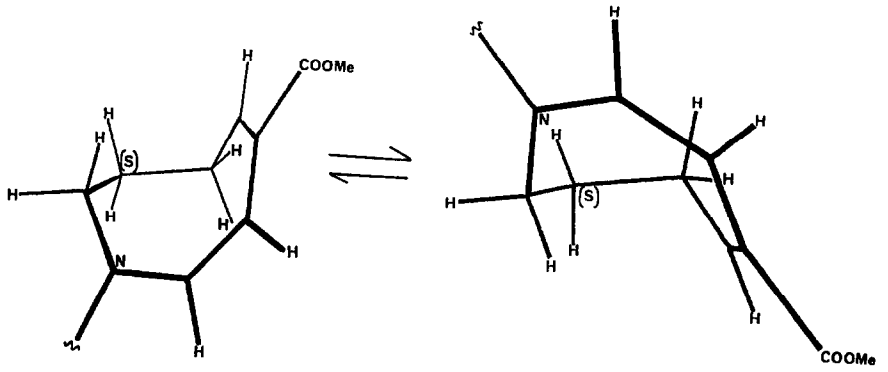
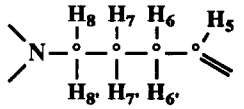


Figure 5. Major Conformations of (6a) and (6c)

Table 4. Observed and Calculated Vicinal Coupling Constants for (6a) Assuming the Crystal Conformation.



Coupling Protons	Ø[a]	$\cos^2$Ø	Calc^{3}J[b](Hz)	Obs^{3}J(Hz)
H_7H_8	-53.1	0.36	4.7	3.1
$H_7'H_8$	185.5	0.99	12.9	13.2
H_7H_8'	47.4	0.46	6.0	3.9[c]
$H_7'H_8'$	-74.1	0.08	1.0	<1.5
H_6H_7	-52.6	0.37	4.8	~3.0
$H_6'H_7$	184.5	0.99	12.9	12.4
H_6H_7'	64.0	0.19	2.5	2.3
$H_6'H_7'$	-58.9	0.27	3.5	4.8
H_5H_6	35.7	0.66	8.6	7.9
H_5H_6'	145.1	0.69	9.0	9.8

a. Torsion angle

b. Assuming $^3J_{max}$ 13.0Hz. Approximate values based on the Karplus equation.

c. This value is reduced as it is trans to the electronegative nitrogen atom.

The azacyclononatriene ring (13) is also inverting slowly at room temperature between two mirror image conformations. Comparison of the observed vicinal coupling constants of the -CH_2CH = fragment with those expected using the torsion angles from the crystal structure of (13)[21] shows good agreement (Table 5). This suggests that the conformation which (13) adopts in the solid state is also present in solution, and is inverting slowly at room temperature with its mirror image.

Table 5. Observed and Calculated Vicinal Coupling Constants for (13)

Protons[a]	Torsion Angle	Calc. J[b]	Obs. J(Hz)
H_5H_6	49.9°	5.6	6.0
H_5H_6'	169.9°	13.0	13.0

a. See Table 3 for numbering system.

b. Assuming $^3J_{max}$ 13.5Hz and using the Karplus $\cos^2\emptyset$ relationship without correction for electronegativity.

The minor conformations observed in the spectra of (6a) and (13) almost certainly reflect isomerism due to partial double bond character in the N-C bond. Presumably, but not definitely, the isomer shown in the crystal structure of (6a) is also favoured in solution.

Experimental. General experimental details were as previously described.[21]

General Procedure for Decarboxylative Cycloaddition-Ring Expansion Reactions. The α-amino acid (1mol), aldehyde (5mol) and acetylenic dipolarophile (4mol) were stirred under nitrogen in degassed toluene at 100°C for 4-16h. Where appropriate dibutyltin(IV)dichloride (10mol%) was added as a mild Lewis acid to promote iminium ion formation. The reaction mixture was then filtered and the solvent removed under reduced pressure. The resulting gum was dissolved in chloroform, and the solution washed with water (3x), dried, and the solvent removed in vaccuo. The crude product was purified by flash chromatography.

