Synthesis of *trans*-Fused Oxabicyclo[5.2.0]nonan-2-ones *via* [2 + 2] Photocycloaddition of Oxepinones to Conjugated Alkenes

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On irradiation (350 nm) in the presence of 2,3-dimethylbuta-1,3-diene, benzoxepinone **2** and dioxepinone **3** were converted regio- and diastereoselectively to *trans*-fused oxabicyclo[5.2.0]nonanones **5** and **9**, respectively.

Introduction. – The synthesis of bicyclo[3.2.0]pentan-2-ones and bicyclo[4.2.0]octan-2-ones *via* stepwise [2 + 2] photocycloaddition of five- or six-membered cyclic enones to alkenes has become one of the most frequently used preparative light-induced reactions [1][2]. For cyclohexenones bearing no substituents at the olefinic C-atoms, the vicinal coupling constant of the bridgehead H-atoms in the photocycloadducts very often allows the distinction between *cis*- and *trans*-fused diastereoisomers [3]. Interestingly, a literature search for analogous bicyclo[5.2.0]nonan-2-ones revealed only two examples. First, an 8,8-dimethyl derivative of this bicyclic ketone has been obtained in very low yield by thermal isomerization of caryophyllene at high temperatures [4], whereas a 9,9-bis(methylsulfanyl) derivative was synthesized by (thermal) BF_3-catalyzed cycloaddition of cycloheptenone to the corresponding ketene S,S-acetal [5]. Unfortunately, in both examples NMR data do not allow a configurational assignment of the ring fusion. The main reason that no photochemical access to such bicycles has been achieved is the fact that, on irradiation, cyclohept-2-enones *a*) undergo efficient (*Z*/*E*)-isomerization, and *b*) the so formed (*E*)-diastereoisomers then dimerize to – *trans*-fused – tricyclic dimers [6–8]. It has been known for some time that the ease of relaxation of (triplet) cyclic enones by twisting around the C=C bond correlates with the triplet energy of the enone itself, and, therefore, cyclohept-2-enone has a lower triplet energy than smaller-ring counterparts. In this context, we have recently observed that the three six-membered ring enones **1a**–**1c** also differ in their rigidity due to the differences in C–S, C–C and C–O bond lengths, respectively [9]. Indeed, the more flexible dihydrothiopyranone **1b** (d(C–S) ≈ 1.81 Å) on excitation undergoes addition to conjugated alkenes efficiently, whereas the more rigid **1a** and **1c** react inefficiently due to competitive energy transfer [10]. We have now used this effect by changing (longer) C–C (≈1.54 Å) by (shorter) C–O (≈1.43 Å) bonds in seven-membered cyclic enones. Here, we report on efficient photocycloadditions of benzoxepinone **2** and dioxepinone **3** to conjugated alkenes (*Fig. 1*).

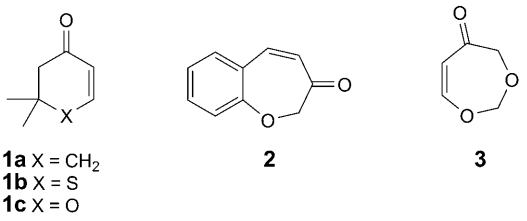
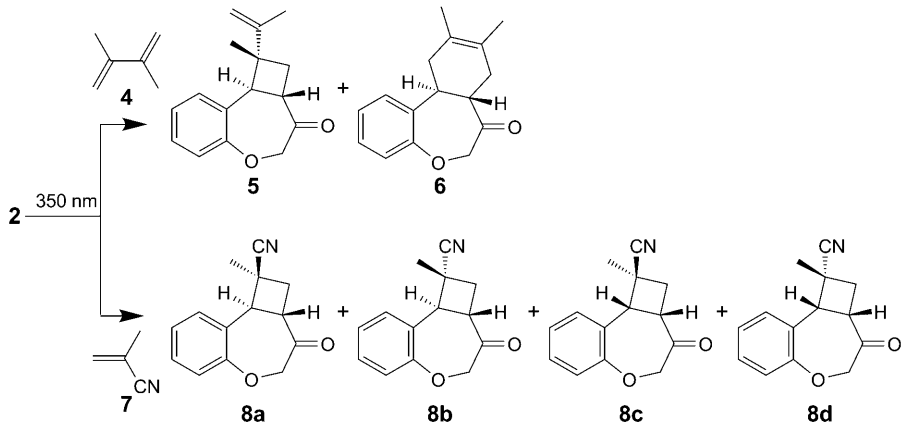


