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Photolysis of the 2-Azabicyclo[4.1.0]heptane-3,5-dione System[1)]

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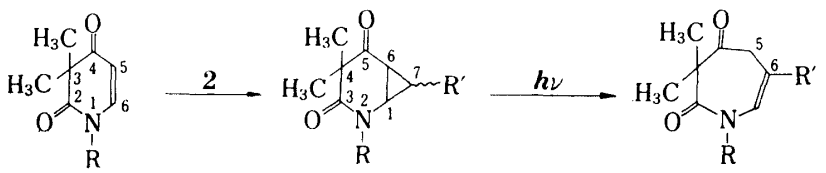
Irradiation of 2-alkyl-4,4-dimethyl-2-azabicyclo[4.1.0]heptane-3,5-dione (**3**), prepared by the reaction of 2,4-dioxo-*N*-alkyl-3,3-dimethyltetrahydropyridine (**1**) with sulfonium ylid, gave 1-alkyl-3,3-dimethyl-1*H*-azepine-2,4(3*H*,5*H*)-dione (**4**) with a ring expansion.

Keywords——2,4-dioxotetrahydropyridine; sulfonium ylid; 2-azabicyclo[4.1.0]-heptane-3,5-dione; 1*H*-azepine-2,4(3*H*,5*H*)-dione; ring expansion; cyclopropane

In the course of our systematic study on the photochemistry of conjugated nitrogen-carbonyl systems,[2,3)] we have recently reported the photodimerization[4)] and photoaddition[1a)] of the 2,4-dioxotetrahydropyridine system (**1**). As a continuation of this work, the present paper deals with the synthesis and photochemical behavior of 2,4-dioxobicyclotetrahydropyridines (**3**), in which the conjugation between carbonyl and amide groups of the 2,4-dioxotetrahydropyridine (**1**) is prevented from both sides by incorporation of a quaternary carbon (C-3) and a cyclopropane ring into the cyclic system, respectively.

When dimethyloxosulfonium methylide (**2a**)[5)] in tetrahydrofuran (THF) was reacted with 2,4-dioxo-*N*-methyl- and 2,4-dioxo-*N*-benzyl-3,3-dimethyltetrahydropyridine (**1**),[6)] the conjugated 5,6-double bond was converted into cyclopropane derivatives (**3**). In this way, **1a** and **1b** gave 2,4,4-trimethyl-2-azabicyclo[4.1.0]-heptane-3,5-dione (**3a**) and 2-benzyl-4,4-dimethyl-2-azabicyclo[4.1.0]heptane-3,5-dione (**3b**), in 25 and 19% yields, respectively. The ultraviolet spectra of **3a** and **3b** showed no absorption maxima at 305 nm, while their nuclear magnetic resonance (NMR) spectra displayed high field peaks characteristic of three-membered ring protons in addition to methyl and benzyl protons: for **3a**, δ 0.83—3.12; **3b**, δ 1.00—3.02 (see "Experimental"). The reactions of **1a** and **1b** with the ylid of tetramethylene sulfonium benzylide (**2b**)[7)] gave 2,4,4-trimethyl-7-phenyl-2-azabicyclo[4.1.0]heptane-3,5-dione (**3c**) and 2-benzyl-4,4-dimethyl-7-phenyl-2-azabicyclo[4.1.0]heptane-3,5 dione (**3d**) in 40 and 32% yields, respectively. The NMR spectra of **3c** and **3d** also displayed high field signals.



1 **3** **4**

a: R=CH_3, R′=H **c**: R=CH_3, R′=Ph **2a**: $(CH_3)_2\overset{O}{\overset{\uparrow}{S}}{}^{+}CH_2^-$

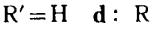
b: R=CH_2Ph, R′=H **d**: R=CH_2Ph, R′=Ph **2b**: 

