Photoreactions of Thiobarbiturates. Intermolecular Cycloaddition with Alkenes and Ring Contraction Reaction of Trithiobarbiturate[1)]

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Upon irradiation of mono-, di-, and trithiobarbiturates in the presence of alkenes, [2+2]cycloaddition occurred regioselectively to give thietanes and their desulfurized products. In the case of trithiobarbiturate, a novel type of ring contraction product, dithiohydantoin, was also obtained.

Key words thiobarbiturate; photocycloaddition; thietane; ring contraction; dithiohydantoin

Although the photochemical reactivities of barbiturates have been well studied,[2)] little is known about that of their sulfur analogs (thiobarbiturates).[3)] During the course of our systematic studies on the photochemistry of nitrogen–thiocarbonyl systems, we found that the major photochemical processes of the cyclic thioimides[4)] and aromatic thioamides[5)] are limited to [2+2]photocycloaddition (Paterno–Büchi reaction) with alkenes, although certain thioimides having a benzylic hydrogen in the *N*-alkyl side chain undergo the Norrish type II reaction to give cyclized products.[6)] As an extension of that work, we have recently initiated studies on thiobarbiturates,[7)] whose skeletons consist of a combination of a thioimide and an amide or a thioamide (two-imide system). In the present paper we wish to present a full account of the intermolecular Paterno–Büchi reaction of thiobarbiturate systems and a novel type of photochemical ring contraction reaction of trithiobarbiturate.

Monothiobarbiturate (**1**, 2,3-dihydro-1,3,5,5-tetramethyl-2-thioxo-4,6(1*H*,5*H*)-pyrimidinedione) was easily obtained by the reaction of dimethylmalonyl dichloride with 1,3-dimethyl-2-thiourea in the presence of triethylamine. Dithio- (**2**) and trithiobarbiturate (**3**) were prepared by direct thionation of **1** with the 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (Lawesson's reagent).

Photolyses of thiobarbiturates (**1**—**3**) in the presence of alkenes (**4a**—**d**) were performed in acetonitrile (10 mM) using a 1 kW high-pressure mercury lamp through a Pyrex filter under a nitrogen atmosphere at room temperature. The progress of photoreaction was monitored by thin-layer chromatography (TLC) until the barbiturates used were

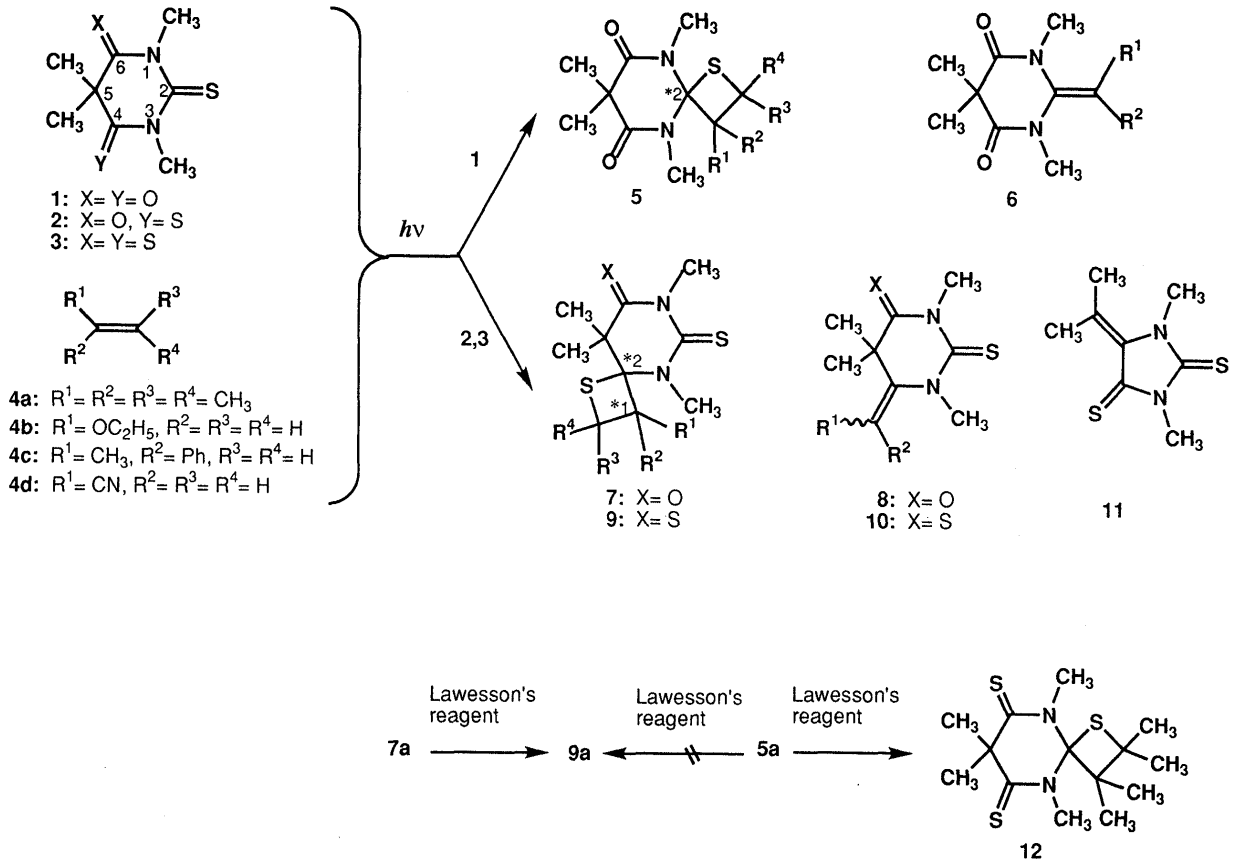

Chart 1

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Table 1. Photoproducts **5**—**11**

