BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 43 1496—1500 (1970)

Oxidative Ring-contraction of Several 1,5-Benzodiazepines with Light

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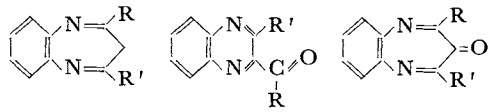
(Received October 14, 1969)

2,4-dimethyl- (I-a), 2-methyl-4-phenyl- (I-b), and 2,4-diphenyl-1,5-benzodiazepine (I-c) were irradiated with a high-pressure mercury arc under an oxygen atmosphere in benzene and in acetic acid. In all cases oxidative ring-contraction products, 2-acylquinoxalines (II), were obtained. It was found that there was a solvent effect in these reactions; *e.g.*, in benzene the diazepine (II-d) leads to 2-benzoyl-3-methylquinoxaline (II-d), while in acetic acid it leads to 2-acetyl-3-phenylquinoxaline (II-b).

The oxidation reaction of 2,4-dimethyl-1,5-benzodiazepine (I-a : R, R′=CH_3) and 2-methyl-4-phenyl-1,5-benzodiazepine (I-b : R=CH_3, R′=Ph) with monopersulfuric acid or with peracetic acid has been reported by Barltrop *et al.*;[1] the corresponding 3,6-diaza-4, 5-benzotropones, (III-a : R, R′=CH_3) and (III-b : R=CH_3, R=Ph), are not obtained, but the ring-contraction products, 2-acetyl-3-methylquinoxaline (II-a) and 2-acetyl-3-phenylquinoxaline (II-b) respectively, are obtained.



(I) (II) (III)

We have also studied the photooxidation of the dimethyl- (I-a) and the diphenylbenzodiazepine

1) J. A. Barltrop, C. G. Richards, D. M. Russel and G. Ryback, *J. Chem. Soc.*, **1959**, 1132.

(I-c) with a low-pressure mercury arc and have previously reported that the benzodiazepine (I-a) is oxidized to the quinoxaline (II-a) and that the photooxidation of the benzodiazepine (I-c) leads to a slight amount of the diazabenzotropone (III-c).[2] We suggested that, in the case of the benzodiazepine (I-a), the 6-oxo intermediate (III-a) may be subjected to a second photochemical reaction, thus forming a ring-contraction product (II-a). In this paper, we will report on the photooxidation reaction of the dimethyl-(I-a), the methylphenyl- (I-b), and the diphenyl-benzodiazepine (I-c) in benzene and in acetic acid employing a 200-W high-pressure mercury arc; the mechanism of the photooxidation reaction will also be discussed.

Results and Discussion

A benzene solution of the dimethylbenzodiazepine (I-a) was irradiated with a 200-w high-pressure mercury arc under an oxygen atmosphere; 2-acetyl-3-methylquinoxaline (II-a) and 3-methyl-2-quinoxalone (IV) were thus formed in yields of 29% and 8% respectively. When glacial acetic acid was used as the solvent, the reaction seemed to be promoted compared with that in benzene. When an 0.1 N sulfuric acid aqueous solution of diazepine (I-a) was irradiated under an oxygen atmosphere at 0-5 and 45–50°C, a slight amount of the quinoxaline (II-a) was formed; it and 2-methylbenziminazole (V-a) was obtained in yields of 5% and 75% respectively. The ring-contraction to 2-methylbenziminazole (V-a) may proceed thermally in an acidic aqueous solution, for it is known to be formed under acidic conditions in the dark.[1]

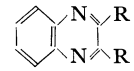
The auto-oxidation of the quinoxaline (II-a) under the action of light gave the quinoxalone (IV), so the product (IV) was probably formed *via* the second photooxidation of the quinoxaline (II-a) in the photooxidation of the diazepine (I-a).

When the methylphenylbenzodiazepine (I-b) in benzene was irradiated under an oxygen atmosphere, the photooxidation reaction proceeded smoothly and, surprisingly, 2-benzoyl-3-methyl-quinoxaline (II-d) was obtained in a yield of 25%, plus a small amount of 3-methylquinoxalone (IV); the oxidation of the benzodiazepine (I-b) with peracids leads to 2-acetyl-3-phenylquinoxaline (II-b). The abnormal ring-contraction product (II-d) was identified by means of its spectroscopic data, as is shown in Table 1 and Table 2.

