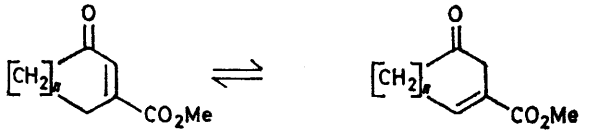
# Equilibrations of 3-Methoxycarbonylcycloalkenones

By **Jerry A. Hirsch** * and **Lynda Y. Lin**, Department of Chemistry, Seton Hall University, South Orange, New Jersey, U.S.A. 07079

Conditions of acid and base catalysis under which 3-methoxycarbonylcycloalk-2-enones and -3-enones with ring sizes 7—10 could be interconverted have been investigated. The use of 1,5-diazabicyclo[4.3.0]non-5-ene as a basic catalyst is recommended, to overcome problems associated with Michael additions. For each ring size, more of the $\Delta^3$-isomer was obtained than in the unsubstituted series. Only the *cis*- and *trans*-3-methoxycarbonyl cyclodec-3-enones were available as starting materials in the ten-membered series, but these were efficiently equilibrated without detectable formation of $\Delta^2$-isomers. A possible explanation of the methoxycarbonyl substituent effect is offered.

WHITHAM and his co-workers [1-3] have prepared the cycloalk-2-enones and cycloalk-3-enones with ring sizes 5—10 and studied interconversion, exchange, and addition phenomena in many of these compounds. Since our studies [4] of keto–enol equilibria had suggested that substituents influenced medium-sized ring equilibria, and since cycloalkenone equilibria involve enol or enolate intermediates,[1-3,5] we have chosen substituted cycloalkenones of ring sizes 7—10 as systems with which to probe substituent effects on equilibria.

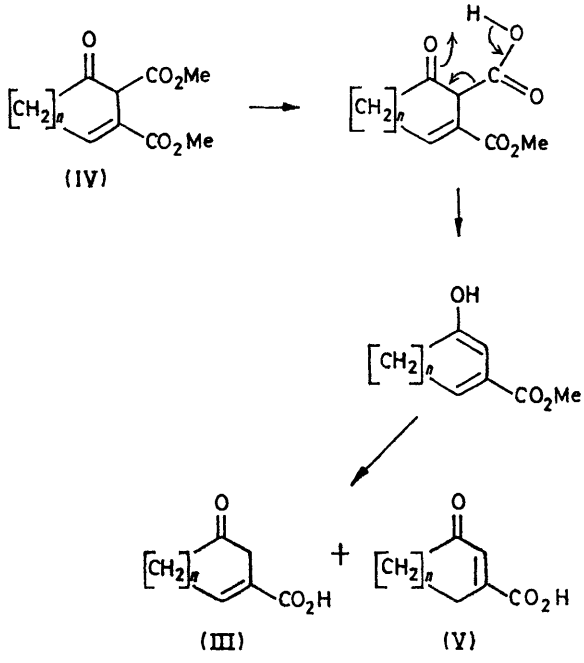
The 3-methoxycarbonylcycloalkenones (I) and (II)



(I) (II)

were studied first for several reasons. Monosubstitution in the 3-position would provide equilibration of trisubstituted alkenes, removing complications resulting from different double-bond substitution patterns.[6] Models suggested that 3-substitution would generate few new non-bonded interactions. Choice of a non-alkyl substituent would restrict the equilibrium to endocyclic isomers. The 3-methoxycarbonylcycloalk-3-enones (II) appeared readily accessible from the previously prepared [4] 3-carboxycycloalk-3-enones (III), by an esterification step previously performed in the cyclo-octenone series [7] with diazomethane or the Fischer procedure.

We also hoped that the equilibration results from the 3-methoxycarbonylcycloalkenones would provide some answer to a surprising result observed [4,8] in the preparation of the 3-carboxycycloalk-3-enones (III). The latter systems are the sole products obtained on hydrolysis and decarboxylation of 2,3-bismethoxycarbonylcycloalk-3-enones (IV). Since acid-catalysed decarboxylations of β-keto-acids are believed to involve the enol of the decarboxylation product [9] (Scheme 1), conditions for double-bond equilibration would appear to be present prior to isolation of the products. Failure



(IV) (III) (V)

SCHEME 1

to isolate cycloalk-2-enone products (V) could reflect (*a*) an overwhelming thermodynamic preference for the $\Delta^3$-isomers (III) (in all ring sizes studied), (*b*) kinetic control of product formation by the preferential protonation at C-2 demonstrated for the unsubstituted cycloalkenones,[1,3] (*c*) operation of a reaction mechanism not involving a dienol intermediate, or (*d*) shortcomings in the isolation procedures.