Compd.	Alkene	Time (h)	Product	Yield (%)	mp (°C)	Appearance (Solvent)	IR (Nujol) (cm^{-1})	MS (*m/z*) (M^+)	Formula	Analysis (%) Calcd (Found)			
										C	H	N	S
1	**4a**	5	**5a**	51	96—98	Colorless prisms (Hexane)	1650, 1630	284	$C_{14}H_{24}N_2O_2S$	59.12 (59.11	8.51 8.63	9.86 9.73	11.25 11.49)
			6a	47	97—99	Colorless needles (Hexane)	1700, 1675	210	$C_{11}H_{18}N_2O_2$	62.83 (62.89	8.63 8.63	13.32 13.19)	
1	**4b**	2	**5b**	17	77—78	Colorless prisms (Hexane–diisopropyl ether)	1670, 1645	272 226[b]	$C_{12}H_{20}N_2O_3S$	272.1194[a] (272.1201)			
			6b	40	94—96	Colorless plates (AcOEt–hexane)	1680, 1655	226	$C_{11}H_{18}N_2O_3$	58.39 (58.22	8.02 8.08	12.38 12.33)	
1	**4c**	12	**5c**	7	107—108.5	Colorless prisms (Hexane–diisopropyl ether)	1675, 1640	272[b]	$C_{17}H_{22}N_2O_2S$	64.12 (64.24	6.97 7.00	8.80 8.65	10.05 10.00)
			6c	88	186—186.5	Colorless prisms (AcOEt–hexane)	1700, 1655	272	$C_{16}H_{20}N_2O_2$	70.56 (70.62	7.40 7.44	10.29 10.33)	
1	**4d**	6	**6d**	63	98—99	Colorless needles (AcOEt–hexane)	2200, 1715, 1680	207	$C_{10}H_{13}N_3O_2$	57.96 (58.08	6.32 6.41	20.28 20.21)	
2	**4a**	0.5	**7a**	91	113—115	Colorless prisms (Hexane)	1705	300	$C_{14}H_{24}N_2OS_2$	55.98 (55.99	8.06 7.99	9.33 9.34	21.31 21.19)
2	**4b**	0.8	**7b**-i	11	63—64.5	Colorless prisms (Hexane)	1705	288 242[b]	$C_{12}H_{20}N_2O_2S_2$	49.98 (50.12	7.00 7.11	9.72 9.75	22.20 22.38)
			7b-ii	35	80—81.5	Colorless prisms (Hexane)	1695	288 242[b]	$C_{12}H_{20}N_2O_2S_2$	49.98 (50.03	7.00 7.04	9.72 9.71	22.20 22.40)
			8b	34	72.5—74	Colorless prisms (Hexane)	1705	242	$C_{11}H_{18}N_2O_2S$	54.52 (54.52	7.49 7.64	11.57 11.43	13.21 13.10)
2	**4c**	2	**7c**[c]	77	Semisolid		1700	334 288[b]	$C_{17}H_{22}N_2OS_2$	334.1173[a] (334.1147)			
			8c	2	Oil			288	$C_{16}H_{20}N_2OS$	288.1296[a] (288.1299)			
2	**4d**	7	**8d**-i	10	82—102	Colorless prisms (AcOEt–hexane)	2210, 1700, 1620	223	$C_{10}H_{13}N_3OS$	53.79 (53.97	5.87 5.92	18.83 18.74	14.33[d] 14.52)
			8d-ii	26	159—160	Colorless needles (AcOEt–hexane)	2220, 1700, 1635, 1620	223					
3	**4a**	1	**9a**	51	130—132	Yellow prisms (Hexane)		316	$C_{14}H_{24}N_2S_3$	53.15 (53.05	7.65 7.62	8.86 8.85	30.34 30.51)
			11	24	125—127	Orange needles (EtOH)	1590	200	$C_8H_{12}N_2S_2$	47.99 (47.90	6.05 6.07	14.00 14.00	31.97 31.70)
3	**4b**	0.5	**9b**	33	100—101	Yellow prisms (Hexane)		304 258[b]	$C_{12}H_{20}N_2OS_3$	47.36 (47.38	6.63 6.55	9.21 9.21	31.54 31.70)
			10b[e]	25		Yellow oil		258	$C_{11}H_{18}N_2OS_2$	258.0860[a,e] (258.0874)			
			11	4									
3	**4c**	2.5	**9c**	19	125—127	Yellow prisms (Hexane)		350 304[b]	$C_{17}H_{22}N_2S_3$	58.27 (58.23	6.33 6.27	8.00 8.03	27.40 27.42)
			11	18									
3	**4d**	3.0	**11**	25									

a) Determined by HR-MS. Upper figure, calcd for M^+; lower figure in parenthesis, found. *b*) ($M^+ - H_2C=S$). *c*) Mixture of **7c**-i and **7c**-ii. *d*) Mixture of **8d**-i and **8d**-ii. *e*) Mixture of **10b**-i and **10b**-ii.

no longer detectable. The results are collected in Chart 1 and Table 1.

Upon irradiation of monothiobarbiturate (**1**) with 2,3-dimethyl-2-butene (**4a**, 20 eq) for 5 h, 2-thietane (**5a**) and a 2-isopropylidene compound (**6a**) were obtained in 51% and 47% yields, respectively. Probably the desulfurized product (**6a**) arises from the initially formed thietane (**5a**) through photochemical fission (cycloreversion) of the thietane ring.[4a,b] In the case of ethyl vinyl ether (**4b**, 20 eq), the 2-thietane (**5b**, 17%) and the 2-ethoxymethylene compound (**6b**, 40%) were obtained after short irradiation. Similarly, in the case of an aromatic conjugated alkene, α-methylstyrene (**4c**, 10 eq), an alkylidene compound (**6c**) was obtained in 88% yield together with the 2-thietane (**5c**, 7%). Further, in the case of acrylonitrile (**4d**, 20 eq), which is an electron-deficient alkene, prolonged reaction (until disappearance of **1**) was required in comparison with the case of electron-rich alkenes such as **4a**, **b**, and only the alkylidene compound (**6d**) was obtained in 63% yield.

Next, photolyses of dithiobarbiturate (**2**), having a 2-thiocarbonyl group and a 4-thiocarbonyl group, with alkenes (**4a**—**d**) were examined. In these systems, photoaddition of alkenes occurred only at the 4-thiocarbonyl group, giving the corresponding thietanes (**7**) and alkylidene compounds (**8**). In the reaction of **2** with 2,3-dimethyl-2-butene (**4a**), only the thietane compound (**7a**) was obtained in 91% yield. Further, in the case of ethyl vinyl ether (**4b**) thietane isomers (**7b**-i and **7b**-ii) were obtained in 11% and 35% yields, respectively, accompanied with an unsaturated product (**8b**). Since compound **8b** was easily obtained from photolysis of each of **7b**-i and **7b**-ii, it was confirmed that **8b** is a secondary product derived from **7b**, and that **7b**-i and **7b**-ii are stereoisomeric

at the methine carbon (*1) on the thietane ring (Charts 1, 2). Similarly, when α-methylstyrene (**4c**) was irradiated with **2**, **7c**-i and **7c**-ii were obtained as an inseparable mixture of stereoisomers at the quaternary carbon (*1) (77%), together with the alkylidene compound (**8c**, 2%). In the reaction with acrylonitrile (**4d**), the alkylidene compounds (**8d**-i, **8d**-ii), *E*-*Z* isomers, were obtained in 10 and 26% yields, respectively. However, since **8d**-i and **8d**-ii were gradually transformed into each other, they were not isolated in a pure form.