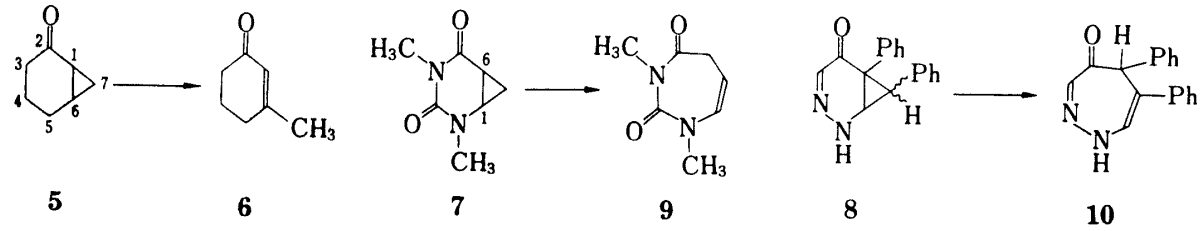
Chart 1

When carbon tetrachloride solutions of **3a** and **3b** were irradiated through a Pyrex filter with a 100-W Ushio high-pressure mercury lamp for 3 h under monitoring by NMR measurement, the seven-membered ring compounds **4a** and **4b** were formed in 47 and 34% yields, respectively.

Compound **4a**, *m/z* 167 (M^+), was identified as 1,3,3-trimethyl-1*H*-azepine-2,4(3*H*, 5*H*)-dione on the basis of the NMR spectrum, which showed signals of methylene protons at δ 3.10 (2H, d, J=7.5 Hz, H_5), and olefinic protons at δ 5.25 (1H, q, J=7.5 Hz, H_6), 6.20 (1H, d, J=7.5 Hz, H_7) in addition to methyl protons. Similarly, compound **4b**, *m/z* 247 (M^+), was identified as 1-benzyl-3,3-dimethyl-1*H*-azepine-2,4(3*H*, 5*H*)-dione on the basis of its NMR spectrum (see "Experimental").[8] The irradiation of **3c** and **3d** gave a complex mixture of products, and all attempts to isolate a ring-expansion product from the mixture failed.

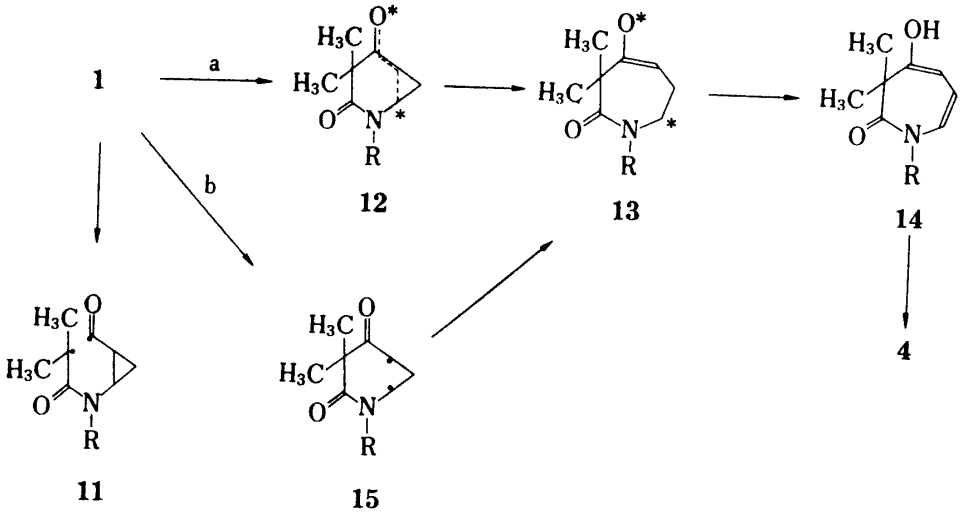
The major photoprocess of cyclopropyl ketones appears to be α-cleavage.[9] However, bicyclic compounds with cyclopropane rings in conjugation with the carbonyl undergo cyclopropane ring opening.[9] The photoisomerization of the cyclopropylcarbonyl chromophore, when contained in fused bicyclic systems, has been shown generally to bring about the cleavage of the better overlapped bond of the cyclopropyl ring with the π-lobe of carbonyl.[10] For example, Dauben *et al.* showed that bicyclo[4.1.0]heptan-2-one (**5**) upon photolysis yields 3-methyl cyclohexenone (**6**).[10] On the other hand, Kunieda and Witkop found that, on irradiation, the 2,4-diazabicyclo[4.1.0]heptane-3,5-dione system (**7**) affords a seven-membered ring compound (**9**),[11] while Nabeya *et al.* reported that 6,7-diphenyl-2,3-diazabicyclo[4.1.0]-3-hepten-5-one (**8**) leads to **10**.[12] Presumably an initial bond rupture of the six-membered ring takes place on account of better overlap of the C_6–C_1 bond with the carbonyl π-orbital, followed by a 1,2-hydrogen migration.[11] In the present study, 2,4-dioxobicyclopyridine (**3**), which is a deaza-analog of uracil with a carbonyl and an amide separated by a cyclopropane in the ring, was found to behave in a manner similar to that of 2,4-diazabicyclo[4.1.0]heptane-3,5-dione (**7**) in photolysis.