Table 1. The spectroscopic data of 2-benzoyl-3-methylquinoxaline (II-d)

UV in ethanol :	$\lambda_{max}(\varepsilon)$	321(6460), 246(22900)
IR in KBr :	(cm^{-1})	1665($\nu_{C=O}$)
MS :	(m/e)	248(100), 233(10), 220(22), 219(62), 105(91)
NMR in $CDCl_3$:	(τ)	7.20 (3H, CH_3), 2.50–2.05 (9H, two Ph)

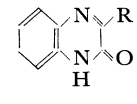
Table 2. The ultraviolet spectra of quinoxalines*



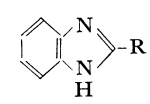
R	R'	$\lambda_{max}(m\mu)$	(ε)
H	H	233(28200)	315(6580) a)
CH_3	CH_3	237(23300)	316(6440) b)
CH_3	CH_3CO	245(32600)	304(6400)
CH_3	PhCO	246(32900)	321(6460)
Ph	CH_3CO	246(34300)	332(7400) b)
Ph	PhCO	252(38200)	340(9470)

* Measured in ethanol.
a) See Ref. 3.
b) See Ref. 1.

On the other hand, in acetic acid the photooxidation of the diazepine (I-b) leads to 2-acetyl-3-phenylquinoxaline (II-b), as in the case of oxidation with peracids. When the diphenylbenzodiazepine (II-c) was treated with peracetic acid, the ring-contraction product, 2-benzoyl-3-phenylquinoxaline (II-c), could not be obtained at all, but an amide (VI) was obtained.[4] On the other hand, in a benzene solution, the benzodiazepine (I-c) was photochemically oxidized very slowly with high-pressure mercury arc to give the corresponding oxidative ring-contraction product, 2-benzoyl-3-phenylquinoxaline (II-c). In the photooxidation of the diazepine (I-c), acetic acid highly promoted the oxidation reaction, and in acetic acid, 2-phenylbenziminazole (V-b), *N,N'*-dibenzoyl-*o*-phenylenediamine (VII), and an amide (VIII) were obtained as by-products. These results are shown in Table 3.



(IV)



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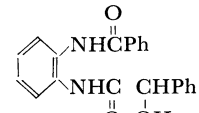
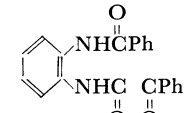


(VI)



(VIII)

In the photooxidation of the benzodiazepine (I), the oxidative ring-contraction to the acylquinoxaline (II) seems to proceed in a different fashion from that in the oxidation with peracids, as has been mentioned above. Though the acylquinoxaline (II) may be produced through the 6-oxo intermediate (III) in the photooxidation of the diazepine (I), as in the oxidation of diazepine (I-a) and (I-b)

2) T. Yonezawa, M. Matsumoto and H. Kato, This Bulletin, **41**, 2543 (1968).

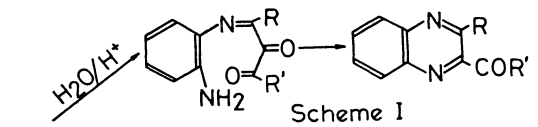
3) R. C. Hirt, *J. Chem. Phys.*, **25**, 574 (1956).

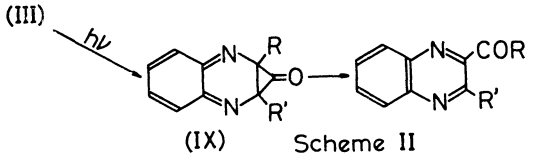
TABLE 3. OXIDATIVE RING-CONTRACTION OF THE BENZODIAZEPINES (I)

Benzodiazepine	Oxidation method	Solvent	Products (Yield, %)
(I-a)	$h\nu/O_2$	benzene	II-a(29), IV(8)
(I-a)	$h\nu/O_2$	acetic acid	II-a(31), IV(9)
(I-a)	$h\nu/O_2$ (at 0—5°C)	0.1 N H_2SO_4	II-a(2), V-a(5)
(I-a)	$h\nu/O_2$ (at 45—50°C)	0.1 N H_2SO_4	II-a(2), V-a(75)
(I-a)[a]	peracetic acid	acetic acid	II-a(27)
(I-b)	$h\nu/O_2$	benzene	II-d(25), IV(3)
(I-b)	$h\nu/O_2$	acetic acid	II-b(34)
(I-b)[a]	peracetic acid	acetic acid	II-b(35)
(I-c)	$h\nu/O_2$	benzene	II-c (trace)*
(I-c)	$h\nu/O_2$	acetic acid	II-c(14), V-b(16), VII, VIII (trace)
(I-c)[b]	peracetic acid	acetic acid	VI(44), (V-a)(9), VII(3)

* Oxidation was not completed within 40 hr.
a) See Ref. 1. b) See Ref. 4.