Furthermore, photoreactivities of 2,4,6-trithiobarbiturate (**3**) with alkenes (**4a**—**d**) were also investigated. As shown in Table 1, the reaction of **3** with **4a**—**c** gave the thietanes (**9a**—**c**) and alkylidene derivative (**10b**) in

Table 2. NMR Spectral Data for the Photoproducts **5**—**11**

Compd.	^{1}H-NMR ($CDCl_3$, 90 MHz) δ	^{13}C-NMR ($CDCl_3$, 90 MHz) δ
5a	1.16 (6H, s, $CH_3\times2$), 1.46 (3H, s, CH_3), 1.48 (3H, s, CH_3), 1.55 (6H, s, $CH_3\times2$), 3.63 (6H, s, $NCH_3\times2$)	23.4 (q)×2, 25.5 (q), 26.5 (q), 28.1 (q)×2, 37.4 (q)×2, 45.2 (s), 45.4 (s), 64.5 (s), 87.9 (s), 173.5 (s)
6a	1.35 (6H, s, $CH_3\times2$), 1.86 (6H, s, $C=C(CH_3)_2$), 3.18 (6H, s, $NCH_3\times2$)	20.1 (q), 20.5 (q), 36.5 (q), 48.8 (s), 118.7 (s), 132.6 (s), 172.5 (s)
5b	1.13 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 1.39 (3H, s, CH_3), 1.42 (3H, s, CH_3), 2.9—3.7 (4H, m, OCH_2, SCH_2), 3.45 (3H, s, NCH_3), 3.53 (3H, s, NCH_3), 5.00 (1H, t, J=8 Hz, $C\underline{H}$–OCH_2)	15.3 (q), 24.7 (q), 25.0 (q), 28.9 (t), 32.8 (q), 33.3 (q), 44.7 (s), 66.2 (t), 84.4 (d), 92.7 (s), 171.7 (s), 172.2 (s)
6b	1.33 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 1.37 (6H, s, $CH_3\times2$), 3.17 (3H, s, NCH_3), 3.28 (3H, s, NCH_3), 3.90 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 5.84 (1H, s, =CH)	15.0 (q), 21.0 (q)×2, 32.7 (q), 33.5 (q), 47.4 (s), 69.4 (t), 123.9 (s), 126.8 (d), 170.1 (s), 170.4 (s)
5c	1.47 (3H, s, CH_3), 1.61 (6H, s, $CH_3\times2$), 2.65 (3H, s, NCH_3), 3.02 (1H, d, J=10 Hz, SCH_2), 3.73 (1H, d, J=10 Hz, SCH_2), 3.82 (3H, s, NCH_3), 7.1—7.5 (5H, m, ArH)	24.5 (q), 28.2 (q), 29.4 (q), 31.0 (t), 35.2 (q), 37.4 (q), 44.7 (s), 68.8 (s), 92.6 (s), 125.4 (d)×2, 127.7 (d), 128.9 (d)×2, 142.1 (s), 172.0 (s), 173.7 (s)
6c	1.52 (6H, s, $CH_3\times2$), 2.15 (3H, s, CH_3), 2.53 (3H, s, NCH_3), 3.32 (3H, s, NCH_3), 7.1—7.5 (5H, m, ArH)	20.7 (q), 35.4 (q), 36.8 (q), 48.7 (s), 119.8 (s), 127.5 (d), 127.8 (d), 128.9 (d), 133.9 (s), 139.9 (s), 171.7 (s), 172.9 (s)
6d	1.46 (6H, s, $CH_3\times2$), 3.29 (3H, s, NCH_3), 3.65 (3H, s, NCH_3), 4.56 (1H, s, =CH)	23.2 (q)×2, 31.9 (q), 34.8 (q), 47.4 (s), 64.7 (d), 116.5 (s), 152.3 (s), 169.8 (s), 170.0 (s)
7a	0.93 (3H, s, CH_3), 1.07 (3H, s, CH_3), 1.16 (3H, s, CH_3), 1.44 (3H, s, CH_3), 1.48 (3H, s, CH_3), 1.80 (3H, s, CH_3), 3.47 (3H, s, NCH_3), 3.83 (3H, s, NCH_3)	23.1 (q), 23.3 (q), 23.5 (q), 25.8 (q), 27.9 (q), 28.6 (q), 34.3 (q), 43.3 (q), 46.0 (s), 47.1 (s), 57.7 (s), 79.8 (s), 172.4 (s), 180.2 (s)
7b-i	1.06 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 1.10 (3H, s, CH_3), 1.74 (3H, s, CH_3), 2.8—3.6 (4H, m, SCH_2, OCH_2), 3.53 (3H, s, NCH_3), 3.78 (3H, s, NCH_3), 4.49 (1H, t, J=8 Hz, $C\underline{H}$–OCH_2)	15.1 (q), 20.4 (q), 21.0 (q), 31.0 (t), 34.8 (q), 41.9 (q), 45.2 (s), 66.3 (t), 81.8 (d), 85.0 (s), 171.7 (s), 179.8 (s)
7b-ii	1.08 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 1.08 (3H, s, CH_3), 1.64 (3H, s, CH_3), 3.0—3.5 (4H, m, SCH_2, OCH_2), 3.53 (3H, s, NCH_3), 4.02 (3H, s, NCH_3), 4.57 (1H, t, J=7 Hz, $C\underline{H}$–OCH_2)	15.5 (q), 21.5 (q), 21.8 (q), 30.5 (t), 35.1 (q), 42.0 (q), 46.0 (s), 65.9 (t), 77.6 (d), 85.9 (s), 170.9 (s), 181.2 (s)
