Investigations on the Reactions of a Carbonylcarbene with Substituted 1,3-Dioxepins

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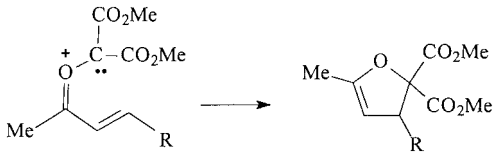
Several dioxepins were treated with dimethyl diazomalonate under bis(acetylacetonato)copper(II) catalysis. The 4,7-dihydro-2-methyl-1,3-dioxepin (**1a**) gave oxonium ylide originated products and a cyclopropane derivative (see **3a** and **2a**, resp., in *Scheme 3,b*). However, the 2,2-dimethyl derivative **1b** of 1,3-dioxepin yielded only the cyclopropanation product **2b** (*Scheme 3,b*), whereas 4,5-dihydro-2-methyl-1,3-dioxepin (**9**) gave the furanofuran derivative **10** (*Scheme 4*).

Introduction. – As known, α,β-conjugated carbonyl compounds are expected to be electron-deficient and, therefore, rather unreactive toward electrophilic additions of carbenes/carbenoids, with a few exceptions [1]. The α- and β-ionones have been shown to give, with dimethyl diazomalonate (dmdm) and ethyl acetodiazoacetate, in a new and selective formal [4 + 1] reaction, dihydrofuran derivatives *via* conjugated carbonyl ylides [2] (*Scheme 1*), whereas cyclohex-2-en-1-one yielded C–H insertion products [3]. No cyclopropanation reactions were observed in either case.

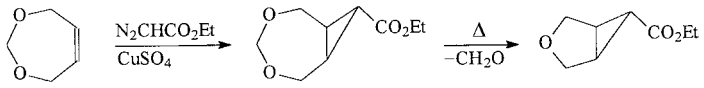
Scheme 1



To obtain cyclopropane derivatives starting from electron-poor enones, we aimed to increase the electron density of the olefin moiety by modifying the keto group to the ethylene ketal derivative [3] by a route similar to that of *Doyle* and co-workers [4]. In that study, while cyclopropanation was achieved in high yields with the cyclic enone ethylene ketals, acyclic analogue gave mainly new [2,3]-sigmatropic-shift and *Stevens*-rearrangement products *via* oxonium ylides. During this study, we also directed our attention to oxonium ylide products. It is known that oxonium ylides are reactive species that readily undergo *Stevens* rearrangement, β-hydride elimination, and [2,3]-sigmatropic reorganizations [4][5]. Although the reactions of carbenes with open-chain ethers and acetals have been extensively studied, only few reactions with cyclic ethers and cyclic allylic acetals are known [6]. For the open-chain analogues, cyclopropanations and the *Stevens* rearrangement compete with [2,3]-sigmatropic shifts in certain cases. Comparative results with allyl ethers demonstrate that a heteroatom-substituted allylic C-atom accelerates ylide rearrangement. This acceleration of ylide rearrangement is thought to be associated with the electronic influence of the α-alkoxy

substituent. *Jendralla* [7] discussed the reaction of ethyl diazoacetate with 4,7-dihydro-1,3-dioxepin in the presence of copper sulfate and obtained only one product, a cyclopropane derivative (*Scheme 2*).

Scheme 2



In the present study, 1,3-dioxepin derivatives **1** were treated with dmdm using bis(acetylacetonato)copper(II) as catalyst to investigate the formation of oxonium ylide products, such as those arising from [2,3]-sigmatropic shifts, *Stevens* rearrangement, and β-hydride elimination, and of cyclopropanation products. The expected reaction products **2**–**7** are shown in *Scheme 3*,*a*.