In view of the presence of the quaternary carbon next to the carbonyl, the type I α-cleavage (**11**) should be the preferred reaction. However, the results obtained in the present work indicate that in bicyclic compounds (**3**) with a cyclopropane ring in conjugation with



5 **6** **7** **9** **8** **10**

Chart 2



11 **15** **12** **13** **14** **4**

Chart 3

the carbonyl, the photoisomerization is competitive with the α-cleavage. The pathway, as shown in Chart 3, probably proceeds *via* species **13** which, on hydrogen rearrangement (or abstraction), gives the dienol (**14**) and ultimately the azepindione product (**4**). The formation of species (**13**) might occur in a concerted process (a) *via* excited species (**12**), or the process may proceed by stepwise radical cleavage (**15**). The latter process (b) is less likely, but cannot be excluded at present.

Experimental

Vacuum distillation was carried out by using a Buühi Kugelrohr apparatus, and boiling points are the uncorrected bath temperature. NMR spectra were taken on a Hitachi R-20B or JEOL JNM-FX 100FT-NMR spectrometer with tetramethylsilane (TMS) as an internal standard. Mass spectra (MS) were obtained with a Model JMS-Q10A JEOL mass spectrometer. Infrared spectra (IR) was recorded with JASCO IRA-1 infrared spectrometer. Preparative layer chromatography (PLC) was carried out on silica gel or aluminium oxide plates (Kieselgel 60 PF_{254} or Aluminiumoxid 60 PF_{254}, Merck, 20×20 cm). The light source was a Type UM-105B (Ushio) 100 W high pressure mercury lamp.

2,4-Dioxo-1,3,3-trimethyltetrahydropyridine (1a)——Prepared according to Masset's procedure,[6] bp 135—140°C/15 mmHg (lit.,[6] bp 120—150°C/13 mmHg).

2,4-Dioxo-1-benzyl-3,3-dimethyltetrahydropyridine (1b)——Sodium hydride (60%) (800 mg, 20 mmol) was washed twice with pet. ether and then suspended in 1.0 ml of anhydrous dimethylformamide (DMF). A solution of 2,4-dioxo-3,3-dimethyltetrahydropyridine[6] (2.78 g, 20 mmol) in 30 ml of anhydrous DMF was added dropwise to the above stirred suspension at 0°C, and the mixture was stirred at room temp. for 30 min until gas evolution ceased. After addition of 3.42 g (20 mmol) of benzyl bromide at 0°C, the reaction mixture was stirred at room temp. for 2 h. Most of the solvent was removed *in vacuo*, and 50 ml of ethyl acetate was edded to the residue. The organic layer was washed with water and then dried over anhydrous sodium sulfate. Removal of the solvent *in vacuo* left an oil. bp 155—158°C/2 mmHg. 4.04 g (88%). IR ν_{max}^{neat} cm^{-1}: 1690 (C=O), 1655 (CON). MS *m/z*: 229 (M^+), 160 and 91 (base). ^{1}H-NMR (CCl_4) δ: 1.45 (6H, s, C–CH_3), 4.85 (2H, s, PhC$\underline{H}_2$), 5.55 (1H, d, J=9 Hz, H_5), 7.20 (1H, d, J=9 Hz, H_6) and 7.36 (5H, s, aromatic). *Anal.* Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.56; H, 6.62; N, 6.02.

