Ring Expansion with Four C Atoms by Tandem (2 + 2)Cycloaddition and Electrocyclic Ring Opening

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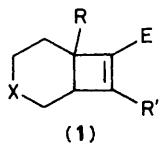
A four-carbon ring expansion is presented which involves reaction of enamines of cyclic ketones with methyl propiolate followed by reaction of the resulting *cis,cis*-cycloalkadienes, also containing an 'enamine' type of double bond, with dimethyl acetylenedicarboxylate (DMAD).

The two-carbon ring expansion by (2 + 2)cycloaddition of an acetylenic ester to an enamine of a cyclic ketone and subsequent opening of the annulated cyclobutene moiety formed, represents a well-known method in organic synthesis.[1] Previously,[1] we have described the influence of the size of the *cis*-fused ring system and of the dialkylamino group at the bridgehead position on the thermal stability of the bicyclic cyclobutene derivatives (**1**, R′ = E) formed in the reactions of enamines of cyclic ketones with dimethyl acetylenedicarboxylate (DMAD) in an apolar solvent. Only with five-membered and in some cases (depending on the dialkylamino group) with six-membered rings can the (2 + 2)cycloadducts actually be isolated. In all cases cyclobutene-ring opening occurs at room temperature in a *conrotatory* fashion to yield the corresponding *cis,trans*-cycloalkadienes (**2**, R′ = E). We found that at higher temperatures the *cis,trans*-cycloalkadienes rearrange by a [1,5]-hydrogen shift to *cis,cis*-cycloalkadienes (**3**, R′ = E). Some *cis,trans*-cycloalkadienes (**2**, R′ = E) isomerise to *cis,cis*-cycloalkadienes (**4**, R′ = E) probably *via* two consecutive [1,5]-hydrogen shifts. For the dimethyl dihydro-6-(1-pyrrolidinyl)-2*H*-thiocine-4,5-dicarboxylates (**2**), (**3**), and (**4**) (R′ = E, X = S, R = 1-pyrrolidinyl) the structure has unequivocally been confirmed by single-crystal *X*-ray analysis.[1]

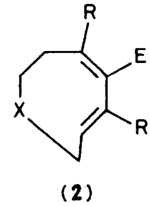
When we compared these results with literature[2] data on the reactions of enamines of cyclic ketones with (m)ethyl propiolate as the acetylenic ester we decided to reinvestigate this reaction also, particularly in respect of the stereochemistry of the ring-enlargement products. With the exception of the result described in a paper of Parham,[2e] the configuration around the double bonds in the ring-expanded products with nine and more C atoms as represented by the formulae given in the literature seem to be correct only by accident, or they are incorrect. We found that in general the course of the reaction and the stereochemistry of the products obtained were rather similar to those with DMAD.†

In principle the three consecutive reactions *viz.* (2 + 2) cycloaddition, electrocyclic ring opening, and [1,5]-hydrogen shift which regenerates a product with a similar type of reactivity as the starting material would offer an ideal opportunity for a tandem ring-enlargement reaction.[3] In this communication we report the first results using methyl propiolate and DMAD as the acetylenic esters in the first and second reaction, respectively.

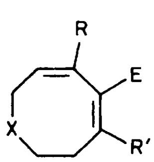
Reaction of an equimolar mixture of 4-(cyclo-oct-1-en-1-yl)morpholine and methyl propiolate for 6 hours in dry toluene at reflux temperature afforded after column chromatography [basic Al_2O_3(IV)–chloroform] a 66% yield of methyl 2-(4-morpholinyl)-*cis,cis*-cyclodeca-2,10-diene-1-carboxylate (**3d**, R′ = H). Evidence for the *cis,cis*-geometry was obtained by comparing the absorptions for the 'enamine' proton (H-3) at δ 4.44 (t) and for the other vinylic proton (H-10) at δ 6.95 (dd) in the ^1H n.m.r. spectrum with those of the corresponding protons in the *cis,cis*-cycloalkadienes (**3**, R′ = E) (δ 4.05—5.04) and (**4**, R′ = E) (δ 6.65—6.88), respectively.[1] Furthermore the stereochemistry of the product (**5d**) obtained in the second reaction is in agreement with the proposed *cis,cis*-arrangement of double bonds in the educt (**3d**, R′ = H) (*vide infra*).



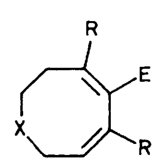
(**1**)



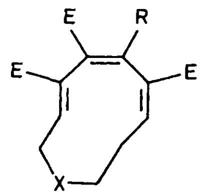
(**2**)



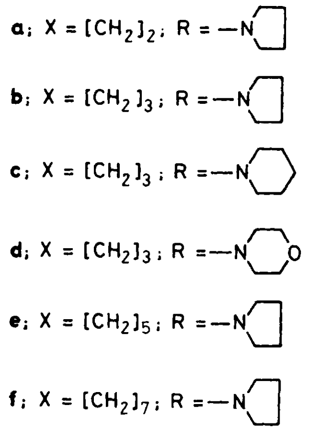
(**3**)



(**4**)



(**5**)



E = CO_2Me

With DMAD, (**3d**, R′ = H) reacted at room temperature in diethyl ether solvent for two days to give after column chromatography (silica gel–ethyl acetate) a solid 1 : 1 addition product [$C_{22}H_{31}NO_7$; m.p. 90—91.5 °C (after trituration with di-isopropyl ether)] in 50% yield. The ^{13}C n.m.r. spectrum revealed the presence of six olefinic C atoms. In the region for the vinylic protons in the ^1H n.m.r. spectrum two double

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† The detailed results of this reinvestigation will be presented separately.

