1,2-Cycloaddition of αβ-Unsaturated Esters to a Biased Enamine. Crystal and Molecular Structure of a *cis*-Bicyclo[4.2.0]octane Derivative

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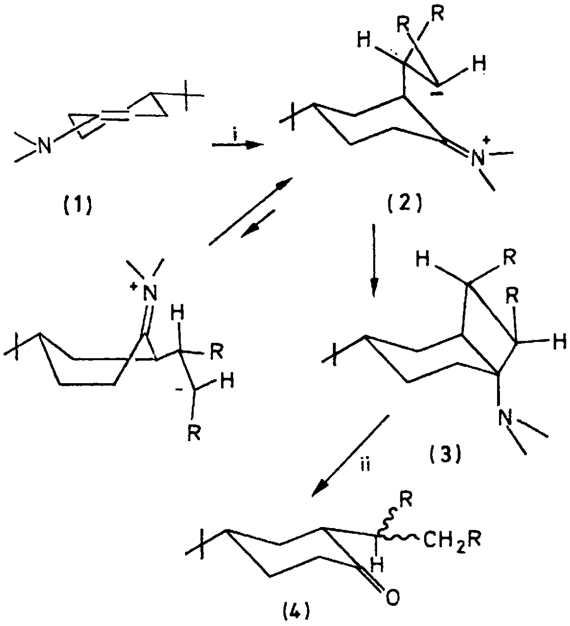
The reactions of 1-morpholino-4-t-butylcyclohexene with diethyl maleate and diethyl fumarate are reported. The configurational aspects of the bicyclo[4.2.0]octane obtained under mild reaction conditions, are examined on the basis of its *X*-ray analysis. The crystal structure has been determined by direct methods and refined by block-diagonal matrix least squares to *R* 0.057. Crystals are monoclinic, space group $P2_1/n$, with $Z = 4$ in a cell with dimensions $a = 13.01(1)$, $b = 14.06(1)$, $c = 12.61(1)$ Å, $\beta = 103.4°$. The cyclohexane and the cyclobutane rings are *cis*-fused and the two adjacent ethoxycarbonyl groups are mutually *trans*.

THE problem of the stereochemistry of cyclobutane, and as a member of fused ring systems, has always received considerable attention.[1,2]

In a bicyclo[4.2.0]octane system in particular, *trans*-fusion [3] allows the cyclohexane ring to be in the preferred, though partially flattened, chair conformation, while the cyclobutane ring is in the puckered conformation (puckering angle 33°). On the other hand, in a structure with a *cis*-fusion between the cyclohexane and cyclobutane rings,[2] the cyclohexane is midway between chair and half-chair and the cyclobutane is midway between planar and puckered forms.



SCHEME

R = ·CO_2Et; Reagents: i, diethyl maleate (or fumarate); ii, H_3O^+

Though a variety of bicyclo[4.2.0]octanes is known in the enamine literature,[4] little can be said about their structure as yet. In only one case [5] has the *cis*-fusion of the rings been demonstrated by chemical methods. As with the geometrical isomerism of the groups eventually present in the rings, it has been detailed only for non-rigid systems derived from cyclohexanone enamines and diethyl maleate.[6] Brannock and his co-workers have in fact shown by chemical methods that the base at C(1) is *trans* with respect to the hydrogen at C(8).

The configurational problems relative to the fusion in the bicyclo[4.2.0]octane derivative (3), obtained from the reaction of (1) with diethyl maleate * (Scheme), could not be solved by way of its ketone derivative, as had been done in a previous case,[5] since (3) did not undergo hydrolysis under non-epimerizing conditions (acetone–water, acetic acid, room temperature, 48 h). Other attempts were made in order to demonstrate the structure through chemical methods, such as Hoffmann and Cope eliminations,[6] but they all failed. *X*-Ray analysis therefore seemed necessary to clarify the structure of (3) and hence the reaction mechanism, already partially suggested for non-rigid systems.[8]