1,6,7,8-Tetrahydro-1-(2'-methoxycarbonylethenyl)-4-methoxycarbonylazocine (6a). Prepared from proline (1.0g, 8.7mM), paraformaldehyde (1.3g, 43mM) and methyl propiolate (3.0g, 36mM) in toluene (50ml) according to the general procedure. Heating was maintained for 4h. Flash chromatography (SiO_2, 1:1 v/v Et_2O-petroleum ether), afforded the **product** (R_f 0.40) (1.7g, 78%) as colourless plates (Et_2O-petroleum ether) m.p. 75-76°C. (Found: C, 62.05; H, 6.8; N, 5.6. $C_{13}H_{17}NO_4$ requires C, 62.15; H, 6.8; N, 5.55%); υ_{max} 2970, 1710, 1610, 1460 and 800 cm^{-1}; m/z(%) 251 (M^+,65), 222(14), 220(24), 192(100) and 132(19); δ1.42-1.72 (br signal, 2H, CH_2), 2.35-2.43 (br signal, 2H, CH_2C=), 3.47-3.65 (br signal, 2H, CH_2N), 3.70 and 3.79 (2xs, 2x3H, OMe), 4.93 (d, 1H, H_A, J13.5Hz), 5.19 (d, 1H, H_D, J10.1Hz), 6.29 (d, 1H, H_C, J10.1Hz), 6.78 (t, 1H, H_E, J8.6Hz) and 7.47 (d, 1H, H_B, J13.3Hz).

1,6,7,8-Tetrahydro-1-(1',2'-dimethoxycarbonylethenyl)-3,4-dimethoxycarbonylazocine (6b). Prepared from proline (1.15g, 10mM), paraformaldehyde (1.5g, 50mM) and dimethyl acetylenedicarboxylate (5.7g, 40mM) in toluene (50ml) according to the general procedure. Heating was continued for 2h. Flash chromatography (SiO_2, 9:1 v/v Et_2O-petroleum ether) afforded the **product** (R_f 0.49) (1.13g, 31%) as colourless rods (Et_2O-petroleum ether), m.p. 124-125°C. (Found: C, 55.55; H, 5.85; N, 3.7. $C_{17}H_{21}NO_8$ requires C, 55.6; H, 5.75; N, 3.8%); υ_{max} 2960, 1730, 1440, 1275 and 1148cm^{-1}; m/z(%) 367 (M^+,84), 336(57), 308(56), 276(100), 249(15), 218(6) and 190(7); δ1.25 and 2.05 (2xm, 2x1H, CH_2), 2.27 and 2.48 (2xm, 2x1H, CH_2C=), 3.33 (m, 1H, HCHN), 3.70, 3.72 and 3.76 (3xs, 3x3H, OMe), 3.89 (m, 1H, HCHN), 3.99 (s, 3H, OMe), 5.33 (s, 1H, H_A), 6.69 (dd, 1H, H_E, J7.14 and 9.97Hz) and 7.50 (s, 1H, H_C).

2,3-Dihydro-3-(2'-methoxycarbonylethenyl)-6-methoxycarbonyl-8H-1,3-thiazocine (6c). Prepared from thiazolidine-4-carboxylic acid (0.5g, 3.7mM), paraformaldehyde (0.54g, 18mM) and methyl propiolate (1.26g, 15mM) in toluene (50ml) according to the general procedure. Heating was continued for 15h. Flash chromatography (SiO_2, 2:3 v/v Et_2O-petroleum ether) gave the **product** (R_f0.20) (0.24g, 24%) as colourless rods (Et_2O-petroleum ether), m.p. 119-120°C. (found: C, 53.75; H, 5.6; N, 5.0; S, 12.15. $C_{12}H_{15}NO_4S$ requires C, 53.5; H, 5.6; N, 5.2; S, 11.9%); υ_{max} 2940, 1720, 1685, 1610, 1435, 1293, 815 and 745cm^{-1}; m/z(%) 269 (M^+,100), 254(29), 238(15), 222(13), 210(71) and 150(8); δ3.36-3.43 (br signal, 2H, CH_2C=), 3.73 and 3.82 (2xs, 2x3H, OMe), ~4.5 (very broad signal, 2H, CH_2N), 5.11 (dd, 2H, H_A and H_D, J10.0 and 13.6Hz), 6.26 (d, 1H, H_C, J10.1Hz), 6.72 (t, 1H, H_E, J8.9Hz) and 7.46 (d, 1H, H_B, J13.6Hz).