Results and Discussion. – The reaction of 4,7-dihydro-2-methyl-1,3-dioxepin (**1a**) with dmdm (mol ratio 4:1) gave a crude product showing two major (ratio 1.5:1) and two minor peaks in the GLC. These two major peaks gave rise to three peaks when the reaction mixture was injected into a chiral capillary column. The GC/MS established that one of the minor peaks arose from the carbene dimer **7** and the other from the addition compound **8**, the latter being generated from the major compounds *anti*-**2**[1]) and *syn*-**2**[1]) by elimination of acetaldehyde, as mentioned in *Jendralla*'s work (*cf. Scheme 2*). The ^{1}H-NMR and ^{13}C-NMR (APT) spectra of the crude product showed the presence of the two adducts *anti*-**2a**[1]) and *syn*-**2**[1]), and of one *Stevens* product **3a** in the ratio of 1.2:2.2:1.25. The ratio of *anti*-**2a** and *syn*-**2a** determined from the ^{1}H-NMR integral of related bridgehead H-atoms and also of the Me groups at C(4) was approximately the same as that determined by chiral capillary GC. The obtained products *anti*- and *syn*-**2a**, **3a**, **7**, and **8** are shown in *Scheme 3*,*b*, together with the result of geometry-optimization studies[2]). Desktop molecular-modelling calculations indicated that the two diatereoisomers *anti*-**2a** and *syn*-**2a** exist in a chair and twist-boat conformation respectively, of lowest energy. NMR Studies supported the MM2 calculations.

The proposed structure of *anti*-**2a** is symmetrical, hence the bridgehead atoms H–C(1) and H–C(7) give rise to a broad ($\omega_{1/2} \approx 10$ Hz) at 1.8 ppm. The configuration of *anti*-**2a** is also evident from the magnetic equivalence of the two equatorial H–C(2) and H–C(6) and also from that of the axial H–C(2) and H–C(6), the latter two appearing as a *dd* (2 H) with $J = 13.5$ and 7 Hz at 4.19 ppm. The major addition compound *syn*-**2a** shows the two non-identical bridgehead H-atoms at 2.12 and 1.98 ppm and signals for non-equivalent H-atoms at C(2) and C(6), in accordance with the proposed structure of *syn*-**2a**. This conformation is different from the chair conformations proposed by *St. Jacques* and co-workers [8] and *Soulier et al.* [9] for 2,2-dimethyl-1,3-dioxa-5,6-benzocycloheptene (=1,5-dihydro-3,3-dimethyl-2,4-benzodioxepine) and 8,8-dichloro-4,4-dimethyl-3,5-dioxabicyclo[5.1.0]octane.

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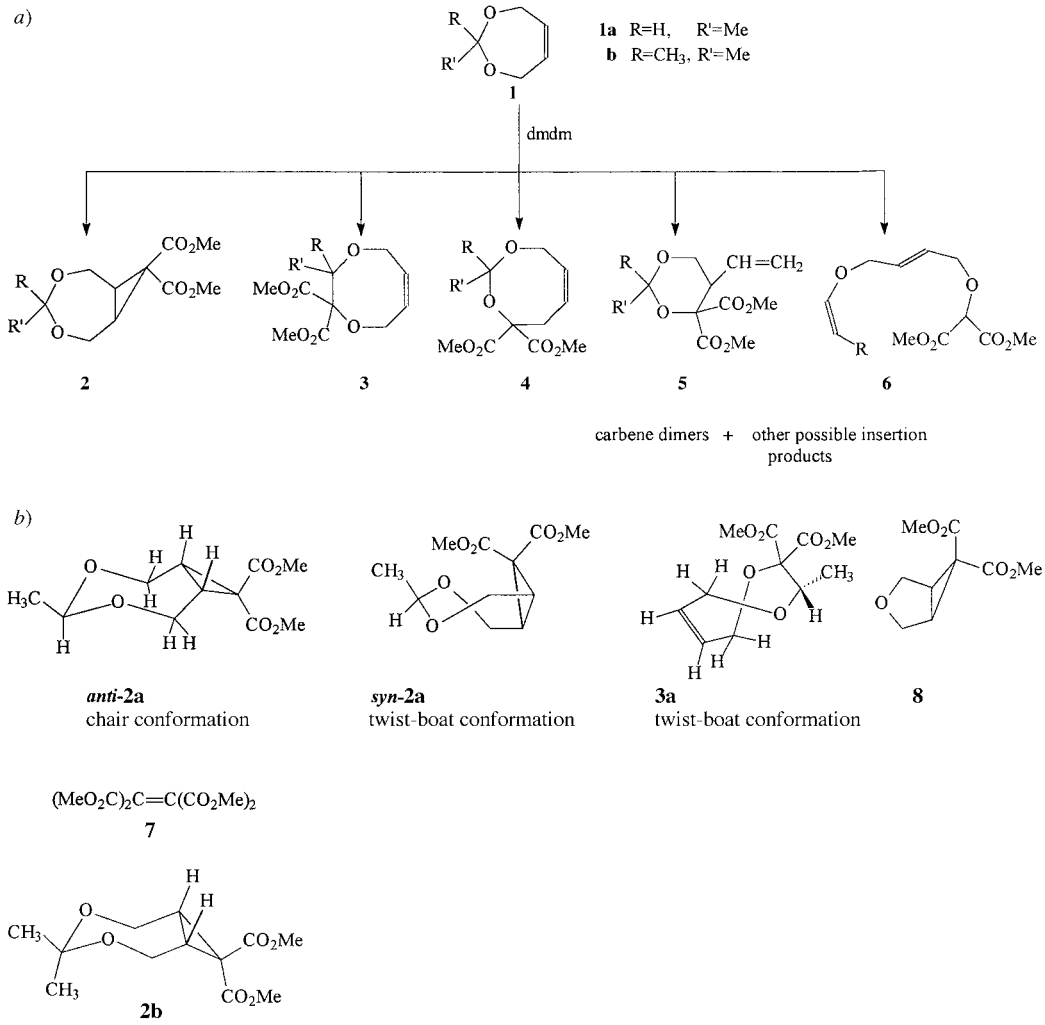
[1]) The terms *syn*/*anti* refer to the addition site of the carbenoid species with respect to the Me group. Possible interpretations such as the triplet behavior of a carbene (although it is out of the question here) are not intended.