2,44-Trimethyl-2-azabicyclo[4.1.0]heptane-3,5-dione (3a)——Dimethyl oxosulfonium methylide (**2a**) was prepared by refluxing a mixture of NaH (50%; 250 mg, 5.2 mmol) and trimethyloxosulfonium chloride (668 mg, 5.2 mmol) in 40 ml of THF under nitrogen for 2 h.[5] **1a** (612 mg, 4.0 mmol) was added to the above ylid and the mixture was gently refluxed under nitrogen for 4 h. The precipitate was removed by filtration and washed with THF. The combined filtrate and washings were concentrated *in vacuo*, and the oily product was purified by silica gel PLC developed with CH_2Cl_2. bp 160°C (bath temp.)/13 mmHg: 130 mg (25%). IR ν_{max}^{neat} cm^{-1}: 1700 (C=O), 1640 (CON). MS *m/z*: 167 (M^+), 153, 139, 97 and 70 (base). ^{1}H-NMR ($CDCl_3$) δ: 0.83 (1H, ddd, J=6, 6 and 4 Hz, H_7endo) 1.30 (3H, s, C–CH_3), 1.43 (3H, s, C–CH_3), 1.44 (1H, m, H_7exo), 2.17 (1H, ddd, J=12, 8 and 6 Hz, H_6), 3.12 (1H, m, H_1), 3.11 (3H, s, N–CH_3). ^{13}C-NMR ($CDCl_3$) δ: 17.61 (t, C_7), 21.37 (q, C_4–$\underline{C}H_3$), 21.90 (d, C_6), 25.71 (q, C_4–$\underline{C}H_3$), 34.23 (q, N–CH_3), 34.46 (d, C_1), 51.49 (s, C_4), 171.60 (s, C_5) and 198.85 (s, C_3). *Anal.* Calcd for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.47; H, 7.88; N, 8.25.

2-Benzyl-4,4-dimethyl-2-azabicyclo[4.1.0]heptane-3,5-dione (3b)——Prepared by the same procedure as described for **3a** from 1.145 g (5 mmol) of **2b**. bp 170°C (bath temp.)/0.35 mmHg, 236 mg (19%). IR ν_{max}^{neat} cm^{-1}: 1700 (C=O), 1640 (CON). MS *m/z*: 243 (M^+) 160, 146 and 91 (base). ^{1}H-NMR ($CDCl_3$) δ: 1.00 (1H, ddd, J=6, 6 and 4 Hz, H_7endo), 1.35 (1H, m, H_7exo), 1.35 (3H, s, C–CH_3), 1.48 (3H, s, C–CH_3), 2.08 (1H, ddd, J=12, 8 and 6 Hz, H_6), 3.02 (1H, ddd, J=8, 6 and 4 Hz, H_1), 4.41 (1H, d, J=14.7 Hz, PhC$\underline{H}_2$), 5.07 (1H, d, J=14.7 Hz, PhC$\underline{H}_2$) and 7.32 (5H, m, aromatic). ^{13}C-NMR ($CDCl_3$) δ: 21.61 (d, C_6 and q, C_4–$\underline{C}H_3$), 25.78 (q, C_4–$\underline{C}H_3$), 32.51 (d, C_1), 50.20 (t, Ph$\underline{C}H_2$), 51.61 (s, C_4), 127.28—128.70 and 136.68 (aromatic), 171.55 (s, C_5) and 206.13 (s, C_3). *Anal.* Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 74.26; H, 7.23; N, 5.95.