6,7,8,9-Tetrahydro-1-(2'-methyoxycarbonylethenyl)-4-methoxycarbonylazonine (6d). Prepared from pipecolinic acid (0.97g, 7.5mM), paraformaldehyde (0.19g, 37.5mM), methyl propiolate (2.52g, 30mM) and a catalytic amount of Bu_2SnCl_2 (0.23g, 10mol%) in toluene (50ml) according to the general procedure. Heating was continued for 16h. T.l.c., eluting with 2:3 v/v Et-$_2$O-petroleum ether showed three spots, R_f 0.40, 0.29, 0.22. The three products were separated using flash chromatography, eluting with 2:3 v/v Et_2O-petroleum ether to give (8a) (0.05g, 4%), (8b) (0.23g, 17%) and (6d) (0.46g, 23%).

6d. Pale yellow oil. (Found: M, 265.1315. $C_{14}H_{19}NO_4$ requires M, 265.1314); υ_{max} 2970, 1700, 1605, 1434 and 810cm^{-1}; m/z(%) 265 (m^+,73), 250(27), 234(32), 206(98), 192(100) and 147(7); δ1.79-2.01 (m, 5H, 2xCH_2 and HCHC=), 2.36 (m, 1H, HCHC=), 2.63 and 3.56 (2xm, 2x1H, CH_2N), 3.70 and 3.77 (2xs, 2x3H, OMe), 4.88 (d, 1H, H_A, J13.4Hz), 5.19 (d, 1H, H_D, J10.3Hz), 6.33 (d, 1H, H_C, J10.4Hz), 7.03 (t, 1H, H_E, J8.8Hz) and 7.49 (d, 1H, H_B, J13.4Hz).

5,6,7,8-Tetrahydro-1-methoxycarbonylindolizine (8a). Pale yellow oil. (Found: M, 179.0945. $C_{10}H_{13}NO_2$ requires M, 179.0946); υ_{max} 2950, 1698, 1545, 1437, 1230 and 725cm^{-1}; m/z(%) 179 (M^+,99), 164(100), 148(61) and 120(50); δ1.70-1.85 (m, 4H, CH_2), 2.95 (m, 2H, CH_2C=), 3.67 (s, 3H, OMe), 3.76 (m, 2H, CH_2N), 6.33 (d, 1H, C=CH, J3.0Hz) and 6.43 (d, 1H, C=CHN, J3.0Hz). Decoupling experiments on the two olefinic protons support these assignments.

5,6,7,8-Tetrahydro-2-methoxycarbonylindolizine (8b). Pale yellow oil. (Found: M, 179.0945. $C_{10}H_{13}NO_2$ requires M. 179.0946); υ_{max} 2960, 1695, 1535, 1440, 1221 and 738cm^{-1}; m/z(%) 179 (M^+,100), 164(9), 148(86), 120(83) and 106(10); δ1.83-1.96 (m, 4H, CH_2), 2.75 (m, 2H, CH_2C=), 3.78 (s, 3H, OMe), 3.93 (m, 2H, CH_2N), 6.23 (d, 1H, C=CH, J1.7Hz) and 7.14 (d, 1H, C=CHN, J1.8Hz).

1,6,7,8-Tetrahydro-1-(2'-methoxycarbonylethenyl)-4-methoxycarbonyl-2-phenylazocine (7). Proline (0.88g, 7.7mM), benzaldehyde (0.81g, 7.7mM) and methyl propiolate (2.57g, 30.6mM) were stirred in toluene (50ml) at 100°C for 4.5h. All the acid dissolved within 1h. The reaction mixture was worked up according to the general procedure. Flash chromatography (SiO_2, 2:3 v/v Et_2O - petroleum ether) gave the **product** (R_f0.5) (0.57g, 23%) as an orange semi-solid m.p. <40°C. Found: C, 69.5; H, 6.75; N, 4.3. $C_{19}H_{21}NO_4$ requires C, 69.7; H, 6.45; N, 4.3%); υ_{max} 2948, 1716, 1605, 1436, 1236, 1152 and 753cm^{-1}; m/z(%) 327 (M^+,36), 291(11), 268(100), 243(30), 236(12), 208(14), 91(22) and 77(8); δ; 1.73 (m, 2H, CH_2), 2.32 (m, 2H, CH_2C=), 3.53 (br signal, 2H, CH_2N), 3.61, and 3.76 (2xs, 2x3H, OMe), 4.83 (d, 1H, H_A, J13.6Hz), ~ 6.0 (very br signal, 1H, H_D),

6.96 (t, 1H, H_E, J8.6Hz) and 7.31-7.48 (m, 6H, 5xArH and H_B).