with peracids, diazabenzotropone (III) can not be expected to rearrange to the acylquinoxaline (II) in the case of the photooxidation, particularly in benzene, as in the case of the oxidation with peracids, for neither 2-benzoyl-3-phenylquinoxaline (II-c) nor 2-benzoyl-3-methylquinoxaline (II-d), but rather, the amide (VI) and 2-acetyl-3-phenylquinoxaline (II-b) were obtained upon treatment with peracetic acid. Thus, in the photooxidation of the diazepine (I) in benzene, the 6-oxo intermediate (III) is thought to undergo ring-contraction to the acylquinoxaline (II) photochemically. As is shown in Scheme II, we postulate that the diazabenzotropone (III) formed under the action of light may be subjected to the second photochemical reaction. In this point in Scheme I, as has been described in the work of Barltrop *et al.*,[1] the methylphenyldiazabenzotropone (III-b) rearranges to the acetylquinoxaline (II-b) through hydrolysis and successive dehydration ; in Scheme II, though diazatropone (III-b) rearranges to benzoylquinoxaline (II-d) photochemically.



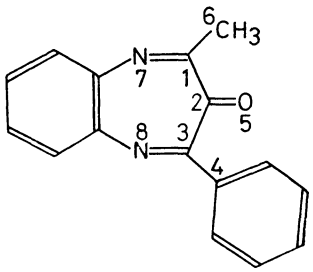


In Scheme II, Hückel calculation could give a reasonable result providing that this reaction occurred as a consequence of an n-π^* transition due the carbonyl group, as in the photochemical reactions of tropone[5] and tropolone,[6] and providing that the lowest vacant molecular orbital (LV) participates in that n-π^* transition.

Table 4 gives the characteristics of the lowest n-π^* excited state : the 1—3, 1—2, and 2—3 bonds show a tendency to be strengthened, while the 1—7 and 3—8 bonds become weak. The calculated results may support the idea that the photochemical reaction proceeds through a norcaradienone intermediate (IX), as shown in Scheme II. Therefore,

TABLE 4. CHANGES IN BOND ORDERS IN EXCITED DIAZABENSOTROPONE (III-b)

Atoms	Coefficients in LV π-MO	Bonds	Changes in bond orders
1	−0.123	1—2	+0.051
2	−0.419	2—3	+0.028
3	−0.195	1—3	+0.024
4	−0.023		
5	+0.272	2—6	−0.011
6	+0.027	2—4	+0.009
7	+0.418		
8	+0.476	1—7	−0.051
		3—8	−0.093



4) M. Matsumoto, A. Iio and T. Yonezawa, This Bulletin, **43**, 281 (1970).

5) W. G. Dauben, K. Koch, O. L. Chapman and S. L. Smith, *J. Amer. Chem. Soc.*, **83**, 1768 (1961).

6) *Cf.*, for example, P. de Mayo and R. W. Yip, *Proc. Chem. Soc.*, **1962**, 84.

the interaction between the phenyl group and the carbonyl group in (IX) may cause the bond fission of the 1—2 and 3—4 bonds. Thus, we can say that the tropone (III-b) in the excited state may rearrange to favor the formation of benzoylquinoxaline (II-d), but not acetylquinoxaline (II-b).

Experimental

2,4-Dimethyl-1,5-benzodiazepine (I-a). Acetylacetone (20 g) and *o*-phenylenediamine (20 g) were refluxed in dried benzene (100 m*l*) with *p*-toluene sulfonic acid (0.1 g) for 1 hr. Then the violet-coloured reaction mixture was filtered and condensed. The oily residue was chromatographed in benzene on silica gel (200 g). The diazepine (I-a) was then crystallized from 1: 1 benzene-cyclohexane; mp 131°C; yield, 70%.

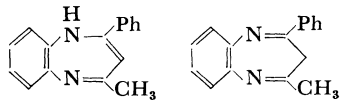
Found: C, 76.39; H, 7.11; N, 16.14%. Calcd for $C_{11}H_{12}N_2$: C, 76.71; H, 7.02; N, 16.27%.

2-Methyl-4-phenyl-1,5-benzodiazepine (I-b). Benzoylacetone (40 g) and *o*-phenylenediamine (20 g) were reacted in xylene (200 m*l*) for an hour, as in the case of the diazepine (I-a). Then the crude product was chromatographed in petroleum ether on silica gel (200 g). Crystallization from aqueous ethanol gave yellow crystals of the diazepine (I-b) monohydrate which melted at 118°C. The IR spectrum showed ν_{N-H} and ν_{OH} at 3450–3300 cm^{-1}. The NMR spectrum in $CDCl_3$ showed three singlets, at $\tau=8.05$ (3H, 2-CH_3 protons), $\tau=6.25$ (2H, water of crystallization), and $\tau=4.10$ (1H, 3-methyne proton), and multiplets at $\tau=3.40$—2.00 (10H). The mass spectrum showed a parent peak at *m/e* 234.