## RESULTS AND DISCUSSION

The 2,3-bismethoxycarbonylcycloalk-3-enones (IV; $n = 3$—6) were prepared as reported,[4] and subjected to

[1] N. Heap and G. H. Whitham, *J. Chem. Soc.* (*B*), 1966, 164.
[2] P. Chamberlain and G. H. Whitham, *J. Chem. Soc.* (*B*), 1969, 1131.
[3] G. H. Whitham and M. Zaidlewicz, *J.C.S. Perkin I*, 1972, 1509.
[4] J. A. Hirsch and F. J. Cross, *J. Org. Chem.*, 1971, **36**, 955.
[5] D. S. Noyce and M. Evett, *J. Org. Chem.*, 1972, **37**, 394.
[6] For equilibration of a seven-membered system containing an additional ring fused at positions three and four, see J. A. Marshall and A. E. Greene, *J. Org. Chem.*, 1971, **36**, 2035.
[7] A. C. Cope, J. M. McIntosh, and M. A. McKervey, *J. Amer. Chem. Soc.*, 1967, **89**, 4020.
[8] A. K. Bose, G. Mina, M. S. Manhas, and E. Rzucidlo, *Tetrahedron Letters*, 1963, 1467.
[9] J. March, 'Advanced Organic Chemistry,' McGraw-Hill, New York, 1968, p. 478; J. Hine, 'Physical Organic Chemistry,' 2nd edn., McGraw-Hill, New York, 1962, p. 303.

the hydrolysis–decarboxylation sequence.[4] The acids obtained were treated with boron trifluoride–methanol complex[10] to produce the desired methyl esters. The eight- and nine-membered ring esters were obtained as pure cycloalk-3-enones (II; $n = 4$ or 5). Two ten-membered ring compounds were obtained in a 4 : 1 ratio, separated, and identified as the *cis*- and *trans*-isomers of 3-methoxycarbonylcyclodec-3-enone (II; $n = 6$), respectively. Unfortunately, unambiguous stereochemical assignment was not possible. The u.v. and i.r. spectra of the diastereoisomers were almost identical. Structural assignment rests primarily on the chemical shift of the vinyl hydrogen at position 4 (Table 1) as a function of ring size. Contrary to earlier reports based on the 3-carboxycycloheptenones,[4,7,8] the 3-methoxycarbonylcycloheptenones were obtained as a 1 : 19 $\Delta^2 : \Delta^3$ mixture (I and II; $n = 3$), which was separated, and the components were identified.

TABLE 1

Chemical shifts of vinyl protons in 3-methoxycarbonylcycloalk-3-enones (II)

| Ring size | Diastereoisomer | δ |
|---|---|---|
| 7 | *cis* | 7·05 |
| 8 | *cis* | 7·00 |
| 9 | *cis* | 6·87 |
| 10 | *cis* | 6·98 |
| 10 | *trans* | 6·17 |

Each available pure compound and the two available mixtures were subjected to equilibration using 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in refluxing benzene. The seven- and eight-membered compounds and the 1 : 19 mixture of the cycloheptenone isomers were also treated with anhydrous toluene-*p*-sulphonic acid[1,3] (*p*-TsOH) in refluxing benzene. As determined by g.l.c. and spectral analyses, equilibrium was reached with equal facility in the two catalyst systems. Because of the difficulties associated with the preparation of anhydrous *p*-TsOH, we feel that DBN (or an equivalent weakly nucleophilic strong base) is the catalyst of choice for such equilibrations as these.

When 3-methoxycarbonylcyclohept-3-enone (II; $n = 3$) was treated with sodium methoxide in refluxing methanol, equilibrium was not established and an unidentified methoxy-containing 3-methoxycarbonylcycloheptanone was formed, presumably as the result of Michael addition.[1,2] No 3-methoxycarbonylcyclohept-2-enone (I; $n = 3$) was observed, suggesting either that this compound was not formed or that methoxide attack on 3-methoxycarbonylcyclohept-2-enone was faster than the interconversion of the $\Delta^2$- and $\Delta^3$-isomers. The latter result is different from that of Chamberlain and Whitham,[2] who report interconversion of cyclohept-2-enone and cyclohept-3-enone (but not of cyclo-oct-2-enone and cyclo-oct-3-enone) prior to addition of methanol. Ascribing this difference to a substituent effect is premature at present.