RESULTS AND DISCUSSION

The *cis*-fusion of the two rings is revealed (Figure 1), but not the *trans*-configuration of the base and the hydrogen atom at C(8) [6] (Figure 2). Furthermore the two ethoxycarbonyl groups are mutually *trans*, and that at C(7) is *exo* with respect to the cyclohexane ring. Thus, the adduct (3) is diethyl *r*-1-morpholino-*c*-4-t-butyl-*c*-6*H*-bicyclo[4.2.0]octane-*c*-7,*t*-8-dicarboxylate. Bond lengths and angles are listed in Table 1. The mean C–C bond length within the four-membered ring is 1.55 Å and mean bond angle 88°, not significantly different from values reported for similar compounds.[3,9,10]

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* Diethyl fumarate reacts similarly.[7]

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Ring conformations may be conveniently described in terms of an angle of twist about each ring bond. These are listed in Table 2, together with twist angles specifying the mutual orientations between the substituents at the fused ring. The four-membered ring is non-planar with internal twist angles nearly approaching reported values.[3,10] Alternatively we also give the value of the dihedral angle between the planes specified by C(1), C(6), and C(8) and C(6)—(8), which is 151° (puckering angle 29°). For a summary of dimensions of cyclobutane rings see ref. 10.

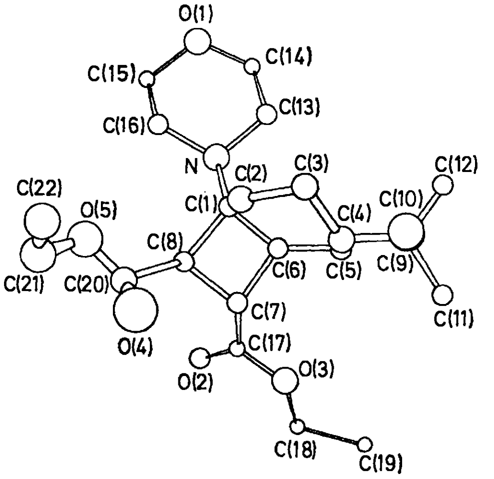

FIGURE 1 Projection of the molecule along the *b* axis, together with the atom numbering scheme used in the crystallographic analysis

The chair conformation of the six-membered ring is considerably flattened. This can be seen by comparison of the twist angle (Table 2) with the ideal value of 60° for a pure chair. As a consequence, the C(6)–C(7) bond is so forced out of perfect axial orientation that the angle C(5)–C(6)–C(7) becomes 118.6°.

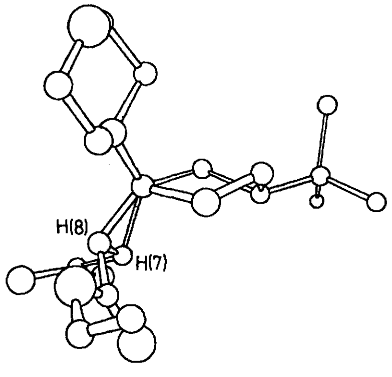

FIGURE 2 Perspective view of the molecule along the direction specified by the C(1)–C(6) bond. The positions of H(7) and H(8) are also shown

As for crystal packing, no unusually short intermolecular contact has been found.

TABLE 1

Bond lengths (Å) and angles (deg.) between non-hydrogen atoms, with standard deviations in parentheses

(*a*) Distances

O(1)–C(14)	1.425(8)	C(3)–C(4)	1.515(8)
O(1)–C(15)	1.426(6)	C(4)–C(5)	1.523(7)
O(2)–C(17)	1.196(7)	C(4)–C(9)	1.579(7)
O(3)–C(17)	1.332(7)	C(5)–C(6)	1.537(6)
O(3)–C(18)	1.452(7)	C(6)–C(7)	1.563(6)
O(4)–C(20)	1.191(7)	C(7)–C(8)	1.541(7)
O(5)–C(20)	1.334(7)	C(7)–C(17)	1.475(7)
O(5)–C(21)	1.458(7)	C(8)–C(20)	1.498(6)
N–C(1)	1.457(6)	C(9)–C(10)	1.530(8)
N–C(13)	1.449(6)	C(9)–C(11)	1.548(9)
N–C(16)	1.472(7)	C(9)–C(12)	1.564(7)
C(1)–C(2)	1.532(6)	C(13)–C(14)	1.514(9)
C(1)–C(6)	1.565(7)	C(15)–C(16)	1.515(8)
C(1)–C(8)	1.534(5)	C(18)–C(19)	1.480(9)
C(2)–C(3)	1.547(7)	C(21)–C(22)	1.453(12)