8b	1.26 (6H, s, $CH_3\times2$), 1.31 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 3.50 (3H, s, NCH_3), 3.63 (3H, s, NCH_3), 3.93 (2H, q, J=7 Hz, OCH_2), 5.77 (1H, s, =CH)	15.2 (q), 22.0 (q)×2, 34.6 (q), 40.4 (s), 43.0 (q), 69.6 (t), 121.1 (s), 134.4 (d), 171.6 (s), 178.8 (s)
7c-i	1.06 (3H, s, CH_3), 1.48 (3H, s, CH_3), 1.83 (3H, d, J=0.9 Hz, CH_3), 2.66 (1H, d, J=9 Hz, SCH_2), 3.44 (3H, s, NCH_3), 3.86 (1H, d, J=9 Hz, SCH_2), 3.96 (3H, s, NCH_3), 8.0—8.5 (5H, m, ArH)	19.7 (q), 21.3 (q), 23.6 (q), 23.7 (q), 26.3 (q), 30.0 (q), 31.2 (t), 31.9 (t), 34.7 (q), 42.3 (q), 45.3 (q), 47.3 (s), 47.7 (s), 59.9 (s), 61.3 (s), 83.4 (s), 85.1 (s), 126.2 (d), 126.6 (d), 127.6 (d), 128.2 (d), 128.6 (d), 141.6 (s), 142.2 (s), 170.8 (s), 172.3 (s), 179.0 (s), 180.0 (s)
7c-ii	1.06 (3H, s, CH_3), 1.58 (3H, s, CH_3), 2.01 (3H, s, CH_3), 2.76 (3H, s, NCH_3), 3.11 (1H, d, J=10 Hz, SCH_2), 3.45 (1H, d, J=10 Hz, SCH_2), 3.58 (3H, s, NCH_3), 8.0—8.5 (5H, m, ArH)	(Mixture of **7c**-i and **7c**-ii)
8c	0.83 (3H, s, CH_3), 1.23 (3H, s, CH_3), 2.02 (3H, s, CH_3), 3.49 (3H, s, NCH_3), 3.68 (3H, s, NCH_3), 7.0—7.4 (5H, m, ArH)	22.9, 25.4, 26.1, 34.6, 45.9, 127.7, 128.2, 128.5, 128.6, 132.3, 137.0, 141.1, 172.0, 180.6
8d-i	1.77 (6H, s, $CH_3\times2$), 3.59 (3H, s, NCH_3), 3.77 (3H, s, NCH_3), 5.07 (1H, s, =CH)	25.5 (q)×2, 35.9 (q), 43.0 (q), 45.7 (s), 82.6 (d), 116.1 (s), 160.3 (s), 169.1 (s), 178.7 (s)
8d-ii	1.43 (6H, s, $CH_3\times2$), 3.55 (3H, s, NCH_3), 3.95 (3H, s, NCH_3), 5.04 (1H, s, =CH)	23.6 (q)×2, 35.3 (q), 44.8 (q), 45.4 (s), 82.4 (d), 115.1 (s), 160.8 (s), 168.6 (s), 178.7 (s)
9a	0.91 (3H, s, CH_3), 1.05 (3H, s, CH_3), 1.13 (3H, s, CH_3), 1.45 (3H, s, CH_3), 1.48 (3H, s, CH_3), 2.03 (3H, s, CH_3), 3.87 (6H, s, $NCH_3\times2$)	23.7 (q), 25.9 (q), 26.3 (q), 27.9 (q), 28.7 (q), 29.2 (q), 43.6 (q), 43.9 (q), 46.1 (s), 53.9 (s), 57.5 (s), 80.0 (s), 177.1 (s), 208.1 (s)
9b	1.07 (3H, s, CH_3), 1.07 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 1.86 (3H, s, CH_3), 2.9—3.5 (4H, m, OCH_2, SCH_2), 4.00 (3H, s, NCH_3), 4.03 (3H, s, NCH_3), 4.48 (1H, t, J=6 Hz, $C\underline{H}$–OCH_2)	15.5 (q), 24.0 (q), 27.7 (q), 30.5 (t), 43.6 (q), 44.7 (q), 51.4 (s), 65.7 (t), 77.9 (d), 84.8 (s), 178.2 (s), 205.3 (s)
10b-i	1.32 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 1.34 (6H, s, $CH_3\times2$), 3.65 (3H, s, NCH_3), 3.94 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 3.97 (3H, s, NCH_3), 5.87 (1H, s, =CH)	15.1 (q), 15.3 (q), 25.7 (q), 26.9 (q), 43.4 (q), 43.8 (q), 44.1 (q), 45.6 (s), 46.2 (q), 47.9 (s), 69.6 (t), 69.9 (t), 120.2 (s), 122.1 (s), 134.7 (d), 142.9 (d), 176.1 (s), 178.2 (s), 207.5 (s), 208.5 (s)
10b-ii	1.27 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 1.49 (6H, s, $CH_3\times2$), 3.71 (3H, s, NCH_3), 3.83 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 3.97 (3H, s, NCH_3), 6.33 (1H, s, =CH)	(Mixture of **10b**-i and **10b**-ii)
9c	1.03 (3H, s, CH_3), 1.57 (3H, s, CH_3), 2.24 (3H, s, CH_3), 2.88 (3H, s, NCH_3), 3.09 (1H, d, J=10 Hz, SCH_2), 3.46 (1H, d, J=10 Hz, SCH_2), 3.98 (3H, s, NCH_3), 7.3—7.6 (5H, m, ArH)	26.5 (q), 26.8 (q), 27.2 (q), 32.0 (t), 43.0 (q), 44.1 (q), 54.4 (s), 60.0 (s), 83.8 (s), 126.5 (d)×2, 127.6 (d), 128.6 (d)×2, 141.7 (s), 176.0 (s), 207.2 (s)
11	2.30 (3H, s, CH_3), 2.58 (3H, d, J=0.9 Hz, CH_3), 3.67 (3H, s, NCH_3), 3.80 (3H, s, NCH_3).	25.6 (q), 25.9 (q), 33.5 (q), 37.8 (q), 137.0 (s), 137.3 (s), 178.1 (s), 184.3 (s)