6,7,8,9-Tetrahydro-1-(2'-methoxycarbonylethenyl)-4-methoxycarbonylbenzo[f]azonine (11). Prepared from (10) (1.0g, 5.7mM), paraformaldehyde (0.84g, 28mM), methyl propiolate (1.93g, 23mM) and a catalytic amount of Bu_2SnCl_2 (0.17g, 10mol%) in toluene (50ml) according to the general procedure. Heating was continued for 16h. Flash chromatography (SiO_2, 1:1 v/v Et_2O-petroleum ether) gave the **product** (R_f0.43) (0.11g, 6%) as pale yellow prisms (Et_2O-petroleum ether) m.p. 93-94°C. (Found: C, 69.05; H, 6.1; N, 4.65. $C_{18}H_{19}NO_4$ requires C, 69.0; H, 6.1; N, 4.45%); υ_{max} 2950, 1723, 1610, 1430, 1258 and 767cm^{-1}; m/z(%) 313 (M^+,85), 298(10), 282(23), 254(100), 222(30) and 195(16); δ; 3.16 (br m, 2H, CH_2), 3.70 (s, 3H, OMe), 3.79 (br m, 2H, CH_2N), 3.86 (s, 3H, OMe), 4.96 (dd, 2H, H_A and H_D, J10.3 and 13.6Hz), 6.00 (d, 1H, H_C, J10.1Hz), 6.88 (d, 1H, ArH, J7.3Hz), 7.06-7.25 (m, 4H, 3xArH and H_B) and 7.90 (s, 1H, H_E).

6,7,8,9-Tetrahydro-1-(2'-methoxycarbonylethenyl)-4-methoxycarbonylbenzo[g]azonine (13). Prepared from (12) (1.0g, 5.7mM), paraformaldehyde (0.84g, 28mM), methyl propiolate (1.93g, 23mM) and a catalytic amount of Bu_2SnCl_2 (0.17g, 10mol%) in toluene (50ml) according to the general procedure. Heating was maintained for 16h. Flash chromatography (SiO_2, 1:1 v/v Et_2O-petroleum ether) afforded the **product** (R_f0.28) (0.37g, 21%) as colourless rods (Et_2O-petroleum ether) m.p. 148-149°C. (Found: C, 69.2; H, 6.05; N, 4.55. $C_{18}H_{19}NO_4$ requires C, 69.0; H, 6.1; N, 4.45%); υ_{max} 2940, 1710, 1610, 1430, 1275 and 750cm^{-1}; m/z(%) 313 (M^+,65), 298(48), 282(16), 254(88), 194(19), 141(37) and 104(100); δ; 3.6 (very br signal, 2H, CH_2C=), 3.61 and 3.76 (2xs, 2x3H, OMe), ~4.5 (very br signal, 2H, CH_2N), 4.95(d, 1H, H_A, J13.5Hz), 5.46 (d, 1H, H_D, J9.8Hz), 6.60 (d, 1H, H_C, J9.8Hz), 6.77 (t, 1H, H_E, J9.1Hz), 7.16-7.27 (m, 4H, ArH) and 7.45 (d, 1H, H_B, J13.5Hz).

Dynamic N.M.R. Studies. N.m.r. spectra were determined on Bruker AM-300 and AM-400 instruments. Low temperature spectra were obtained only on the 400MHz instrument. The more complex low temperature spectra of (6a) were assigned by spin decoupling experiments. In general, 16 pulses were accumulated for each spectrum with a 3μ sec pulse (30°) in 32K data points. Figure 5 was generated on a CALCOMP 81 plotter, attached to a molecular graphics system (VAX 11/750 plus Evans and Sutherland MPS workstation).

Crystal Data for (6a): $C_{13}H_{17}NO_4$, M = 251.3, monoclinic, space group $P2_1/c$ (No. 14), a = 14.135(14), b = 11.194(11), c = 8.915(9)Å, β = 103.8(1)°, U = 1369.9Å^3, Dc = 1.22 g cm^{-3}, Z = 4, F(000) = 536, μ(Mo-Kα) = 0.95 cm^{-1}, thin colourless plates, dimensions 1.0 x 0.9 x 0.05 mm.