Fig. 1. *Structures of compounds* **1**–**3**

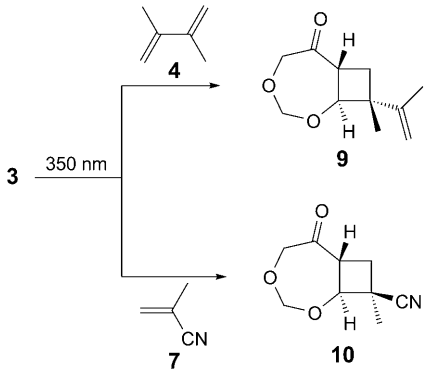
Results. – Irradiation (350 nm) of benzoxepinone **2** in the presence of a tenfold molar excess of 2,3-dimethylbuta-1,3-diene (**4**) afforded a 5:1 mixture of the [2+2] cycloadduct **5** and the [2+4] cycloadduct **6**. Irradiation of **2** in the presence of 2-methylacrylonitrile (**7**) afforded regioselectively a 5:3:2:1 mixture of [2+2] cycloadducts **8a**–**8d**. Both reactions proceed with high efficiency, total conversion of starting material being achieved after 2–3 h (*Scheme 1*). All products were separated and purified by column chromatography, and fully characterized by NMR spectroscopy. Irradiation of dioxepinone **3** in the presence of **4** afforded a single [2+2] photoproduct **9**, which was isolated by preparative thin layer chromatography. Finally, irradiation of **3** in the presence of **7** gave a major (65%) [2+2] cycloadduct **10** and a minor unidentified diastereoisomer, but, in addition, a relatively high amount of polymeric material from **7** was formed as well. Attempted purification of these acetals failed due to rapid decomposition on SiO_2. The reactions of **3** proceed much slower than those of **2**, 16–18 h being required for total conversion of the starting material (*Scheme 2*).

Scheme 1



Discussion. – As expected, seven-membered oxacycles **2** and **3** behave quite similarly towards (six-membered) thiacycle **1b** upon irradiation in the presence of conjugated alkenes, *i.e.*, for all three compounds, the reactive triplet state is intercepted by the olefin, thus preventing (*Z*/*E*)-isomerization of the enone. Not surprisingly, the

Scheme 2



relative amount of *trans*-fused bicycles is much higher for the seven-membered enones (75–100%) as compared to **1b** (5–10%), as the heat contents of *cis*- and *trans*-fused bicyclo[5.2.0]nonanes have been estimated to be similar [11], and, indeed, compounds **5**, and **8a** and **8b** are stable towards SiO_2, whereas *trans*-fused bicyclo[4.2.0]octan-2-ones readily isomerize to the – more stable – *cis*-diastereoisomers under these conditions. As already well-established for these 6/4-bicycles, the vicinal coupling constants, determined in the present study, for the bridgehead di-pseudoaxial H-atoms for *trans*-fused bicyclononanones were again larger than the corresponding ones in *cis*-fused counterparts, *e.g.*, **8c** or **8d** ($J_{trans} \approx 13$, $J_{cis} \approx 11$ Hz). The CH_2 H-atoms in the cyclobutane rings in these *trans*-fused cycloadducts could be easily differentiated. As the four-membered ring adopts a rigid puckered conformation (*Fig. 2*), one of the H-atoms is in a *pseudo*-axial- and the other one in a *pseudo*-equatorial position, the former appearing as a triplet due to almost identical geminal and vicinal coupling constants. NOESY Spectra then allow the assignment of the relative configuration of the substituents (methyl, 1-methylethenyl, cyano) at the quaternary C-atom. For 2,3-dimethylbuta-1,3-diene cycloadducts **5** and **9**, the 1-methylethenyl group is *pseudo*-equatorial, while, in the major 2-methylacrylonitrile cycloadducts **8a** and **10**, the CN group is *pseudo*-axial.

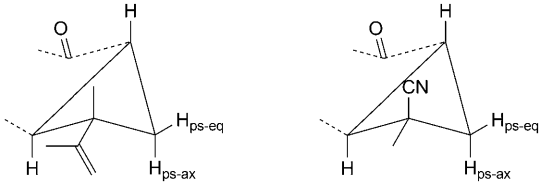


Fig. 2. *Preferred configuration/conformation for photocycloadducts* **5** *and* **8**–**10**, *respectively*

Experimental Part

1. *General.* Photolyses: *Rayonet RPR-100* photoreactor equipped with 350-nm lamps, and with solvents of spectrophotometric grade. Column chromatography (CC): silica gel *60* (230–400 mesh, SiO_2;

Merck). ^{1}H- and ^{13}C-NMR spectra (including 2D plots): *Bruker WM-500*; at 500.13 and 125.8 MHz, resp.; δ in ppm rel. to Me_4Si as internal standard, J in Hz. GC/EI-MS: *Varian MAT-311A* at 70 eV.