19—51% and 25% yields, respectively, *via* regioselective [2+2]cycloaddition at the 4-position, in a similar manner to that seen in the reaction of dithiobarbiturate (**2**). Interestingly, in each case of the reaction of trithiobarbiturate (**3**) with **4a—c**, besides the Paterno–Büchi products (**9**, **10**), a novel type of ring contraction product, dithiohydantoin (**11**) was obtained in 4—24 % yield. Compound **11** was also obtained in the absence of alkene. This result showed that trithiobarbiturate (**3**) by itself undergoes the ring contraction reaction to give **11**. Further, in the reaction with acrylonitrile (**4d**), only the dithiohydantoin (**11**) was obtained in preference to Paterno–Büchi products.

The structures of these products were determined on the basis of analytical and spectral data. The mass spectra (MS) of the thietanes (**5a, b**, **7a—c**, **9a—c**) showed molecular ion peaks (M^+) consistent with the adducts of alkenes (**4a—c**) to thiobarbiturates (**1—3**), and the alkylidene compounds (**6a—d**, **8b—d**, **10b**) showed molecular ion peaks (M^+) corresponding to the loss of thioacetone or thioformaldehyde from the corresponding parent thietane compounds **5**, **7**, and **9**, respectively. Since the MS and elemental analysis data of **6a—d** showed the absence of a sulfur atom, the occurrence of Paterno–Büchi reaction of monothiobarbiturate (**1**) with alkenes at the 2-thiocarbonyl was suggested. Further, the addition site of the alkene could easily be distinguished on the basis of the nuclear magnetic resonance (NMR) spectra (Table 2). For **5a**, the signals due to C5-dimethyl and a pair of *N*-methyl protons appeared at δ 1.16 (6H, s, $CH_3 \times 2$) and δ 3.63 (6H, s, $NCH_3 \times 2$), respectively. Further, compound **6a**, derived from **5a**, exhibits three singlets at δ 1.35 (6H, s, $CH_3 \times 2$), 1.86 (6H, s, $C=C(CH_3)_2$), and 3.18 (6H, s, $NCH_3 \times 2$), which indicate a symmetrical structure. In contrast, the ^{1}H-NMR spectrum of **9a** rules out a symmetrical structure, being indicative of thietane formation between an alkene (**4a**) and a thiocarbonyl at the 4-position of **3**. The structures of the thietanes (**5a—c**, **7a—c**, **9a—c**) were also confirmed by comparison of their ^{13}C-NMR spectra. For **5a**, a signal due to a quaternary carbon atom (*2) adjacent to two nitrogens and a sulfur atom appeared at δ 87.9 (s), whereas the corresponding signals of **7a** and **9a** appeared at δ 79.8—80.0, at higher field (by about 8 ppm) in comparison with that of **5a**. Similarly, the signals due to the quaternary carbon (*2) of the 4-thietanes (**7b—c**, **9b—c**) at δ 83.4—85.9 showed a similar upfield shift to those at δ 92.6—92.7 for the 2-thietanes (**5b, c**). To confirm the position of cycloaddition chemically, 4-thietane (**7a**) was treated with Lawesson's reagent. The resulting product was indistinguishable by NMR spectroscopy from **9a** derived from **3** and **4a**, and **9a** was not identical with the thionation product (**12**) which is derived from the 2-thietane (**5a**) and Lawesson's reagent (Chart 1).

The stereostructures of thietane isomers (**7b**, **9b**) and the alkylidene compound (**8b**) were assigned from the results of nuclear Overhauser effect (NOE) experiments (Chart 2). In the case of **7b**-ii, irradiation at the signal of the methine proton [δ 4.57 (1H, t)] on the thietane ring enhanced the signal intensity (8%) of the methyl protons