Found: C, 75.84; H, 6.38; N, 11.06%. Calcd for $C_{16}H_{14}N_2\cdot H_2O$: C, 76.16; H, 6.39; N, 11.10%.

From these results, the diazepine (I-b) which melted at 118° was determined to have the 1-H form (I-b)′.

Veibel and Hromadko[7] give a mp of 87—88°C for the diazepine (I-b); we also obtained crystals which melted at 87°C. The NMR spectrum of the diazepine (I-b) which melted at 87°C in $CDCl_3$ showed two singlets, at $\tau=7.77$ (3H, CH_3 protons) and $\tau=6.83$ (2H, 3-methylene protons), and multiplets at $\tau=2.90$—1.85 (9H). Thus, the diazepine (I-b) which melted at 87°C was 3-H form (I-b)″.



(I-b)′ (I-b)″

2,4-Diphenyl-1,5-benzodiazepine (I-c). The diazepine (I-c) was prepared from dibenzoylmethane and *o*-phenylenediamine as has been described by Barltrop *et al.*[1] The diazepine (I-c) was crystallized from methanol as colourless needles; mp 140°C.

Found: C, 85.20; H, 5.41; N, 9.51%. Calcd for $C_2H_{16}N_2$: C, 85.11; H, 5.44; N, 9.45%.

Photooxidation of the Diazepine (I-a) in Benzene. The diazepine (I-a) (3.0 g) in benzene (330 m*l*) was irradiated with a 200-W high-pressure mercury arc under an oxygen atmosphere for 8 hr. The irradiation was continued until the reaction mixture did not colour upon the addition of acetic acid. After irradiation, the reaction mixture was condensed *in vacuo*, and the oily residue was chromatographed in benzene on silica gel (200 g). 2-Acetyl-3-methylquinoxaline (II-a) was obtained as colourless needles which melted at 87°C by crystallization from aqueous ethanol yield 29%. Then 3-methyl-2-quinoxalone (IV) was obtained, mp 243°C from hot water as brown crystals; yield, 8%.

The quinoxaline (II-a): $\nu_{C=O}$ (in KBr) at 1689 cm^{-1}. Its phenylhydrazone, mp 174°C.

Found: C, 80.02; H, 5.46; N, 15.93%. Calcd for $C_{11}H_{10}ON_2$: C, 79.95; H 5.41; N, 15.95%.

The quinoxalone (IV); $\nu_{C=O}$ (in KBr) at 1668 cm^{-1}.

Found C: 67.49, H: 5.10, N: 17.40%, Calcd for $C_9H_8ON_2$ C: 67. 48, H: 5.03, N: 17.49%.

Photooxidation of the Diazepine (I-a) in Acetic Acid. After irradiation for 5 hr while an oxygen gas was being bubbled in, a violet-coloured acetic acid solution (330 m*l*) of the diazepine (I-a) (3.0 g) faded to a reddish brown. From the reaction mixture, acetic acid was removed *in vacuo*; the residue was treated as in previous experiments. The quinoxaline (II-a) and the quinoxalone (IV) were thus obtained in yields of 31 and 9% respectively.

Photooxidation of the Diazepine (I-a) in a 0.1 N H_2SO_4 Aqueous Solution. When a violet solution of the diazepine (I-a) (3.0 g) in a 0.1 N H_2SO_4 aqueous solution (330 m*l*) was irradiated for 5 hr at 0—5°C, the solution turned a reddish brown. After the solution had been neutralized by alkali and dried *in vacuo*, the dark brown oil was washed with chloroform. The washings, chromatographed on silica gel and eluted with benzene, gave, succesively, the quinoxaline (II-a) and 2-methylbenziminazole (V-a) in yields of 2 and 5% respectively.

When the diazepine in a 0.1 N H_2SO_4 aqueous solution was photooxidized at 45—50°C, the quinoxaline (II-a) and the benziminazole (V-a) were obtained in yields of 2 and 75% respectively. 2-Methylbenziminazole (V-a): mp 175°C obtained as needles from ethanol.

Found: C, 72.81; H, 6.13; N, 21.13%. Calcd for $C_8H_8N_2$: C, 72.70; H, 6.10; N, 21.20%.