2. *Starting Materials. 1-Benzoxepin-3(2*H*)-one* (**2**) was synthesized according to [12] and *1,3-dioxepin-5(4*H*)-one* (**3**) according to [13]. *2,3-Dimethylbuta-1,3-diene* (**4**) and *2-methylacrylonitrile* (=*2-methylprop-2-enenitrile*; **7**) were commercially available.

3. *Photochemical Reactions.* Ar-Degassed solns. of **2** and **3** were irradiated (concentration, solvent, added reaction partner, duration, and workup as described).

3.1. *Photocycloaddition of* **2** *to* **4**. A soln. of **2** (160 mg, 1 mmol) and **4** (820 mg, 10 mmol) in benzene (2 ml) was irradiated for 3 h up to total conversion to give a 5:1 mixture **5/6**, as monitored by GC. CC (SiO_2, CH_2Cl_2) afforded first 12.1 mg (5%) of *(7a*S*,11a*S*)-7a,8,11,11a-tetrahydro-9,10-dimethyldibenzo[*b,d*]oxepin-7(6*H*)-one* (**6**; R_f 0.55). Colorless oil. ^{1}H-NMR ($CDCl_3$): 7.35–7.05 (*m*, 4 H); 4.59, 4.25 (*AB*, J = 17.0, 2 H); 3.85 (*ddd*, J = 4.5, 11.5, 11.6, 1 H); 2.85 (*ddd*, J = 5.5, 11.1, 11.2, 1 H); 2.60 (*m*, 1 H); 2.35–2.25 (*m*, 2 H); 1.98 (*m*, 1 H); 1.69 (*s*, 3 H); 1.66 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$): 209.5 (*s*); 159.9 (*s*); 130.2 (*s*); 128.7 (*d*); 128.5 (*d*); 127.9 (*d*); 127.5 (*d*); 125.2 (*s*); 125.1 (*s*); 81.2 (*t*); 48.2 (*d*); 43.0 (*t*); 41.1 (*d*); 32.1 (*t*); 18.7 (*q*); 18.5 (*q*). EI-MS: 242 (100, M^+).

The second fraction consisted of 98 mg (40%) of *(1*R*,2a*S*,9b*R*)-1-methyl-1-(prop-1-en-2-yl)-1,2,2a,9b-tetrahydrocyclobuta[*d*][1]benzoxepin-3(4*H*)-one* (**5**; R_f 0.4). Light yellow oil. ^{1}H-NMR ($CDCl_3$): 7.35–7.05 (*m*, 4 H); 4.87 (*s*, 1 H); 4.83 (*s*, 1 H); 4.63, 4.53 (*AB*, J = 17.1, 2 H); 4.09 (*ddd*, J = 7.4, 10.2, 12.6, 1 H); 3.67 (*d*, J = 12.6, 1 H); 2.20 (*dd*, J = 10.4, 10.5, 1 H); 1.92 (*dd*, J = 7.4, 10.6, 1 H); 1.77 (*s*, 3 H); 1.25 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$): 209.1 (*s*); 159.8 (*s*); 152.1 (*s*); 130.3 (*s*); 128.9 (*d*); 128.7 (*d*); 127.8 (*d*); 127.7 (*d*); 108.5 (*t*); 78.1 (*t*); 48.0 (*s*); 47.1 (*d*); 43.5 (*d*); 33.1 (*t*); 19.0 (*q*); 18.1 (*q*). EI-MS: 242 (30, M^+), 132 (100).

3.2. *Photocycloaddition of* **2** *to* **7**. A soln. of **2** (160 mg, 1 mmol) and **7** (670 mg, 10 mmol) in benzene (2 ml) was irradiated for 3 h up to total conversion to give a 1:0.6:0.5:0.2 mixture **81a/8b/8c/8d**, as monitored by GC. CC (SiO_2; Et_2O/pentane 1:1) afforded first 23 mg (10%) of *(1*R*,2a*S*,9b*R*)-1,2,2a,3,4,9b-hexahydro-1-methyl-3-oxocyclobuta[*d*][1]benzoxepine-1-carbonitrile* (**8b**; R_f 0.50). Colorless oil. ^{1}H-NMR ($CDCl_3$): 7.35–7.05 (*m*, 4 H); 4.65, 4.36 (*AB*, J = 17.7, 2 H); 4.22 (*ddd*, J = 7.1, 10.3, 13.4, 1 H); 3.92 (*d*, J = 13.4, 1 H); 2.82 (*dd*, J = 11.0, 11.1, 1 H); 2.17 (*dd*, J = 7.3, 11.1, 1 H); 1.25 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$): 211.0 (*s*); 159.9 (*s*); 130.2 (*s*); 128.7 (*d*); 128.5 (*d*); 127.9 (*d*); 127.5 (*d*); 124.1 (*s*); 79.5 (*t*); 47.5 (*d*); 45.0 (*d*); 35.0 (*s*); 32.5 (*t*); 20.0 (*q*). EI-MS: 227 (2, M^+), 160 (100).