(*b*) Angles

O(1)–C(14)–C(13)	111.2(5)	C(2)–C(1)–C(6)	111.1(4)
O(1)–C(15)–C(16)	111.1(5)	C(2)–C(1)–C(8)	112.6(3)
O(2)–C(17)–O(3)	122.3(5)	C(3)–C(4)–C(5)	109.9(4)
O(2)–C(17)–C(7)	126.8(5)	C(3)–C(4)–C(9)	113.9(4)
O(3)–C(17)–C(7)	110.9(4)	C(4)–C(5)–C(6)	113.3(4)
O(3)–C(18)–C(19)	106.7(4)	C(4)–C(9)–C(10)	110.3(4)
O(4)–C(20)–O(5)	123.1(5)	C(4)–C(9)–C(11)	110.2(4)
O(4)–C(20)–C(8)	125.5(5)	C(4)–C(9)–C(12)	111.3(4)
O(5)–C(20)–C(8)	111.4(4)	C(5)–C(4)–C(9)	112.7(4)
O(5)–C(21)–C(22)	109.0(5)	C(5)–C(6)–C(7)	118.6(4)
N–C(1)–C(2)	117.6(4)	C(6)–C(1)–C(8)	86.2(3)
N–C(1)–C(6)	118.8(4)	C(6)–C(7)–C(8)	87.8(3)
N–C(1)–C(8)	112.3(4)	C(6)–C(7)–C(17)	115.9(4)
N–C(13)–C(14)	109.3(4)	C(7)–C(8)–C(20)	116.2(4)
N–C(16)–C(15)	109.1(4)	C(8)–C(7)–C(17)	118.1(4)
C(1)–N–C(13)	114.9(4)	C(10)–C(9)–C(11)	110.0(5)
C(1)–N–C(16)	114.0(4)	C(10)–C(9)–C(12)	107.7(4)
C(1)–C(2)–C(3)	114.8(4)	C(11)–C(9)–C(12)	107.3(4)
C(1)–C(6)–C(5)	120.5(4)	C(13)–N–C(16)	108.7(4)
C(1)–C(6)–C(7)	89.3(3)	C(14)–O(1)–C(15)	109.3(4)
C(1)–C(8)–C(7)	89.4(3)	C(17)–O(3)–C(18)	118.2(4)
C(1)–C(8)–C(20)	120.0(4)	C(20)–O(5)–C(21)	118.1(5)

Resolution of the structure enables us to give a more detailed mechanism for the reaction. Once more it has been verified that the stereoelectronic antiparallel attack of the olefin occurs, although the unusual parallel attack sometimes takes place on biased enamines of this

TABLE 2

Some significant torsion angles (deg.). Hydrogen atoms are numbered according to the carbon atoms to which they are bonded

(*a*) Cyclohexane ring

C(1)–C(2)–C(3)–C(4)	57.1	C(4)–C(5)–C(6)–C(1)	−37.2
C(2)–C(3)–C(4)–C(5)	−61.1	C(5)–C(6)–C(1)–C(2)	30.6
C(3)–C(4)–C(5)–C(6)	50.5	C(6)–C(1)–C(2)–C(3)	−39.2