Photolysis of 2-Acetyl-3-methylquinoxaline (II-a). The quinoxaline (II-a) (0.5g) in benzene (100 m*l*) was irradiated with a 100-W high-pressure mercury arc, while oxygen gas was being bubbled in, for 5 hr. The product was chromatographed on silica gel in chloroform, giving, successively, the starting material (210 mg) and 3-methylquinoxalone (IV) (30 mg); mp 245°C (from hot water).

Photooxidation of the diazepine (I-b) in Benzene. The diazepine (3.5 g) in benzene (330 m*l*) was irradiated under an oxygen atmosphere for 6 hr. The mixture was concentrated to a small bulk and then chromatographed on silica gel in benzene; we thus obtained 2-benzoyl-3-methylquinoxaline (II-d) and the quinoxalone (IV) in yields of 25 and 3% respectively. The quinoxaline (II-d) was in the form of colourless needles which melted at 88—89°C. Upon crystallization from aqueous ethanol and which were identified as has been described above. The quinoxaline (II-d) oxime was obtained as needles, which melted at 208°C.

The quinoxaline (II-d): $\nu_{C=O}$ (in KBr) at 1665 cm^{-1}.

Found: C, 77.46; H, 4.92; N, 11.32%. Calcd for $C_{16}H_{12}ON_2$: C, 77.40; H, 4.87; N, 11.28%.

Photooxidation of the Diazepine (I-b) in Acetic Acid. The diazepine (3.5 g) was oxidized photo-

7) S. Veibel and S. F. Hromadko, *Chem. Ber.*, **93**, 2752 (1960).

chemically in acetic acid (330 ml) for 8 hr, after which the reaction mixture was condensed and chromatographed on silica gel in benzene. Then 2-acetyl-3-phenylquinoxaline (II-b) was isolated as needles, mp 110°C by crystallization from ethanol. Lutz and Stuart[8] give a mp 110—111°C. The quinoxaline (II-b): $\nu_{C=O}$ at 1698 cm^{-1}.

Found: C, 77.45; H, 4.92; N, 11.33%. Calcd for $C_{16}H_{12}ON_2$: C, 77.40; H, 4.87; N, 11.28%.

Photooxidation of the Diazepine (I-c) in Benzene. The diazepine (3.0 g) in benzene (330 ml) was irradiated for 40 hr under an oxygen atmosphere. Almost the only thing recovered was the starting material; the oxidation product, 2-benzoyl-3-phenylquinoxaline (II-c), was detected only by T. L. C.

Photooxidation of the Diazepine (I-c) in Acetic Acid. The diazepine (3.0 g) in acetic acid (330 ml) was irradiated under an oxygen atmosphere. After 36 hr, the violet solution was faded to a reddish brown. The reaction mixture was then concentrated *in vacuo*, chromatographed on silica gel, and eluted with chloroform; it thus gave, succesively, 2-benzoyl-3-phenylquinoxaline (II-c) (14%), the amide (VIII) (0.7%), *N,N'*-dibenzoyl-*o*-phenylenediamine (VII), and 2-phenylbenziminazole (V-b) (16%). The quinoxaline (II-c) was identified by comparing it with a specimen prepared from diphenyltriketone and *o*-phenylenediamine. Colourless needles; mp 153.5—154.5°C; crystallization from diethyl ether. $\nu_{C=O}$ (in KBr) at 1660 cm^{-1}.

Found: C, 81.33; H, 4.60; N, 9.00%. Calcd for $C_{21}H_{14}ON_2$: C, 81.27; H, 4.55; N, 9.03%.

The amide (VIII) was in the form of colourless needles which melted at 198°C and which were crystallized from benzene-petroleum ether. The mass spectrum showed a parent peak at *m/e* 344. The IR spectrum showed $\nu_{C=O}$ at 1670 and 1650 cm^{-1} in KBr.

Found: C, 73.27; H, 4.73; N, 8.19%. Calcd for $C_{21}H_{16}O_2N_2$: C, 73.24; H, 4.68; N, 8.14%.

The amide (VII) and *N,N'*-dibenzoyl-*o*-phenylenediamine prepared by the condensation of *o*-phenylenediamine and benzoyl chloride had identical infrared spectra. Mp 324°C, $\nu_{C=O}$ at 1664 cm^{-1}.

Found: C, 76.01; H, 5.13; N, 8.79%. Calcd for $C_{20}H_{16}O_2N_2$: C, 75.93; H, 5.10; N, 8.86%.

The iminazole (V-b) melted at 313—314°C.

Found: C, 80.45: H, 5.26; N, 14.50%. Calcd for $C_{13}H_{10}N_2$: C, 80.38; H, 5.19; N, 14.42%.

8) Lutz and Stuart, *J. Amer. Chem. Soc.*, **59**, 2316 (1937).