The second fraction consisted of 12 mg (5%) of *(1*S*,2a*S*,9b*S*)-1,2,2a,3,4,9b-hexahydro-1-methyl-3-oxocyclobuta[*d*][1]benzoxepine-1-carbonitrile* (**8c**; R_f 0.46). Colorless oil. ^{1}H-NMR ($CDCl_3$): 7.35–7.05 (*m*, 4 H); 4.64 (*d*, J = 11.1, 1 H); 4.61, 4.53 (*AB*, J = 17.0, 2 H); 3.93 (*ddd*, J = 4.6, 8.1, 11.1, 1 H); 2.84 (*m*, 2 H); 1.55 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$): 208.1 (*s*); 159.9 (*s*); 130.1 (*s*); 128.6 (*d*); 128.5 (*d*); 127.9 (*d*); 127.3 (*d*); 122.1 (*s*); 77.5 (*t*); 45.1 (*d*); 45.0 (*d*); 31.5 (*t*); 31.0 (*s*); 18.1 (*q*). EI-MS: 227 (1, M^+), 160 (100).

The third fraction consisted of 65 mg (30%) of the main product, *(1*S*,2a*S*,9b*R*)-1,2,2a,3,4,9b-hexahydro-1-methyl-3-oxocyclobuta[*d*][1]benzoxepine-1-carbonitrile* (**8a**; R_f 0.41). White solid. M.p. 121–124°. ^{1}H-NMR ($CDCl_3$): 7.35–7.05 (*m*, 4 H); 4.56 (*s*, 2 H); 4.25 (*ddd*, J = 7.3, 10.9, 12.9, 1 H); 3.45 (*d*, J = 12.9, 1 H); 2.65 (*dd*, J = 7.3, 11.1, 1 H); 2.35 (*dd*, J = 11.0, 11.1, 1 H); 1.75 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$): 209.5 (*s*); 159.8 (*s*); 130.2 (*s*); 128.7 (*d*); 128.5 (*d*); 127.9 (*d*); 127.6 (*d*); 121.3 (*s*); 79.1 (*t*); 52.1 (*d*); 47.1 (*d*); 37.0 (*s*); 34.1 (*t*); 27.1 (*q*). EI-MS: 227 (0.5, M^+), 160 (100).

The fourth fraction consisted of 8 mg (3%) of *(1*R*,2a*S*,9b*S*)-1,2,2a,3,4,9b-hexahydro-1-methyl-3-oxocyclobuta[*d*][1]benzoxepine-1-carbonitrile* (**8d**; R_f 0.38). Light yellow oil. ^{1}H-NMR ($CDCl_3$): 7.35–7.05 (*m*, 4 H); 4.62, 4.48 (*AB*, J = 17.4, 2 H); 4.05 (*d*, J = 10.9, 1 H); 3.87 (*ddd*, J = 4.0, 8.8, 10.9, 1 H); 3.36 (*dd*, J = 4.0, 12.4, 1 H); 2.29 (*dd*, J = 8.8, 12.4, 1 H); 1.79 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$): 208.5 (*s*); 159.9 (*s*); 130.5 (*s*); 128.9 (*d*); 128.7 (*d*); 127.9 (*d*); 127.8 (*d*); 121.0 (*s*); 80.5 (*t*); 49.0 (*d*); 47.0 (*d*); 38.0 (*s*); 32.1 (*t*); 27.3 (*q*). EI-MS: 227 (1, M^+), 160 (100).