[2]) MM2 Calculations were performed by desktop molecular modelling on a PC *Windows* platform.

Scheme 3



The ^{1}H- and ^{13}C-NMR data could not clarify the exact conformation of the *Stevens* product **3a**. However, geometry-optimization studies showed that the twist-boat structure, in which the Me group is in equatorial position, is the more favorable conformation.

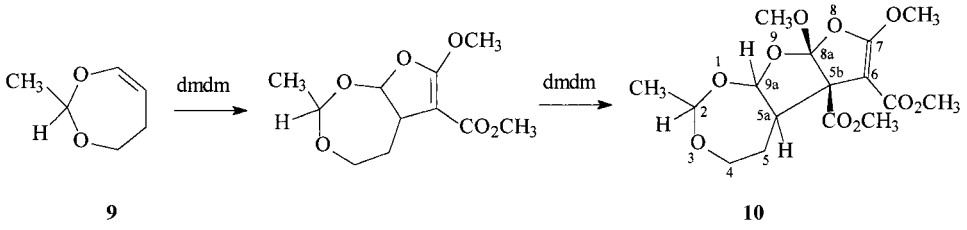
To investigate the effect of the number of substituents at C(2) of 1,3-dioxepin in carbene reactions, 4,7-dihydro-2,2-dimethyl-1,3-dioxepin **1b** was treated with dmdm. GLC, GCMS, ^{1}H-NMR, and ^{13}C-NMR analysis of the obtained products showed the presence of only a carbene-addition compound, **2b**, besides a small amount of carbene dimer. The conformation of **2b** was established as chair by the ^{1}H-NMR data (see *Scheme 3,b*), in contrast to the results of *St. Jacques* and co-workers [8]. The preference for the chair conformation of **2b** was attributed to the non-bonding repulsive

interactions between the axial Me group at C(4) and one ester Me group. In the twist-boat form, the distance between these two Me groups is shorter than in the chair form (0.65 *vs.* 0.95 Å).