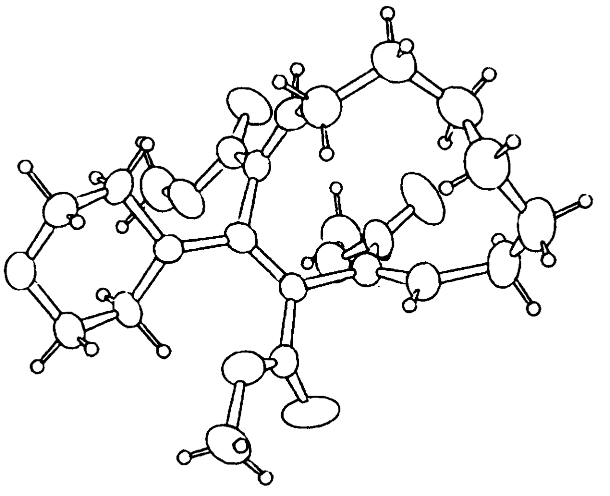

Figure 1. ORTEP[4] view of (**5d**). *Crystal data:* $C_{22}H_{31}NO_7$, orthorhombic, space group *Pbca*, a = 13.965(2), b = 11.078(2), c = 28.201(4) Å, Z = 8, D_c = 1.29 g cm^{-3}. Reflections measured at room temperature on a Philips PW1100 diffractometer (graphite monochromated Mo-K_α radiation, ω–2θ scan mode, $2.5 < \omega < 25°$, scan width (ω) ($1.2 + 0.5$ tg ω)°. Structure solution by direct methods[5] and refinement by least-squares[6] based on 1450 reflections with $I > \sigma(I)$ (from counting statistics). Hydrogen atoms were found from difference Fourier synthesis. Final R-factor 5.3%. [396 Parameters refined: scale factor, extinction parameter, positional parameters, thermal parameters (isotropic for H, anisotropic for non H-atoms)].

doublets are present: one at δ 6.94 and one at δ 6.02. The former absorption might be attributed to a H atom at a *cis*-double bond, the latter one to a H atom at a *trans*-double bond on the basis of the absorptions of the vinylic protons in compounds (**4**, R′ = E) (δ 6.65—6.88) and (**2**, R′ = E) (δ 5.40—6.06), respectively.[1] An X-ray structure determination‡ proved definitely the stereochemistry of trimethyl 3-(4-morpholinyl)-*cis,cis,trans*-cyclododeca-2,4,12-triene-1,2,4-tricarboxylate (**5d**) (Figure 1). (Endocyclic torsion angles for the double bonds: 3.9, −5.7, and −174.7°.)

Compounds (**3a—c**), (**3e**), and (**3f**) (R′ = H),§ could similarly be obtained by carrying out the reaction of the enamine with methyl propiolate in refluxing dry toluene.¶ The ^{1}H n.m.r. spectra of compounds (**3**, R′ = H) showed absorptions at δ 4.01—4.44 for the 'enamine' proton and at δ 6.88—7.04 for the other vinylic proton.

The reaction of the *cis,cis*-cycloalkadienes (**3**, R′ = H) with DMAD in diethyl ether at room temperature proved to be a general one.‖ Starting from the enamines the *cis,cis,trans*-cycloalkatrienes (**5**) were isolated as oils in overall yields of 40 (**5a**), 73 (**5b**), 74 (**5c**), and 42% (**5e,f**). The ^{1}H n.m.r. spectra of (**5**) showed diagnostic absorptions at δ 6.77—6.94 and at δ 5.83—6.02.

The formation of the *cis,cis,trans*-cycloalkatrienes (**5**) can be explained by (2 + 2)cycloaddition of DMAD to the 'enamine' double bond of (**3**, R′ = H) followed by an electrocyclic ring opening of the cyclobutene moiety which occurs in the symmetry-allowed conrotatory fashion.[7]

The tandem reaction described in this communication enables a ring expansion with four C atoms in two steps. Hitherto such a ring enlargement was only possible in a multistep reaction sequence *via* the cyclic ketone with two carbon atoms more than the enamine of the starting ketone.[2b—d] Furthermore this tandem ring expansion makes some medium-sized carbocycles, particularly 11- and 16-membered rings, more easily accessible from readily available starting materials.

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‡ The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

§ The ^{1}H and ^{13}C n.m.r. and mass spectral data are consistent with the proposed structures of compounds (**3**, R′ = H) and (**5**).

¶ Performing the reaction of the enamines with methyl propiolate at room temperature the *cis,trans*-cycloalkadienes (**2**, R′ = H) were contaminated with the corresponding methyl (*E*)-3-dialkylaminoprop-2-enoates. The formation of the latter compounds could be suppressed by carrying out the reaction at higher temperatures yielding predominantly the *cis,trans*-cycloalkadienes (**2**, R′ = H) (refluxing hexane for some hours) or the isomeric *cis,cis*-cycloalkadienes (**3**, R′ = H) (refluxing toluene). Only starting from 1-(cyclododec-1-en-1-yl)pyrrolidine both in refluxing hexane and in refluxing toluene a mixture of the *cis,trans*- and *cis,cis*-cyclotetradecadiene (**2f**) and (**3f**) (R′ = H), together with some methyl (*E*)-3-(1-pyrrolidinyl)prop-2-enoate, results.

‖ Instead of (**3f**, R′ = H) the mixture mentioned in the previous footnote was used, as this could not be separated on basic Al_2O_3(IV). Similarly, (**3e**, R′ = H) could not be purified in this way.