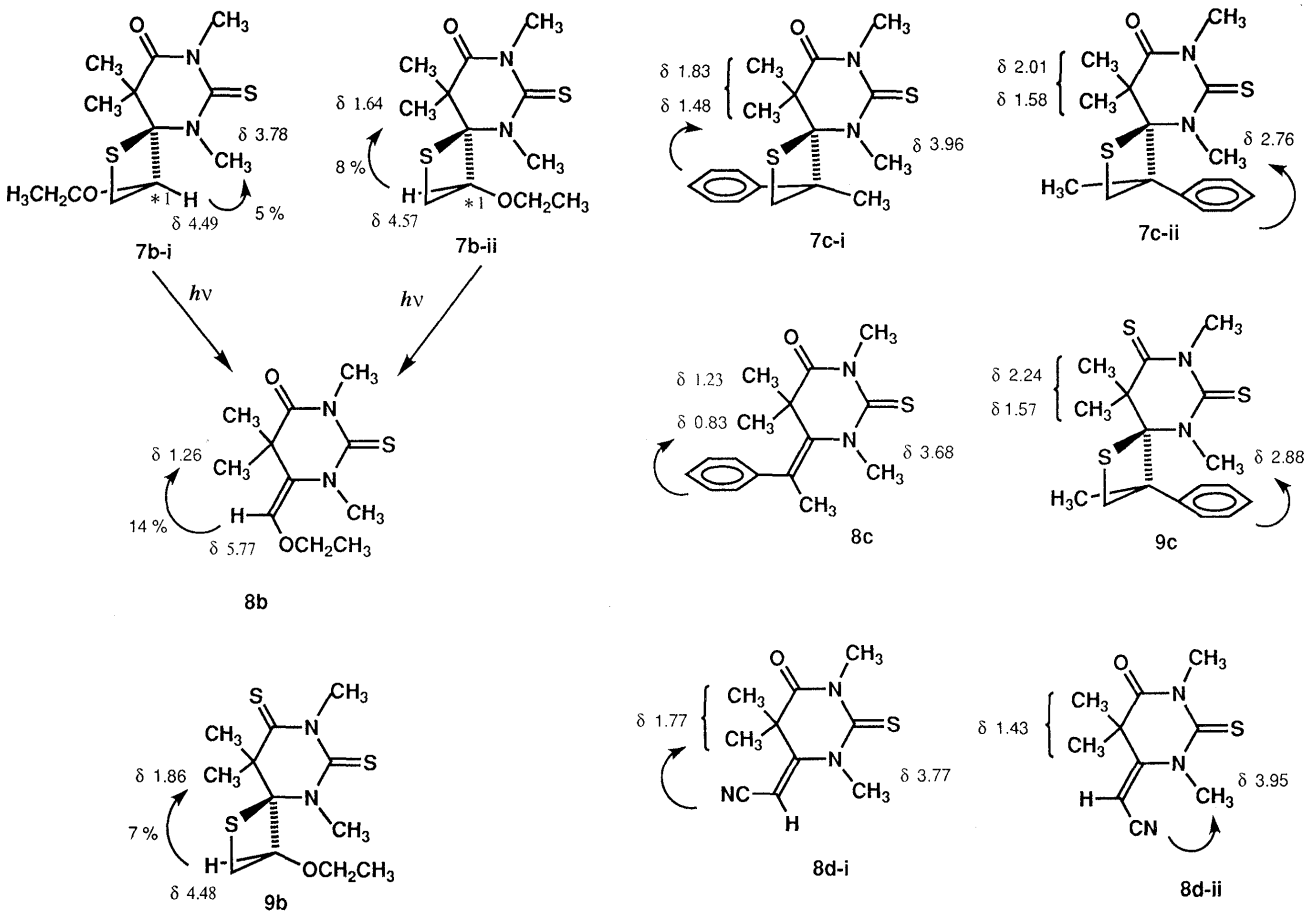


Chart 2

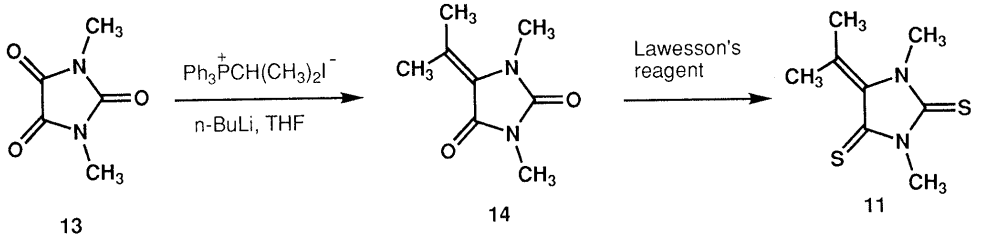
at the 5-position [δ 1.64 (3H, s)]. On the other hand, on irradiation at the methine proton [δ 4.49 (1H, t)] in **7b**-i, a 5% increment of the *N*-methyl signal [δ 3.78 (3H, s)] was observed, supporting the structures of **7b**-i and **7b**-ii as shown in Chart 2. In **9b**, NOE was also observed between the methine proton [δ 4.48 (1H, t)] and C5-methyl protons [δ 1.86 (3H, s)], indicating that **9b** has the same stereochemistry as **7b**-ii. The geometry of the alkylidene compound (**8b**) was also determined to be (*Z*)-form by the NOE enhancement between the signals of the vinyl proton [δ 5.77 (1H, s)] and C5-methyl protons [δ 1.26 (3H, s)].

Further, the stereochemistry of the thietanes (**7c**, **9c**) and alkylidene compounds (**8c**, **8d**) was determined with the aid of the anisotropic effects of the benzene or cyano moiety. In the ^{1}H-NMR spectrum of **7c**-ii, the signal due to the *N*-methyl protons at the 3-position was observed to be shifted upfield [δ 2.76 (3H, s)], owing to the influence of the benzene ring. However, this upfield shift was not observed in **7c**-i [δ 3.96 (3H, s)]. Similarly, the signal due to the *N*-methyl protons of **9c** showed an upfield shift [δ 2.88 (3H, s)], indicating that **9c** has the same stereochemistry as **7c**-ii, in which the benzene ring and *N*-methyl group are close to each other (Chart 2). Further, in the ^{1}H-NMR spectrum of **8c**, the signal of the C5-methyl protons showed a notable upfield shift [δ 0.83 (3H, s)], indicating this product to be the (*E*)-form, as shown in Chart 2, though the geometrical isomer of **8c** was not obtained.

The structures of the geometrical isomers of **8d**-i and **8d**-ii were also elucidated on the basis of ^{1}H-NMR spectra. The C5-dimethyl proton of **8d**-i appeared as a singlet at δ 1.77 (6H, s) at lower field than those of the isomer **8d**-ii [δ 1.43 (6H, s)], probably owing to the anisotropic effect of the cyano group. On the other hand, the signal of the *N*-methyl protons at the 3-position of **8d**-ii was observed at lower field [δ 3.95 (3H, s)] than in the case of **8d**-i [δ 3.77 (3H, s)], indicating that the structures of **8d**-i and **8d**-ii are (*E*) and (*Z*), respectively, as shown in Chart 2.

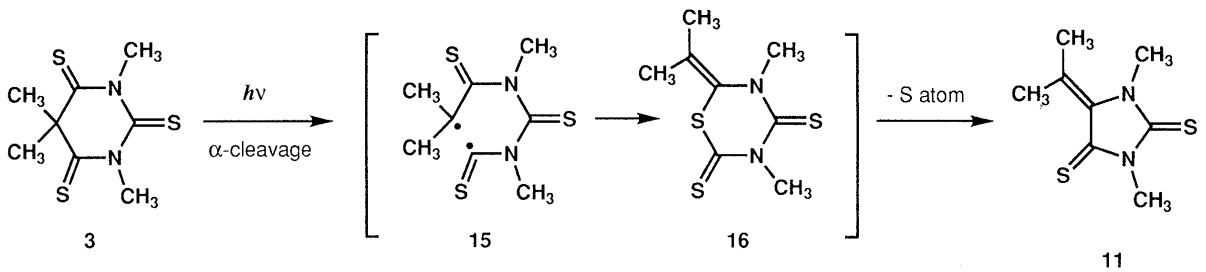
In the previous paper,[7a] the structure of the ring contraction product (**11**) was assigned in error as dithiouracil [1,3,5,6-tetramethyl-2,4-(1*H*,3*H*)-pyrimidinedithione]. In the present paper, the structure of **11** was revised to dithiohydantoin. The ^{1}H-NMR spectrum of **11** consisted of signals due to dimethyl protons at δ 2.30 and 2.58, and two *N*-methyl protons at δ 3.67 and 3.80. The ^{13}C-NMR spectrum showed the presence of two methyl groups [δ 25.6 (q), 25.9 (q)], two *N*-methyl groups [δ 33.5 (q), 37.8 (q)], and two quaternary carbons [δ 137.0 (s), 137.3 (s)] in addition to two thiocarbonyl groups [178.1 (s), 184.3 (s)], supporting the revised structure of **11**. In order to confirm the structure of this compound, an alternative synthesis was performed, as outlined in Chart 3. 1,3-Dimethylparabanate (**13**, dimethylimidazolidinetrione)[8] prepared by the reaction of oxalyl chloride with 1,3-dimethylurea in the presence of triethylamine, was transformed into the alkylidene compound (**14**) by means of the Wittig reaction, followed by treatment with Lawesson's reagent to give dithiohydantoin (**11**, 5-isopropylidene-1,3-dimethyl-2,4-imidazolidinedithione). The melting point and ^{1}H-NMR spectrum of this compound were in agreement with those of the photoproduct **11** from **3**, indicating that **11** is dithiohydantoin. The formation of **11** can be reasonably explained in terms of a 1,6-biradical intermediate (**15**), formed by α-cleavage (Norrish type I reaction) of the thiocarbonyl group (4-position) in **3**, followed by recyclization to the thiolactone (**16**), and then formation of the ring-contracted product (**11**) with the loss of a sulfur atom (Chart 4).

In conclusion, thiobarbiturates (**1**—**3**) undergo efficient [2+2]photocycloaddition with various alkenes to give thietanes and/or fission products, as well as simple cyclic thioimide systems.[4a,b,d] When the substrates have multiple thiocarbonyls (at the 2-, 4-, and/or 6-positions) in the molecular framework, as in **2** and **3**, the photocycloaddition occurs at the 4-thiocarbonyl (thiocarbonyl of the amide system) in preference to the 2-thiocarbonyl (thiocarbonyl of the urea system). This preference seems to be related to the more intense absorption of the chromophoric system involving the 4-thiocarbonyl group at



13 14 11

Chart 3



3 15 16 11

Chart 4

longer wavelengths as compared with the 2-thiocarbonyl system, under these irradiation conditions, resulting in more effective excitation of the terminal thiocarbonyl.