The results of our equilibration experiments are summarized in Table 2. Comparison with the Heap and Whitham results[1] for the unsubstituted cycloalkenones (Table 3) indicates that less of the $\Delta^2$-isomer is present at equilibrium when a methoxycarbonyl group is attached at position 3. Since models suggest that the methoxycarbonyl group does not introduce non-bonded interactions or conformational restraints involving the cycloalkenone systems and can rotate freely in order to assume maximal electronic interaction with the π-electrons of the ring double bond in all isomers, the substituent effect cannot be explained in any of the above ways.

An attractive explanation of this substituent effect involves recognition that 3-methoxycarbonylcycloalk-2-enones are conjugated enedione systems whereas 3-methoxycarbonylcycloalk-3-enones are enone systems possibly interacting with a non-conjugated carbonyl group. Effective electron delocalization requires proper coplanar orientation of three ring carbons and an exocyclic carbonyl group in the enedione, yet coplanarity of only two ring carbons and the exocyclic carbonyl group in the enone. The $\Delta^3$-isomers may therefore be effectively conjugated from the electron point of view while making fewer conformational demands on the medium-sized ring system than the $\Delta^2$-isomers. In addition, the facility with which many enediones rearrange[11] suggest that the electronic stabilization associated with an enedione system is less than that associated with a analogous conjugated enone system. This would provide an additional cause for an increase in the $\Delta^3$-isomers in the 3-methoxycarbonylcycloalkenones relative to the parent cycloalkenones.[1]

TABLE 2

Equilibrations of 3-methoxycarbonylcycloalkenones

| Ring size | Catalyst | Equilibration time (h) [a] | Composition |
|---|---|---|---|
| 7 | DBN, *p*-TsOH | 24 | 15% $\Delta^2$, 85% $\Delta^3$ |
| | NaOMe | 1 | [b] |
| 8 | DBN, *p*-TsOH | 36 | 3·5% $\Delta^2$, 96·5% $\Delta^3$ |
| 9 | DBN | 72 | <1% $\Delta^2$, >99% $\Delta^3$ |
| 10 | DBN | 72 | trace $\Delta^2$, ⩾99% [c] $\Delta^3$ |

[a] Samples taken at 12 h intervals after first 12 h. [b] Product composed of $\Delta^3$-isomer and a saturated methoxy-containing compound. [c] Composed of 97·6% *cis*-$\Delta^3$- and 2·4% *trans*-$\Delta^3$-isomer (tentative structural assignments).

TABLE 3

Equilibrations of cycloalk-2- and -3-enones [1]

| Ring size | Composition |
|---|---|
| 7 | 73% $\Delta^2$, 27% $\Delta^3$ |
| 8 | 20% $\Delta^2$, 80% $\Delta^3$ |
| 9 | <0·3% $\Delta^2$, >99·7% $\Delta^3$ |
| 10 | [a] |

[a] $\Delta^2$-Isomers produced 96% *cis*,4% *trans* equilibrium. Equilibration of $\Delta^2$- and $\Delta^3$-isomers not achieved.

The results with the 3-methoxycarbonylcyclodec-3-enones are different from those reported by Whitham

[10] G. Hallas, *J. Chem. Soc.*, 1965, 5770.
[11] J. A. Hirsch and A. J. Szur, *Tetrahedron*, **1972**, **28**, 2961; *J. Heterocyclic Chem.*, 1972, **9**, 523.

and Zaidlewicz [3] with the unsubstituted system. They equilibrated the cyclodec-2-enones to a 96% *cis*,4% *trans* mixture very similar in proportion to that determined by us for the 3-methoxycarbonylcyclodec-3-enones (Table 2). However, they did not observe isomerization of *cis*-cyclodec-3-enone and detected only very slow and incomplete interconversion of *trans*-cyclodec-3-enone and the $\Delta^2$-isomers. From deuterium incorporation studies, they concluded that *trans*-cyclodec-3-enone does not enolise as readily as the *cis*-diastereoisomer, which does enolise rapidly but does not isomerise. The difference between their results and ours in the $\Delta^3$-series may be ascribed to the involvement of the aqueous media in their systems as well as to the electron-withdrawing demands of the methoxycarbonyl substituent in ours. Whether the cyclodec-3-enones are overwhelmingly favoured thermodynamically, as might be expected from the cyclononenone results (Tables 2 and 3), must await further investigation.