From the ^{1}H-NMR spectrum of **2b** a chemical-shift difference ($\Delta\delta$) of 0.1 ppm (19.25 Hz) is deduced for the two geminal H-atoms at C(2) or C(6) ($\Delta\delta = \delta(2(6)ax)\text{-}\delta(2(6)eq)$). This value is characteristic for a chair conformation, because higher $\Delta\delta$ values (*i.e.,* 0.64–0.70 ppm) are representative for a twist-boat form of 2,2-disubstituted 1,3-dioxepins [8]. In addition, the 2 H–C(2) and 2 H–C(6) show 2 *ABX* instead of 4 *ABX* patterns, thus confirming the chair conformation of **2b**. The 2 acetal Me groups are not equivalent, giving rise to two *s*.

Finally, 4,7-dihydro-2-methyl-1,3-dioxepin (**1a**) was treated with k^{t}BuO to shift the C=C bond [10][11], and then the new cyclic vinyl acetal **9** was treated with dmdm (*Scheme 4*). In this attempt, the aim was to compare the reaction probabilities of the [3 + 2] cycloaddition with the enol-ether function and of the formation of an oxonium ylide at the non-conjugated O-atom. None of the oxonium-ylide products could be found in the reaction mixture; instead the double [3 + 2] cycloaddition product **10** was observed. The ^{1}H-NMR spectrum revealed the presence of two stereoisomers in the ratio of 45 : 55. This finding was consistent with GC/MS data. The two stereoisomers could not be separated by prep. chromatography.

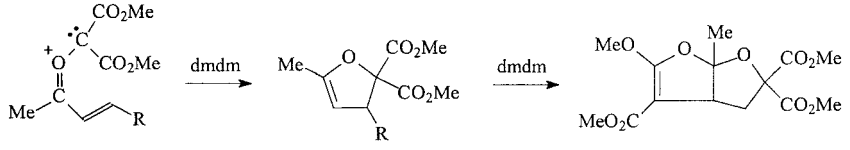
Scheme 4



9 **10**

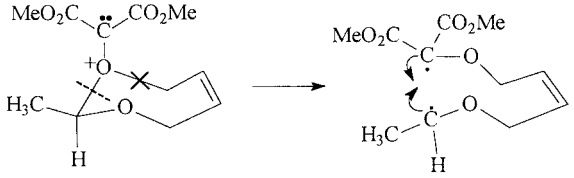
Several research groups have investigated the reaction of enol ethers with diazodicarbonyl compounds and have proposed different mechanisms [12–16]. Reviewing these reports with respect to product distribution *vs.* the kind of diazocarbonyl compounds involved leads to the conclusion that ethyl diazoacetate yields mainly cyclopropanes, rarely rearrangement products, that dmdm gives addition-elimination and rearrangement products, and that ethyl acetodiazoacetate produces mainly dihydrofurans and rearrangement products. In our previous study [2], an unexpected furofuran compound was obtained although dmdm was used as the diazodicarbonyl compound (*Scheme 5*). The reaction of 4,5-dihydro-2-methyl-1,3-dioxepin (**9**) with dmdm also gave a similar furofuran derivative in one step (see above).

Scheme 5



Conclusion. – To investigate the effect of the substituents at C(2) of 1,3-dioxepin in carbene reactions, 2-methyl- and 2,2-dimethyl-substituted 4,7-dihydro-1,3-dioxepins **1** were treated with dmdm. It has been established that increased bulk near the O-atom (*e.g.*, 2 Me groups in **1b**) promotes cyclopropanation [6], and accordingly 4,7-dihydro-2,2-dimethyl-1,3-dioxepin **1b** did not yield any oxonium-ylide products. However, the monosubstituted 1,3-dioxepin **1a** gave an oxonium ylide product **3a**, along with cyclopropane derivatives **2a**. The *Stevens* reaction occurred only at the O–C–O moiety of **1a**. This result supports the idea of a positive electronic effect of the two alkoxy substituents in the diradical structure of the intermediate on the rate of the ylide rearrangement, as claimed by *Doyle et al.* [4] (*Scheme 6*).

Scheme 6



Another interesting point was the absence of any [2,3]-sigmatropic rearrangement product in our experiments with **1** and **9**. Although many examples of ring expansion by [2,3]-sigmatropic shifts are described in the literature, ring contraction was never observed, except in one case involving a sulfonium ylide [17]. We also did not identify any β-hydride elimination products in the mixtures obtained from **1** and **9**.