2,4,4-Trimethyl-7-phenyl-2-azabicyclo[4.1.0]heptane-3,5-dione (3c)——A solution of potassium *tert*-butoxide (269 mg, 2.4 mmol) in 10 ml of THF was added dropwise over 10 min to a stirred suspension of 306 mg (2.0 mmol) of **1a** and 622 mg (2.4 mmol) of benzyl(tetramethylene)sulfonium bromide[7] in 5 ml of THF under nitrogen at −50°C. The mixture was allowed to come to room temp, then stirred overnight. The precipitate was removed by filtration and washed with THF. The combined filtrate and washings were concentrated *in vacuo*, and the oily product was purified by alumina PLC developed with $CHCl_3$. Distillation gave **3c** as a colorless oil: bp 220°C (bath temp.)/0.2 mmHg, 391 mg (40%). IR ν_{max}^{neat} cm^{-1}: 1705 (C=O) 1640 (CON). MS *m/z*: 243 (M^+), 215 and 144 (base). ^{1}H-NMR (CCl_4) δ: 1.38 (3H, s, C–CH_3), 1.47 (3H, s, C–CH_3), 2.27 (1H, dd, J=6 and 4 Hz, H_6), 2.57 (1H, dd, J=8 and 6 Hz, H_7), 3.30 (1H, dd, J=8 and 4 Hz, H_1) and 7.00—7.50 (5H, m, aromatic). ^{13}C-NMR ($CDCl_3$) δ: 20.93 (q, C_4–$\underline{C}H_3$), 25.98 (q, C_4–$\underline{C}H_3$), 31.29 (d, C_7), 34.35 (q, N–$\underline{C}H_3$), 35.37 (d, C_6), 42.15 (d, C_1), 51.69 (s, C_4), 125.93, 127.28, 128.78 and 136.77 (aromatic), 171.40

(s, C_5) and 204.45 (s, C_3). *Anal.* Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 74.06; H, 6.83; N, 5.84.

2-Benzyl-4,4-dimethyl-7-phenyl-2-azabicyclo[4.1.0]heptane-3,5-dione (**3d**)——**3d** was obtained from 458 mg (2.0 mmol) of **1b** and 622 mg (2.4 mmol) of **2b** in the manner described for **3c**. Colorless oil, bp 250°C (bath temp.)/0.2 mmHg, 206 mg (32%). IR ν_{max}^{neat} cm^{-1}: 1705 (C=O), 1640 (CON). MS *m/z*: 215 (M^+), 220 and 91 (base). ^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, s, C–CH_3), 1.42 (3H, s, C–CH_3), 2.00 (1H, dd, J=6 and 4 Hz, H_6), 2.36 (1H, dd, J=8 and 6 Hz, H_7), 3.04 (1H, dd, J=8 and 4 Hz, H_1), 4.68 (2H, s, PhC$\underline{H}_2$), 6.60—7.40 (5H, m, aromatic) and 7.20 (5H, s, aromatic). ^{13}C-NMR ($CDCl_3$) δ: 21.19 (q, C_4-$\underline{C}H_3$), 25.89 (q, C_4-$\underline{C}H_3$), 30.35 (d, C_7), 35.75 (d, C_6), 40.45 (d, C_1), 50.31 (t, Ph$\underline{C}H_2$), 51.72 (s, C_4), 125.81—136.40 (aromatic), 171.20 (s, C_5) and 204.25 (s, C_3). *Anal.* Calcd for $C_{21}H_{21}NO_2$: C, 78.97; H, 6.63; N, 4.39. Found: C, 78.79; H, 6.56; N, 4.54.

1,3,3-Trimethyl-1*H*-azepine-2,4(3*H*,5*H*)-dione (**4a**)——A solution of **3a** (240 mg, 1.4 mmol) in 5 ml of CCl_4 was irradiated for 3 h through a Pyrex filter with a 100 W high-pressure mercury lamp. The solvent was removed *in vacuo*, and the residue was subjected to silica gel PLC with CH_2Cl_2 as a developing solvent: 110 mg of colorless oil (47%), bp 140°C (bath temp.)/13 mmHg. IR ν_{max}^{neat} cm^{-1}: 1705 (C=O), 1635 (CON). MS *m/z*: 167 (M^+, base) and 139. ^{1}H-NMR (CCl_4) δ: 1.40 (6H, s, C–CH_3), 3.10 (2H, d, J=7.5 Hz, H_5), 3.15 (3H, s, N–CH_3), 5.25 (1H, q, J=7.5 Hz, H_6) and 6.20 (1H, d, J=7.5 Hz, H_7). *Anal.* Calcd for $C_9H_{13}NO_2$: 64.65; H, 7.84; N, 8.38. Found: C, 64.40; H, 8.00; N, 8.15.