## EXPERIMENTAL

$^1$H N.m.r. spectra were recorded on a Varian A-60A instrument for *ca.* 10% solutions in deuteriochloroform, with tetramethylsilane as internal standard. I.r. spectra were determined for solutions in chloroform with a Beckman IR-10 spectrophotometer; u.v. spectra were measured for methanolic solutions with a Beckman DK-2 spectrophotometer. Gas chromatographs were obtained with F & M model 720 gas chromatographs.

*6-Oxocyclohept-1-enecarboxylic Acid.*—A solution of dimethyl 3-pyrrolidino-*cis*,*cis*-cyclohepta-2,7-diene-1,2-dicarboxylate [4] (60 g) in 10% hydrochloric acid (800 ml) was refluxed for 17 h. The crystalline material and the solution were extracted three times at room temperature with methylene chloride. Evaporation of the dried ($MgSO_4$) extract under reduced pressure produced an oily residue, which was recrystallized from benzene–pentane and kept at room temperature for 3 days. The yellowish crystals (14 g, 38%), m.p. 74—75·5°, corresponded in all respects to those reported previously.[4]

*7-Oxocyclo-oct-1-enecarboxylic Acid.*—A solution of dimethyl 3-morpholino-*cis*,*cis*-cyclo-oct-2,8-diene-1,2-dicarboxylate [4] (103 g) in 10% hydrochloric acid (1 l) was treated as above. The oily slurry was recrystallized from benzene–hexane to produce crystals (36·5 g, 58·5%), m.p. 103·5—105°, corresponding in all respects to those reported previously.[4]

*8-Oxocyclonon-1-enecarboxylic Acid.*—A solution of dimethyl 3-pyrrolidino-*cis*,*cis*-cyclonona-2,9-diene-1,2-dicarboxylate [4] (70 g) in 10% hydrochloric acid (800 ml) was refluxed for 12 h. On cooling, white crystals separated and were filtered off. The filtrate was extracted with methylene chloride, and the extract dried ($MgSO_4$) and concentrated to a slurry. The slurry and the crystals were combined and recrystallized from benzene to produce soft, white crystals (42%), m.p. 108—110°, identical with material reported previously.[4]

*9-Oxocyclodec-1-enecarboxylic Acid.*—A solution of dimethyl 3-pyrrolidino-*cis*,*cis*-cyclodeca-2,10-diene-1,2-dicarboxylate [4] (30 g) in 10% hydrochloric acid (400 ml) was refluxed for 10 h and treated as above.[12] On recrystallization from benzene, crystals (10 g, 37·8%) were obtained after 3 days. This material, m.p. 121—140°, was identified as a mixture of *cis*- and *trans*-isomers, δ 7·10 (t), 6·30 (t), and 11·85 (1H, s, $CO_2H$).

*Preparation of 3-Methoxycarbonylcycloalkenones.*—A solution of the 3-carboxycycloalkenone in methanol was refluxed for 2 h with 1 : 2 $BF_3$–MeOH complex [4,10] under nitrogen. This solution was cooled, poured into chloroform, extracted with water, washed with saturated brine, dried ($MgSO_4$), and concentrated.

*Methyl 6-Oxocyclohept-1-enecarboxylate.* A solution of the acid (9 g) in methanol (45 ml) with the complex (180 ml) produced an oil (8·5 g, 90%) on distillation under reduced pressure, b.p. 120—123° at 6 mmHg. G.l.c. showed two components in a 19 : 1 ratio. Column chromatography on silica gel permitted isolation of a pure major fraction, which was identified as the desired *ester* (Found: C, 64·1; H, 7·0. $C_9H_{12}O_3$ requires C, 64·25; H, 7·2%), $\nu_{max.}$ 1640 and 1695—1720 cm$^{-1}$, δ 7·05 (1H, t, 2-H), 3·68 (3H, s, Me), 3·47 (2H, s, 7-H), and 2·60—1·80 (6H, m).