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Experimental Part

General. Dimethyl diazomalonate (dmdm) [16] and the dioxepins [11][18] were prepared by literature methods. Product distributions were established by GC and NMR and refer to relative rather than isolated yields. IR Spectra: *Jasco-FT-IR-5300* apparatus. NMR ($CDCl_3$): 200-MHz-*Bruker* apparatus; SiMe as internal standard; δ in ppm, J in Hz; ^{13}C at 50 MHz. Capillary GC: 30-m column (0.3 mm i.d.), β-cyclodextrin trifluoroacetate in the liquid phase; column conditions: 150°, 0.32 bar N_2, 1 bar H_2. GC/MS: *Hewlett-Packard* instrument with a 24-m *HP-1* capillary column, packed with cross-linked phenylmethylsiloxane; EI-MS detector; column conditions: 150° for 30 min, then 15°/min to 280°; He pressure 0.54 bar; *m/z* (rel. %).

Reaction of Dimethyl Diazomalonate and Dioxepins: General Procedure. A soln. of 1 equiv. of dmdm in benzene (4 mmol/1 ml) was added very slowly within 12 h to a refluxing benzene soln. of dioxepin (4 equiv.; 2 mmol/1 ml benzene) and [Cu(acac)$_2$] (0.007 equiv.) under N_2. Consumption of dmdm was monitored by IR. After the complete disappearance of the band at 2130 cm^{-1}, the mixture was passed through a column of neutral aluminium oxide to remove the catalyst and highly colored impurities. Then, the solvent was evaporated and the residue distilled under vacuum.

Dimethyl anti-*4-Methyl-3,5-dioxabicyclo[5.1.0]octane-8,8-dicarboxylate* (*anti*-**2a**)[1]). Yield 26%. ^{1}H-NMR: 1.23 (*d*, J = 5.4, *Me*); 1.8 (br. *s*, H–C(1), H–C(7)); 3.8 (*m*, H–C(4)); 3.72 (*s*, MeO); 4.19 (*dd*, J = 13.5, 7, H_{ax}–C(2), H_{ax}–C(6)); 4.00 (*dd*, J = 13.5, 1.3, H_{eq}–C(2), H_{eq}–C(6)). ^{13}C-NMR: 20.2 (Me); 32.1 (bridgehead C); 52.1 (MeO); 65.2 (CH_2O); 68.3 (C(8)); 104.5 (C(4)); 170.1 (C=O). EI-MS: 244 (5, $M^{+\bullet}$), 229 (10), 213 (17), 200 (17), 185 (22), 169 (63), 157 (96), 136 (83), 125 (35), 113 (62), 108 (90), 81 (70), 69 (75), 59 (100). HR-MS: 244.2409 ($C_{11}H_{16}O_6^+$, M^+; calc. 244.2418).

Dimethyl syn-*4-Methyl-3,5-dioxabicyclo[5.1.0]octane-8,8-dicarboxylate* (*syn*-**2a**)[1]). Yield 47%. ^{1}H-NMR: 1.35 (*d*, J = 5.4, Me); 2.1 (*dd*, J = 9.6, 2.6, H–C(1) or H–C(7)); 1.9 (*dd*, J = 9.6, 2.6, H–C(7) or H–C(1)); 3.79

(*s*, MeO); 3.8, 4.3 (*dd*, *J* = 13.5, 2.3 CH_2O). ^{13}C-NMR: 20.3 (Me); 32.3 (C(1), C(7)); 52.1 (MeO); 64.1 (CH_2O); 69.3 (C(8)); 102.4 (C(4)); 170.1 (C=O). EI-MS: 244 (5, $M^{+\cdot}$), 229 (10), 213 (17), 200 (17), 185 (22), 169 (63), 159 (96), 132 (83), 125 (35), 113 (62), 108 (90), 81 (70), 69 (75), 59 (100). HR-MS: 244.2409 ($C_{11}H_{16}O_6^+$, M^+; calc. 244.2418).