(*b*) Cyclobutane ring

C(1)–C(6)–C(7)–C(8)	−20.7	C(7)–C(8)–C(1)–C(6)	−20.4
C(6)–C(7)–C(8)–C(1)	20.4	C(8)–C(1)–C(6)–C(7)	20.1

(*c*) Torsion angles involving substituents

O(3)–C(17)–C(7)–C(8)	182.8	C(5)–C(6)–C(7)–H(7)	−36.0
O(5)–C(20)–C(8)–C(7)	168.6	C(13)–N–C(1)–C(2)	−64.7
N–C(1)–C(8)–H(8)	−20.9	C(17)–C(7)–C(6)–C(5)	85.8
N–C(1)–C(8)–C(20)	73.7	C(17)–C(7)–C(8)–C(20)	−82.1
C(2)–C(1)–C(8)–C(20)	−29.2	C(18)–O(3)–C(17)–C(7)	176.8
C(3)–C(4)–C(9)–C(10)	−55.5	C(21)–O(5)–C(20)–C(8)	179.6

type.[11,12] Since the cycloaddition does not involve a concerted, but rather a two-step process,[8] in which the zwitterion (2) is the initially formed intermediate, the carbon anion may collapse onto C(1), leaving the base in the pseudoaxial conformation. An eventual *trans*-fusion would have involved an energetically unfavoured boat form of the intermediate, strongly destabilized also by an $A^{(1,3)}$ strain [13] between the base and the side-chain.

As to the relative configuration of the ethoxycarbonyl groups, it depends upon the steric preference of the ester during the approach. The ethoxycarbonyl group at the electrophilic carbon atom in fact is *exo*-oriented with respect to the cyclohexene ring, thus avoiding steric interferences with the ring itself. During the formation of the cyclobutane ring, the second ethoxycarbonyl group necessarily assumes a *trans*-configuration with respect to the first, in order to avoid dipole–dipole and steric interactions with it. Moreover, if the ethoxycarbonyl groups were *cis–exo*, an additional quasi-eclipsed interaction between the base and the group at C(8) would be present.

Compound (3) does not equilibrate into a more stable cyclobutane derivative or into a mixture of cyclobutanes, at least under the equilibration conditions used, *i.e.* EtOH and EtO^-Na^+, room temperature, 48 h. Under more forcing conditions,[14] the cyclobutane derivative (3) appeared to be thermally unstable, since it led to the reactants, together with the ketone (4) whose stereochemistry has not so far been investigated. However, the fact that (4) does not epimerize by treatment with TsOH when heated under reflux in benzene, leads to the conclusion that the ketone is *cis*.

EXPERIMENTAL

I.r. spectra were recorded for Nujol mulls with a Perkin-Elmer 257 spectrophotometer. ^1H N.m.r. spectra were recorded with a JEOL JNM C 60 HL spectrometer with tetramethylsilane as internal standard, for $CDCl_3$ solutions. G.l.c. was carried out on a Varian Aerograph, series 1 400, 5 ft × 1/8 in column, stationary-phase SE 30.

Reactions with Diethyl Maleate (*and Diethyl Fumarate*).—Equimolar quantities of (1) and diethyl maleate (or fumarate) were allowed to react in anhydrous CH_3CN, at 25°, for 36 h. Only *diethyl* 1-*morpholino*-4-*t*-*butylbicyclo*-[4.2.0]*octane*-7,8-*dicarboxylate* (3) was isolated (40%), m.p. 124—125 °C (from benzene–light petroleum) (Found: C, 66.25; H, 9.55; N, 3.60. $C_{22}H_{37}NO_5$ requires C, 66.81; H, 9.43; N, 3.54%); $\nu_{max.}$ 1 730, 1 720 (CO_2Et), and 1 110 cm^{-1} ($CH_2{\cdot}O{\cdot}CH_2$); δ 0.90 (9 H, s, Bu^t), 1.30 (t, $CH_2{\cdot}CH_3$), 2.70 (4 H, m, $CH_2{\cdot}N{\cdot}CH_2$), 3.10 (2 H, m, H-7 and H-8), 3.70 (4 H, m, $CH_2{\cdot}O{\cdot}CH_2$), 4.20 (4 H, q, $CH_2{\cdot}CH_3$). The thermal reversibility of (3) was demonstrated by g.l.c., since it decomposed into its starting materials.