3.3. *Photocycloaddition of* **3** *to* **4**. A soln. of **3** (57 mg, 0.5 mmol) and **4** (410 mg, 5 mmol) in benzene (1 ml) was irradiated for 16 h up to total conversion to give one main product **9**, as monitored by GC, which was purified by prep. TLC (SiO_2; Et_2O/pentane 2:1) to afford 33 mg (32%) of *(1*S*,7*R*,9*R*)-9-methyl-9-(prop-1-en-2-yl)-2,4-dioxabicyclo[5.2.0]nonan-6-one* (**9**; R_f 0.55). Colorless liquid. ^{1}H-NMR ($CDCl_3$): 5.41 (*d*, J = 7.3, 1 H); 4.73 (*s*, 1 H); 4.65 (*s*, 1 H); 4.64 (*d*, J = 7.3, 1 H); 4.47, 4.15 (*AB*, J = 18.1, 2 H); 3.71 (*ddd*, J = 8.0, 9.0, 10.0, 1 H); 3.61 (*d*, J = 9.3, 1 H); 1.95 (*dd*, J = 10.7, 10.8, 1 H); 1.75 (*dd*,

$J = 8.3, 10.8, 1$ H); 1.66 (*s*, 3 H); 1.35 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$): 210.8 (*s*); 151.5 (*s*); 115.0 (*t*); 99.2 (*t*); 79.9 (*d*); 78.5 (*t*); 49.9 (*d*); 48.2 (*s*); 27.2 (*t*); 19.0 (*q*); 18.5 (*q*). EI-MS: 196 (0.25, M^+), 82 (100).

3.4. *Photocycloaddition of* **3** *to* **7**. A soln. of **3** (57 mg, 0.5 mmol) and **7** (335 mg, 5 mmol) in benzene (1 ml) was irradiated for 18 h up to total conversion to give a 2 : 1 mixture of cycloadduct **10** and a minor isomer, as monitored by GC. NMR Spectra of the crude mixture indicated that relatively large amounts of polymeric material originating from **7** were also formed. Attempted purification of the photoproducts on SiO_2 led to isomerization and partial decomposition, and, therefore, the spectroscopic data for the major product *(1S,7R,9S)-9-methyl-6-oxo-2,4-dioxabicyclo[5.2.0]nonane-9-carbonitrile* (**10**) stem directly from this product mixture. ^{1}H-NMR ($CDCl_3$): 5.52, 4.64 (*AB*, $J = 7.6$, 2 H); 4.51, 4.15 (*AB*, $J = 18.4$, 2 H); 3.96 (*ddd*, $J = 8.3, 9.6, 11.5$, 1 H); 3.53 (*d*, $J = 9.6$, 1 H); 2.42 (*dd*, $J = 8.3, 11.5$, 1 H); 1.86 (*dd*, $J = 11.4, 11.5$, 1 H); 1.56 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$): 208.8 (*s*); 120.5 (*s*); 100.0 (*t*); 79.2 (*d*); 79.0 (*t*); 51.9 (*d*); 38.2 (*s*); 27.8 (*t*); 22.8 (*q*). EI-MS: 191 (0.8, M^+), 84 (100).

REFERENCES

[1] J. Hehn, C. Mueller, T. Bach, in 'Handbook of Synthetic Photochemistry', Eds. A. Albini, M. Fagnoni, Wiley-VCH, Weinheim, 2010, pp. 171 – 215.
[2] P. Margaretha, in 'Molecular and Supramolecular Photochemistry', Eds. A. G. Griesbeck, J. Mattay, Marcel Dekker, New York, 2005, pp. 211 – 238.
[3] K. Schmidt, J. Kopf, P. Margaretha, *Helv. Chim. Acta* **2005**, *88*, 1922.
[4] G. Ohloff, G. Uhde, K. H. Schulte-Elte, *Helv. Chim. Acta* **1967**, *50*, 561.
[5] K. Narasaka, Y. Hayashi, H. Shimadzu, S. Niihata, *J. Am. Chem. Soc.* **1992**, *114*, 8865.
[6] A. B. Smith III, J. L. Wood, T. P. Keenan, N. Liverton, M. Visnick, *J. Org. Chem.* **1994**, *59*, 6652.
[7] R. A. Bunce, V. L. Taylor, E. M. Holt, *J. Photochem. Photobiol., A* **1991**, *57*, 317.
[8] H. Hart, E. Dunkelblum, *J. Org. Chem.* **1979**, *44*, 4752.
[9] B. Lohmeyer, K. Schmidt, P. Margaretha, *Helv. Chim. Acta* **2006**, *89*, 854.
[10] P. Margaretha, K. Schmidt, J. Kopf, V. Sinnwell, *Synthesis* **2007**, 1426.
[11] N. L. Allinger, M. Nakazaki, V. Zalkov, *J. Am. Chem. Soc.* **1959**, *81*, 4074.
[12] P. Kahnberg, O. Sterner, *Tetrahedron* **2001**, *57*, 7181.
[13] V. Y. Fedorenko, T. V. Bulgyna, Y. G. Shtyrlin, E. N. Klimovitskii, *Russ. J. Org. Chem.* **2004**, *40*, 1830.

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