This reaction would provide a useful method for the construction of heterocycles through regioselective C–C bond formation, *e.g.*, a variety of ring-condensed pyrimidine compounds. Further, it is worth noting that trithiobarbiturate (**3**) undergoes Norrish type I reaction to give a ring contraction product, dithiohydantoin (**11**), since the occurrence of α-cleavage is very rare in thiocarbonyl photochemistry.[9] The generality of α-cleavage in trithiobarbiturates is under investigation.

Experimental

All melting points were determined on a Yamato melting point apparatus (model MP-21) and are uncorrected. Infrared (IR) spectra were recorded on a JASCO A-102 spectrometer. NMR spectra were taken on JEOL-FX-90Q and JEOL JNM-EX 400 spectrometers. Chemical shifts are reported in ppm (δ) with tetramethylsilane as an internal standard. The abbreviations used are as follows: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. MS were determined with a JEOL JMS-QH-100 gas chromatograph–mass spectrometer with a direct inlet system and high-resolution MS (HR-MS) were recorded using a JEOL JMS-DX 303 mass spectrometer.

Irradiations of substrates were conducted using a 1 kW high-pressure mercury lamp and a water-cooled quartz immersion well (Eikosha EHB-W-1000). Stirring of the reaction mixture was effected by the introduction of a stream of nitrogen at the bottom of the outer jacket. All column chromatography was conducted using silica gel (Wakogel C-300, 200—300 mesh).

2,3-Dihydro-1,3,5,5-tetramethyl-2-thioxo-4,6(1*H*,5*H*)-pyrimidinedione (Monothiobarbiturate 1) Triethylamine (10.1 g, 100 mmol) was added to a mixture of dimethylmalonyl dichloride (8.45 g, 50 mmol) and 1,3-dimethyl-2-thiourea (5.2 g, 50 mmol) in benzene (40 ml) at 60 °C. The reaction mixture was refluxed for 2 h, then diluted with water and extracted with benzene. The organic layer was washed with saturated aqueous $NaHCO_3$, and brine, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica gel with AcOEt–hexane (1 : 10, v/v) to give **1** (5.38 g, 54%). Recrystallization from hexane afforded pale yellow needles, mp 78—79 °C (lit.[3] mp 75—76.5 °C). IR (Nujol): 1730, 1690 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 90 MHz) δ: 1.57 (6H, s, $CH_3 \times 2$), 3.68 (6H, s, $NCH_3 \times 2$). MS *m/z*: 200 (M^+).

2,3,4,5-Tetrahydro-1,3,5,5,-tetramethyl-2,6-dithioxo-4(1*H*)-pyrimidinone (Dithiobarbiturate 2) and 1,3,5,5-Tetramethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrithione (Trithiobarbiturate 3) A solution of monothiobarbiturate **1** (3.80 g, 19 mmol) and Lawesson's reagent (3.80 g, 9.4 mmol) in xylene (40 ml) was heated to reflux for 5 h. The solution was concentrated to one-third of its original volume, and the residue was directly subjected to column chromatography on silica gel with AcOEt : hexane (1 : 10, v/v) to give **2** (2.42 g, 59%) and **3** (1.19 g, 27%), accompanied with **1** (0.47 g, 12%). **2**: Orange needles, mp 38.5—39.5 °C. IR (Nujol): 1710 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 90 MHz) δ: 1.67 (6H, s, $CH_3 \times 2$), 3.67 (3H, s, NCH_3), 4.21 (3H, s, NCH_3). ^{13}C-NMR ($CDCl_3$, 90 MHz) δ: 29.5 (q) × 2, 36.2 (q), 44.8 (q), 55.1 (s), 170.4 (s), 177.9 (s), 207.4 (s). MS *m/z*: 216 (M^+). *Anal.* Calcd for $C_8H_{12}N_2OS_2$: C, 44.44; H, 5.60; N, 12.96; S, 29.60. Found: C, 44.30; H, 5.57; N, 12.84; S, 29.45. **3**: Red prisms, mp 45—46 °C. ^{1}H-NMR ($CDCl_3$, 90 MHz) δ: 1.76 (6H, s, $CH_3 \times 2$), 4.20 (6H, s, $NCH_3 \times 2$). ^{13}C-NMR ($CDCl_3$, 90 MHz) δ: 32.9 (q) × 2, 45.5 (q) × 2, 61.6 (s), 174.6 (s), 205.6 (s) × 2. MS *m/z*: 232 (M^+). *Anal.* Calcd for $C_8H_{12}N_2S_3$: C, 41.38; H, 5.21; N, 12.07; S, 41.34. Found: C, 41.30; H, 5.22; N, 12.09; S, 41.17.

Irradiation of Thiobarbiturate Derivatives (1—3) in the Presence of Alkenes (4a—d). General Procedure A solution of **1—3** (10 mM) and **4a—d** (**1—3**/**4a, 4b, 4d** = 1/20 molar ratio, **1—3**/**4c** = 1/10 molar ratio) in acetonitrile was irradiated with a 1 kW high-pressure mercury lamp through a Pyrex filter with water cooling. After removal of the solvent *in vacuo*, the residue was subjected to silica gel column chromatography. The solvent systems used were as follows: **5a, 6a**, AcOEt : hexane = 1 : 1, v/v; **5b, 6b, 5c, 6c, 6d**, AcOEt : hexane = 1 : 2, v/v; **7a, 7b, 8b, 7c, 8c, 9a, 11**, AcOEt : hexane = 1 : 10, v/v; **8d**, AcOEt : hexane = 1 : 10 to 1 : 4, v/v; **9b, 10b**, AcOEt : hexane = 1 : 12, v/v; **9c**, AcOEt : hexane = 1 : 20, v/v.

Irradiation of (3*R*,4*R*)-3-Ethoxy-5,7,9,9-tetramethyl-6-thioxo-1-thia-5,7-diazaspiro[3,5]nonan-8-one (7b—i) and (3*S*,4*R*)-3-Ethoxy-5,7,9,9-tetramethyl-6-thioxo-1-thia-5,7-diazaspiro[3,5]nonan-8-one (7b-ii) A solution of **7b**-i (16 mg, 0.055 mmol) in acetonitrile (5 ml) was irradiated for 3.5 h under similar conditions to those described above. Separation by silica gel column chromatography (eluent: AcOEt : hexane = 1 : 10, v/v) gave **8b** (6 mg, 45%). Similarly, irradiation of **7b**-ii gave **8b** in 78% yield.