1-Benzyl-3,3-dimethyl-1*H*-azepine-2,4(3*H*,5*H*)-dione (**4b**)——A solution of 279 mg (1.15 mmol) of **3b** in 3 ml of CCl_4 was irradiated as in the case of **3a** for 3 h; bp 170°C (bath temp.)/0.3 mmHg, 95 mg (34%). IR ν_{max}^{neat} cm^{-1}: 1700 (C=O), 1640 (CON). MS *m/z*: 243 (M^+), 146 and 91 (base). ^{1}H-NMR (CCl_4) δ: 1.42 (6H, s, C–CH_3), 3.08 (2H, d, J=7 Hz, H_5), 5.11 (2H, s, PhC$\underline{H}_2$), 5.35 (1H, q, J=7 Hz, H_6) and 6.25 (1H, d, J=7 Hz, H_7). *Anal.* Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 74.26; H, 7.05; N, 5.86.

A Test for Possible Acid-catalyzed Isomerization of 3a into 4a——CCl_4 (0.7 ml) was irradiated for 3 h through a Pyrex filter with a 100 W high-pressure mercury lamp, then 48 mg (0.29 mmol) of **3a** was dissolved in the solution. The mixture was kept for 3 h. Compound **3a** was also allowed to stand in the presence of 0.1% HCl in CCl_4 for 24 h. In both solutions the isomerized product (**4a**) was not detected at all.

References and Notes

1) *a*) Photochemistry of Conjugated Nitrogen–Carbonyl Systems. I. Part I: ref. 2. *b*) Photoinduced Reactions. LXII. Part LXI: E. Sato, Y. Kanaoka and A. Padwa, *J. Org. Chem.*, **47**,4256 (1982).
2) Y. Kanaoka, M. Hasebe and Y. Hatanaka, *Heterocycles*, **13**, 263 (1979).
3) Y. Kanaoka, *Accounts Chem. Res.*, **11**, 407 (1978).
4) E. Sato, Y. Kanaoka, I.L. Karle and B. Witkop, "submitted."
5) E.J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **87**, 1353 (1965).
6) E. Masset, *Chem. Abstr.*, **45**, 3426*b* (1951).
7) M. Hetschko and J. Gosselck, *Chem. Ber.*, **106**, 996 (1973).
8) Treatment of **3a** with carbon tetrachloride, which had previously been irradiated with a high-pressure mercury lamp, or contained 0.1% hydrogen chloride, caused no rearrangement into **4a**. Therefore this isomerization is not an acid-catalyzed process but a photochemical one.
9) O.L. Chapman and D.S. Weiss, "Organic Photochemistry," Vol. 3, ed. by O.L. Chapman, Marcel Dekker Inc., New York, 1973, p. 197.
10) *a*) W.G. Dauben and G.W. Shaffer, *Tetrahvdron Lett.*, **1967**, 4415; *b*) *Idem*, *J. Org. Chem.*, **34**, 2301 (1969); *c*) W.G. Dauben, L. Schutte, R.E. Wolf and E.J. Deviny, *J. Org. Chem.*, **34**, 2512 (1969); *d*) W.G. Dauben, G.W. Shaffer and E.J. Deviny, *J. Am. Chem. Soc.*, **92**, 6273 (1970); *e*) W.G. Dauben, L. Schutte, G.W. Shaffer and R.B. Gagasian, *ibid.*, **95**, 468 (1973).
11) T. Kunieda and B. Witkop, *J. Am. Chem. Soc.*, **93**, 3478 (1971).
12) A. Nabeya, K. Kurita and J.A. Moor, *J. Org. Chem.*, **38**, 2954 (1973).