Dimethyl 2,3,5,8-Tetrahydro-3-methyl-1,4-dioxocin-2,2-dicarboxylate (**3a**). Yield 27%. ^{1}H-NMR: 1.18 (*d*, *J* = 6.3, Me); 3.7 (*s*, MeO); 4.7–4.8 (^2J = 18.6, ^3J = 9.3, 2.7, CH_2(5), CH_2(8)); 5.6 (*dt*, *J* = 3.3, H–C(7)); 5.8 (*td*, J_{cis} = 12.2, *J*(6,5eq) = 5.9, *J*(6,5ax) = 7.7, H–C(6)). ^{13}C-NMR: 18.2 (Me_3); 52.3 (MeO); 62.1 (CH_2O); 64.2 (CH_2O); 73.4 (CH); 128.1 (olef. C); 132.2 (olef. C); 165.1 (C=O). EI-MS: 244 (1, $M^{+\cdot}$), 229 (2), 200 (16), 185 (2), 169 (17), 159 (20), 132 (60), 125 (10), 115 (27), 100 (25), 85 (5), 81 (20), 69 (100), 59 (34). HR-MS: 244.2438 ($C_{11}H_{16}O_6^+$, M^+; calc. 244.2438).

Dimethyl 4,4-Dimethyl-3,5-dioxabicyclo[5.1.0]octane-8,8-dicarboxylate (**2b**). Yield 90%. ^{1}H-NMR: 1.26 (*s*, Me); 1.28 (*s*, Me); 1.95 (br. *s*, H–C(1), H–C(7)); 3.79 (*s*, MeO); 4.04–4.13 (*td*, ^2J = 13.15, $^3J_{ax}$ = 4.7, $^3J_{eq}$ = 2.7, 4 H). ^{13}C-NMR: 32.1 (Me_3); 32.3 (C(1), C(7)); 53.2 (MeO); 58.1 (C(8)); 64.2 (CH_2); 104.3 (C(4)). EI-MS: 258 (2, $M^{+\cdot}$), 243 (32), 227 (18), 200 (25), 199 (25), 169 (100), 157 (58), 141 (52), 132 (55), 126 (18), 59 (48). HR-MS: 258.2709 ($C_{12}H_{18}O_6^+$, M^+; calc. 258.2712).

*Dimethyl (5b*RS*,8a*RS*)-4,5,5a,5b,8a,9a-Hexahydro-7,8a-dimethoxy-2-methylfuro[3′,2′:4,5]furo[2,3-*d*]-[1,3]dioxepin-5b,6-dicarboxylate* (**10**). ^{1}H-NMR: 1.3 (*d*, *J* = 5.2, 3 H, $Me_{endo(exo)}$); 1.5 (*d*, *J* = 6.5, 3 H, $Me_{exo(endo)}$); 1.7–1.8 (*m*, 4 H, CH_2); 2.8–3.0 (*m*, 2 H, 2CH); 3.32 (*s*, 6 H, MeO–C(7)); 3.42 (*s*, 6 H, MeO–C(8a)); 3.45 (*m*, 4 H, CH_2(4)); 3.73–3.83 (4*s*, 12 H, 2 COOMe); 4.78 (*m*, 4 H, CH_2(4)); 4.93 (*d*, *J* = 7.2, 1 H, $H_{endo(exo)}$–C(2)); 5.3 (*m*, 1 H, $H_{exo(endo)}$–C(2)); 5.5 (*d*, *J* = 7.2, 2 H, H–C(9a)). ^{13}C-NMR: 22.6, 25.2 (*Me*–C(2)); 29.3 (C(5)); 29.6 (C(5a)); 58.3 (MeO); 60.8 (MeO); 63.6 (C(4)); 66.9 (COO*Me*); 75.1 (C(5b)); 101.1 (C(9a)); 127.5 (C(6)); 131.05 (C(8a)); 165.8 (C=O); 168.5 (C(7)). EI-MS: 374 (5, $M^{+\cdot}$), 359 (8), 317 (15), 305 (12), 299 (20), 273 (100), 261 (95), 229 (70), 201 (65), 169 (65), 159 (25), 141 (70), 113 (80), 84 (87), 71 (98). HR-MS: 374.3439 ($C_{16}H_{22}O_{10}^+$, M^+; calc. 374.3458).

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