Thionation of 2,2,3,3,5,7,7,9-Octamethyl-1-thia-5,9-diazaspiro[3,5]-nonane-6,8-dione (5a) and 2,2,3,3,5,7,9,9-Octamethyl-6-thioxo-1-thia-5,7-diazaspiro[3,5]nonan-8-one (7a) A solution of **5a** (57 mg, 0.2 mmol) and Lawesson's reagent (161 mg, 0.4 mmol) in xylene (3 ml) was refluxed for 7 h, and separation by silica gel column chromatography (eluent: AcOEt : hexane = 1 : 10, v/v) to afford **12** (56 mg, 89%). Pale yellow needles, mp 152—153 °C. ^{1}H-NMR ($CDCl_3$, 90 MHz) δ: 1.17 (6H, s, $CH_3 \times 2$), 1.58 (6H, s, $CH_3 \times 2$), 1.92 (3H, s, CH_3), 2.09 (3H, s, CH_3), 4.22 (6H, s, $NCH_3 \times 2$). ^{13}C-NMR ($CDCl_3$, 90 MHz) δ: 23.4 (q), 28.0 (q), 34.2 (q), 41.1 (q), 45.8 (s), 47.8 (q), 57.4 (s), 67.5 (s), 92.2 (s), 208.4 (s). HR-MS *m/z*: Calcd for $C_{14}H_{24}N_2S_3$: 316.1100 (M^+). Found: 316.1130. Under similar conditions, the thietane (**7a**) was converted to **9a** in 62% yield.

Alternative Synthesis of Dithiohydantoine (11) A solution of *n*-BuLi (1.6 M in hexane; 3.2 ml, 5.1 mmol) was added at room temperature to a suspension of isopropyltriphenylphosphonium iodide (1.9 g, 4.4 mmol) in tetrahydrofuran (THF) (20 ml) under an argon atmosphere and the reaction mixture was stirred at the same temperature for 10 min. Then a solution of dimethylimidazolidinetrione (**13**, 568 mg, 4.0 mmol), prepared according to the reported method,[8] with triethylamine in place of Na_2CO_3, in THF (10 ml) was added dropwise to the above mixture at room temperature until the red solution was decolorized. The reaction mixture was stirred for 30 min, then poured into saturated NH_4Cl solution, and the aqueous mixture was extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel with AcOEt–hexane (4 : 1, v/v) to give **14** (112 mg, 17%). Recrystallization from hexane afforded colorless needles, mp 73.5—74.5 °C. ^{1}H-NMR ($CDCl_3$, 90 MHz) δ 2.12 (3H, s, CH_3), 2.34 (3H, s, CH_3), 3.06 (3H, s, NCH_3), 3.37 (3H, s, NCH_3). MS *m/z*: 168 (M^+). Next, a mixture of the resulting **14** (84 mg, 0.5 mmol) and Lawesson's reagent (270 mg, 0.67 mmol) in xylene (2 ml) was warmed at 120 °C for 1 h, and separation by silica gel column chromatography (eluent: AcOEt : hexane = 1 : 10, v/v) gave **11** (4 mg, 4%). Recrystallization from EtOH afforded orange needles, mp 124—126 °C. The *Rf* value on TLC and the ^{1}H-NMR spectrum of this compound were identical with those of **11** obtained by photolysis.

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References

1) Photochemistry of the Nitrogen-Thiocarbonyl Systems. 28. Part 27: Oda K., Hiratsuka R., Machida M., *Heterocycles*, **43**, 463—470 (1996).
2) *a*) Otsuji Y., Kuroda T., Imoto E., *Bull. Chem. Soc. Jpn.*, **41**, 2713—2718 (1968); *b*) Bartoń H., Mokrosz J., Bojarski J., Klimczak M., *Pharmazie*, **35**, 155—158 (1980); *c*) Bartoń H., Bojarski J., Mokrosz J., *Tetrahedron Lett.*, **23**, 2133—2134 (1982); *d*) Bartoń H., Żurowska A., Bojarski J., Welna W., *Pharmazie*, **38**, 268 (1983); *e*) Bartoń H., Bojarski J., Żurowska A., *Arch. Pharmazie*, **319**, 457—461 (1986); *f*) Bartoń H. J., Paluchowska M. H., Mokrosz J. L., Szneler E., *Synthesis*, **1987**, 156—158; *g*) Aoyama H., Hatori H., *Tetrahedron*, **46**, 3781—3788 (1990).
3) Gotthardt H., Nieberl S., Donecke J., *Justus Liebigs Ann. Chem.*, **1980**, 873—885.
4) *a*) Machida M., Oda K., Yoshida E., Kanaoka Y., *J. Org. Chem.*, **50**, 1681—1688 (1985); *b*) Machida M., Oda K., Sato E., Kanaoka Y., *Yuki Gosei Kagaku Kyoukai Shi*, **44**, 1071—1080 (1986); *c*) Oda K., Yoshida E., Ohno K., Machida M., Kanaoka Y., *Chem. Pharm. Bull.*, **37**, 642—647 (1989); *d*) Machida M., Oda K., Yoshida E., Kanaoka Y., *Heterocycles*, **26**, 147—156 (1987); *e*) Takechi H., Machida M., Kanaoka Y., *Synthesis*, **1992**, 778—782 and references cited therein.
5) *a*) Oda K., Machida M., Kanaoka Y., *Tetrahedron Lett.*, **30**, 4421—4422 (1989); *b*) Oda K., Machida M., *Chem. Pharm. Bull.*, **41**,

1299—1301 (1993); *c*) Oda K., Tsujita H., Ohno K., Machida M., *J. Chem. Soc., Perkin Trans. 1*, **1995**, 2931—2935 and references cited therein.
6) Oda K., Machida M., Kanaoka Y., *Chem. Pharm. Bull.*, **40**, 585—587 (1992).
7) *a*) Takechi H., Machida M., Kanaoka Y., *Chem. Pharm. Bull.*, **37**, 1431—1433 (1989); *b*) Takechi H., Machida M., *Heterocycles*, **42**, 117—120 (1996).
8) Larson D. B., Arnett J. F., McGlynn S. P., *J. Am. Chem. Soc.*, **95**, 6928—6935 (1973).
9) Coyle J. D., *Tetrahedron*, **41**, 5393—5425 (1985).