Crystal Data for (13): $C_{18}H_{19}NO_4$, M = 313.4, triclinic, space group $P\bar{1}$ (No. 2), a = 15.224(15), b = 10.565(11), c = 5.319(5)Å, α = 77.6(1), β = 92.65(1), γ = 99.47°, U = 824.2Å^3, Dc = 1.23 g cm^{-3}, Z = 4, F(000) = 332, μ(Mo-Kα) = 0.97 cm^{-1}, colourless plates, dimensions 1.0 x 0.9 x 0.05 mm. We thank Dr. J. Montgomery for assistance with this structure determination.

Data Collection, Structure Analysis and Refinement: Crystals of (6a) were shown by preliminary oscillation and Weissenberg photographs (Cu-Kα radiation) to consist of parallel rotation twins, twin axis *c*. Reciprocal lattic points for the twin pair coincided only for reflections with $l = 4n$ and it was possible to collect intensity data from one twin for data with $l \neq 4n$. Thus *hk*0-3 and *hk*5-6 data were recorded. *hk*4 data were neglected

as coincident reflections were not symmetry-equivalent. Although *hk*0 data were also coincident the twin pairs were symmetry-equivalent and, by measuring for only half the time, these were placed on a common scale with the other data.

Crystals of (6a) and (13) were mounted with the *c* axis coincident with the ω-axis of a Stöe STADI-2 two circle diffractometer. Using the background - ω-scan - background technique with Mo-Kα radiation 1017 unique data with $I > 0$ were measured for (6a); 1934 for (13). These were corrected for Lorentz and polarisation effects and the structures were solved by the direct phasing methods of SHELX76.[22] They were refined by least squares with allowance for anisotropic vibrations for non-hydrogen atoms. Hydrogens were included at positions calculated from the geometries of the molecules and common isotropic temperature factors for methyl, methylene and olefinic/aromatic hydrogens refined to final values of 0.17(3), 0.11(2) and 0.09(2)Å^2 respectively for (6a); 0.13(1), 0.06(1) and 0.09(1)Å^2 respectively for (13). In the final cycles the 524 data with $I > 3\sigma(I)$ yielded R = 0.095, Rw = 0.097 with $w = 4.4/[\sigma^2(F) + 0.00104F^2]$ for (6a); 1348 data with $I > 3\sigma(I)$ yielded R = 0.095, Rw = 0.103 with $w = 3.8/[\sigma^2(F) + 0.00261F^2]$ for (13). Tables of atomic coordinates, temperature factors, bond lengths, angles and torsion angles for both structures have been deposited with the Cambridge Crystallographic Data Centre. There are no intermolecular contacts less than 3.3Å between non-hydrogen atoms in either structure.

Table 6. Measured and Calculated Torsion Angles for 8-Membered Rings[a]

	Compound 6a	Cycloocta-1,3-diene (Allinger)[16]	Cycloocta-1,3-diene (AM1)	1-Azacycloocta-2,4-diene (AM1)
N1-C1-C2-C3	-5	-4	-1	-5
C1-C2-C3-C4	-41	-47	-39	-47
C2-C3-C4-C5	+2	+2	+3	+4
C3-C4-C5-C6	+86	+94	+85	+110
C4-C5-C6-C7	-52	-53	-55	-62
C5-C6-C7-N1	-58	-57	-56	-50
C6-C7-N1-C1	+88	+79	+92	+116
C7-N1-C1-C2	-10	0	-18	-27

a. Atom numbering scheme is shown in Figure 6.

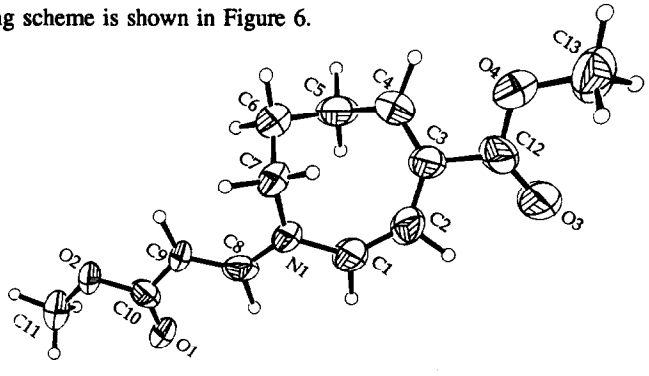


Figure 6. Atom numbering scheme for (6a)

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