Hydrolysis of (3).—(3) underwent hydrolysis with acetic acid when heated under reflux in ethanol–water for 2 h to give *diethyl* (2-*oxo*-5-*t*-*butylcyclohexyl*)*succinate* (4) in quantitative yield, b.p.$_{0.4}$ 168—170 °C (Found: C, 66.30; H,

TABLE 3

Fractional co-ordinates (for non-hydrogen atoms × 10^4, for hydrogen × 10^3) with standard deviations in parentheses. Hydrogen atoms are numbered according to the carbon atoms to which they are bonded

Atom	*x*	*y*	*z*
O(1)	2 395(3)	−126(3)	8 635(3)
O(2)	1 299(3)	−486(3)	2 710(4)
O(3)	2 733(3)	156(3)	2 343(3)
O(4)	385(3)	2 165(3)	3 564(3)
O(5)	−256(3)	1 394(3)	4 808(3)
N	2 302(3)	459(3)	6 452(3)
C(1)	2 323(3)	1 060(3)	5 516(4)
C(2)	2 523(3)	2 125(3)	5 722(4)
C(3)	3 694(4)	2 431(3)	5 913(5)
C(4)	4 169(3)	2 154(3)	4 968(4)
C(5)	4 135(3)	1 077(3)	4 830(4)
C(6)	3 040(3)	648(3)	4 785(4)
C(7)	2 131(3)	839(3)	3 756(4)
C(8)	1 360(3)	855(3)	4 516(4)
C(9)	5 305(4)	2 581(4)	5 038(4)
C(10)	5 282(4)	3 665(4)	5 145(6)
C(11)	5 700(5)	2 302(5)	4 013(5)
C(12)	6 125(4)	2 187(5)	6 052(5)
C(13)	3 296(4)	397(4)	7 256(4)
C(14)	3 208(5)	−355(5)	8 090(5)
C(15)	1 412(4)	−50(5)	7 852(4)
C(16)	1 463(4)	707(4)	7 011(4)
C(17)	1 979(4)	105(4)	2 898(4)
C(18)	2 735(4)	−553(4)	1 497(4)
C(19)	3 797(5)	−521(5)	1 259(5)
C(20)	466(4)	1 552(4)	4 230(4)
C(21)	−1 182(5)	2 023(5)	4 626(6)
C(22)	−963(6)	2 806(6)	5 399(9)
1H(2)	209(4)	253(3)	502(4)
2H(2)	224(3)	236(3)	636(3)
1H(3)	366(3)	317(3)	603(3)
2H(3)	418(4)	210(4)	665(4)
H(4)	366(4)	243(3)	423(4)
1H(5)	436(3)	89(3)	407(4)
2H(5)	466(3)	78(3)	553(3)
H(6)	312(3)	−8(3)	491(3)
H(7)	218(3)	151(3)	346(3)
H(8)	103(3)	20(3)	456(3)
1H(13)	385(4)	19(3)	683(4)
2H(13)	342(4)	104(3)	762(4)
1H(14)	304(4)	−102(4)	766(4)
2H(14)	386(4)	−46(4)	866(5)
1H(15)	123(4)	−72(4)	748(4)
2H(15)	89(4)	20(4)	829(5)
1H(16)	75(4)	71(3)	642(4)
2H(16)	165(4)	137(4)	737(4)
1H(10)	601	396	518
2H(10)	478	395	445
3H(10)	512	387	588
1H(11)	507	254	332
2H(11)	641	267	399
3H(11)	578	157	398
1H(12)	616	140	605
2H(12)	690	250	598
3H(12)	605	242	681
1H(18)	212	−38	77
2H(18)	257	−126	180
1H(19)	389	−102	68
2H(19)	410	15	110
3H(19)	439	−67	200
1H(21)	−187	164	476
2H(21)	−135	232	381
1H(22)	−30	308	544
2H(22)	−154	336	516
3H(22)	−97	241	610

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9.30. $C_{18}H_{30}O_5$ requires C, 66.23; H, 9.26%); $\nu_{max.}$ 1 732, 1 708 (CO_2Et; CO); δ 0.93 (9 H, s, Bu^t), 1.24 (3 H, t, $CH_2{\cdot}CH_3$), 4.05 (4 H, q, $CH_2{\cdot}CH_3$).