The minor fraction was identified as *methyl 3-oxocyclohept-1-enecarboxylate* (Found: C, 64·15; H, 7·15%), δ 6·78 (1H, s, 2-H), 3·75 (3H, s, Me), and 2·83—1·72 (8H, m).

*Methyl 7-Oxocyclo-oct-1-enecarboxylate.* A solution of the acid (15 g) in methanol (75 ml) was treated with the complex (300 ml). Distillation at 4 mmHg gave an oil (14 g, 88%), b.p. 140—142°, corresponding to that reported,[7] δ 7·00 (1H, t, 2-H), 3·71 (3H, s, Me), 3·35 (2H, s, 8-H), and 2·50—1·63 (8H, m).

*Methyl 8-Oxocyclonon-1-enecarboxylate.* A solution of the acid (15 g) in methanol (75 ml) was treated with the complex (300 ml) to give, on distillation under reduced pressure, an *oil* (14 g, 90%), b.p. 132—134° at 1·75 mmHg (Found: C, 67·2; H, 8·2. $C_{11}H_{16}O_3$ requires C, 67·3; H, 8·2%), $\nu_{max.}$ 1650 and 1690—1720 cm$^{-1}$, δ 6·87 (1H, t, 2-H), 3·72 (3H, s, Me), 3·35 (2H, s, 9-H), and 2·66—1·45 (10H, m).

*Methyl 9-Oxocyclodec-1-enecarboxylates.* The mixture of acids (10 g) in methanol (50 ml) was treated with the complex (180 ml). The resulting thick slurry was washed with 5% sodium hydroxide, redried, and distilled under reduced pressure to give an oil (8 g, 75%), b.p. 120—122° at 0·75 mmHg, found to be a 4 : 1 mixture by spectral and g.l.c. evidence. The components were separated by preparative g.l.c.† The *material* with shorter retention time is tentatively assigned the *trans*-stereochemistry (Found: C, 68·4; H, 8·45. $C_{12}H_{18}O_3$ requires C, 68·55; H, 8·65%), $\nu_{max.}$ 1645 and 1690—1710 cm$^{-1}$, δ 6·17 (1H, t, 2-H), 3·78 (3H, s, Me), 3·28 (2H, s, 10-H), and 2·88—1·12 (12H, m), $\lambda_{max.}$ 218 nm (ε 10,350).

The *component* with the longer retention time is tentatively assigned the *cis*-stereochemistry (Found: C, 68·45; H, 8·5%), $\nu_{max.}$ 1645 and 1690—1710 cm$^{-1}$, δ 6·98 (1H, t, 2-H), 3·77 (3H, s, Me), 3·42 (2H, s, 10-H), and 2·50—1·20 (12H, m), $\lambda_{max.}$ 215 nm (ε 9700).

*Equilibrations of 3-Methoxycarbonylcycloalkenones.*—Mixtures were analysed spectroscopically and chromatographically † in triplicate. Three general procedures were utilised.

(*A*) The appropriate keto-ester (2 g) was heated under reflux with toluene-*p*-sulphonic acid (1 g; previously dried by azeotropic distillation with benzene for 2 h) in benzene (50 ml). Refluxing was continued until equilibrium was

† Columns were ¼ in × 6 ft 10% Carbowax 20M or 10% NPGS on Chromosorb W (60—80) at 195 °C.

[12] W. A. Meresak, unpublished information.

reached as shown by g.l.c. This solution was washed with aqueous 5% sodium carbonate, dried, and concentrated.

(*B*) The appropriate keto-ester (2 g) was heated under reflux with a solution of 1,5-diazabicyclo[4.3.0]non-5-ene (1 g) in dry benzene (50 ml), until equilibrium was reached as shown by g.l.c. The solution was washed with ice and 5% sulphuric acid, and extracted several times with petroleum. The extract was dried and concentrated.

(*C*) The 3-methoxycarbonylcyclohept-3-enone (332 mg) in dry methanol (50 ml) was refluxed with sodium methoxide (590 mg) for 1 h. The mixture was neutralised with dilute hydrochloric acid (to about pH 7) and extracted with ether. The organic layer was dried and evaporated under reduced pressure. G.l.c. analysis indicated the presence of starting keto-ester and another material and the absence of the $\Delta^2$-isomer. The $^1$H n.m.r. spectrum suggested the addition of a methoxy-unit in an amount equivalent to the diminution in the vinyl proton signal.

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