Crystallography

Rectangular prisms were obtained from benzene–ligroin. The crystal used had an approximately square cross-section (0.17 × 0.17 × 0.8 mm).

Crystal Data.—$C_{22}H_{37}NO_5$, $M = 395.5$. Monoclinic, $a = 13.01(1)$, $b = 14.06(1)$, $c = 12.61(1)$ Å, $\beta = 103.4°$, $U = 2\,242.8$ Å^3, D_m (by flotation) = 1.16, D_c (for $Z = 4$) = 1.17 g cm^{-3}. Space group $P2_1/n$.

Initial cell parameters were determined from Weissenberg photographs taken with Cu-K_α radiation, and then refined from a least-squares fit to the angular co-ordinates of 25 reflections measured on a Philips single-crystal diffractometer, by use of Mo-K_α radiation ($\lambda = 0.7\,107$ Å).

Intensity Measurements.—Three-dimensional intensity data were collected on the diffractometer, equipped with a graphite monochromator, by use of the θ—2θ scan technique and Mo-K_α radiation up to 2θ 42°; each reflection was scanned at a rate of 4.2° min^{-1} over a range of 1.1°.

Of 2 459 reflections measured, 1 560 had $I > 3\sigma(I)$. During data collection the intensities of three reference reflections showed no significant changes. No absorption correction was applied.

Structure Determination and Refinement.—Structure amplitudes were put on absolute scale by the Wilson[15] statistical method, and normalized unitary structure factors derived. The structure was solved by a multisolution and sign permutation technique from a basic set of 27 reflections. The method consists of evaluating a figure of merit depending on triplets of reflections as well as on their products in pairs.[16,17] The same highest value of the figure of merit was shown by 4 sign combinations. All of them were used to attribute the sign to the greatest number of the 408 reflections with $|E| > 1.3$ and to calculate a Fourier synthesis.

The correct combination gave the sign to all 408 reflections and the correspondent Fourier synthesis revealed all non-hydrogen atom positions, one spurious peak being rejected as being incongruous with molecular structure and reasonable bond distances. A structure-factor calculation led to R 0.265 and this value was lowered to 0.159 after three cycles of block-diagonal matrix least-squares refinement with isotropic temperature factors. Three further cycles, allowing for the thermal anisotropy of all non-hydrogen atoms, led to R 0.100. At this stage a difference-Fourier synthesis was calculated and all hydrogens located. Some problems arose in locating those of the methyl groups, owing to a noticeable broadening of the electron density maxima. An average isotropic thermal factor of 4.5 Å^2 was assumed for hydrogen atoms in the subsequent-structure factor calculation, and gave R 0.070. At this stage all non-hydrogen atoms were split into two groups of neighbouring ones and then each group refined by two cycles of full-matrix least-squares. After the second cycle the shift-to-error ratio was <0.4 for all atoms. The final refinement procedure was carried out on hydrogen atoms corresponding to the highest peaks on the difference-Fourier synthesis. Two cycles of block-diagonal matrix least-squares refinement on these atoms led to the final R of 0.057.

Atomic scattering factors were calculated according to ref. 18 for hydrogen atoms, and for oxygen, nitrogen, and carbon atoms, according to ref. 19.

The final weighting scheme was $w = 1/(A + B|F_o| + C|F_o|^2)$, where $A = 9.0$, $B = 1.0$, $C = 0.011$ chosen in order to maintain $w(|F_o| - |F_c|)^2$ essentially constant over all ranges of $|F_o|$ and sin θ/λ. A list of structure factors together with anisotropic thermal parameters is deposited as Supplementary Publication No. SUP 21437 (14 pp., 1 microfiche).* Final atomic parameters are listed in Table 3 together with their estimated standard deviations, calculated from the residuals and the diagonal elements of the inverse matrix of the least squares cycle. The atom numbering scheme is shown in Figure 1.

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* See Notice to Authors No. 7 in *J.C.S. Perkin II*, 1974, Index issue.

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