Photoreaction of *N*,*N'*-Dibromo-2,5-piperazinedione

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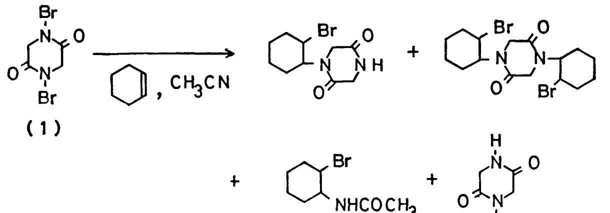
The photolysis of *N*,*N'*-dibromo-2,5-piperazinedione in dichloromethane gave an unstable photoproduct. The alcoholysis of the photoproduct in the presence of a small amount of hydrogen bromide yielded 3,6-diethoxy-2,5-piperazinedione and its alcoholyzed products, ethyl diethoxyacetate, ethyl 2-(diethoxyacetylamino)-2-ethoxyacetate, *N*-(1-ethoxy-1-ethoxycarbonylmethyl)oxamide, and ethyl *N*-(diethoxyacetyl)glycinate. The reactions of the photoproduct with other nucleophiles also gave the corresponding substituted 2,5-piperazinediones. The structure of the primary photoproduct was deduced to be 3,6-dibromo-2,5-piperazinedione on the basis of these observations.

In recent years, attention has been focused on the chemical reactivity and selectivity of the succinimido radical produced from *N*-bromosuccinimide(NBS).[1-3] The preferential attack of the succinimido radical to a carbon-carbon double bond has been reported to proceed in competition with hydrogen abstraction reactions.[2,3] The presence of two states of the imido radical, a ground state π-radical and an exited state σ-radical was suggested to explain the reaction patterns observed under homogeneous conditions.

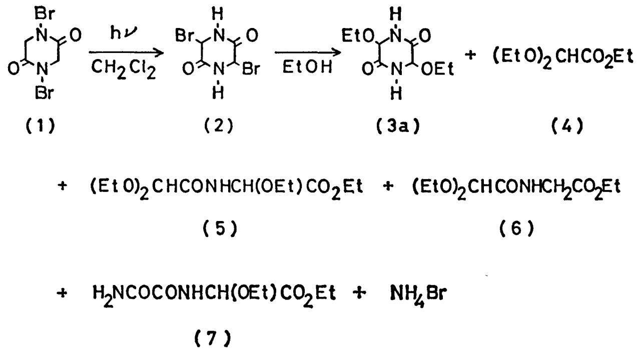
In the course of our investigation on the reactivity of *N*,*N'*-dibromo-2,5-piperazinedione (**1**, NBP), we reported a photo-induced alkoxybromination of some olefins with NBP in the presence of alcohols.[4] Because the structure of NBP is similar to that of NBS, photoreactions of NBP with olefins proceeded easily to give the corresponding addition products in aprotic media. A solvent incorporated product was also produced. However, no rearranged product was detected, such as was often found in the photoreactions of NBS. Thus, detailed examination of the photochemical behavior of NBP is desirable. This paper concerns the photoreaction of NBP in dichloromethane.



Results and Discussion

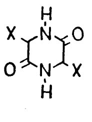
Photolysis of NBP in dichloromethane was carried out in a Pyrex apparatus. The concentration of NBP was usually around 0.4 mol dm^{-3}. Because of the low solubility of NBP in dichloromethane (and in most of organic solvents), the irradiation was carried out under heterogeneous conditions with agitation. In a few hours the reaction mixture turned red. After 8 h, the photolysate was filtered to give a pale yellow solid (**2**) which was found not to be NBP. The solid **2** was so unstable that we could not recrystallize it satisfactorily. However, the bromine analysis of a specimen of **2** (not completely pure)[5] revealed the presence of two bromine atoms in the molecule. The methine proton signal was observed at $\delta=5.0$. A photo-enolization of the amide group of NBP and a subsequent 1,3-bromine shift might result in the unstable **2**.

Accordingly, immediately after filtration and quick rinsing with dichloromethane, **2** was allowed to react with ethanol to give 3,6-diethoxy-2,5-piperazinedione (**3a**, 3%), ethyl diethoxyacetate (**4**, 4%), ethyl 2-(diethoxyacetylamino)-2-ethoxyacetate (**5**, 25%), ethyl *N*-(diethoxyacetyl)glycinate (**6**, 16%), *N*-(1-ethoxy-1-ethoxycarbonylmethyl)oxamide (**7**, 2%), and ammonium bromide, respectively.



The structures of the above products were all determined taking into account their elemental analyses, and IR, NMR, and mass spectra. Compound **3a** had an infrared absorption pattern in its finger print region similar to that of 2,5-piperazinedione, except for the presence of C–O stretching bands in the former. The NMR spectrum of **3a** showed a distinct ring proton signal at $\delta=4.5$ (dd, $J=4$ and 1 Hz), an NH proton signal ($\delta=8.9$, d, $J=4$ Hz), and ethoxy proton signals. Elemental analysis and the MS fragment pattern[6] also confirmed the structure of **3a**. Compound **3a** was considered to be a primary alcoholysis product of **2** as described latter. The spectra of **4** were found to be identical with those of authentic ethyl diethoxyacetate prepared by the recorded method.[7] Compound **5** showed IR absorptions at $3400(\nu_{NH})$, 1760, $1710(\nu_{C=O})cm^{-1}$, and its NMR spectra revealed the presence of two methine protons ($\delta=4.7$, s and 5.3, d, $J=9$ Hz), one NH proton ($\delta=7.3$, d, $J=9$ Hz), and four ethoxyl groups. Compound **6** also showed C=O (1760, 1690 cm^{-1}) and NH (3350 cm^{-1}) absorptions, and CH_2 ($\delta=3.9$, d, $J=6$ Hz), CH ($\delta=4.7$, s), NH ($\delta=7.0$, t, $J=6$ Hz), and three ethoxyl proton signals. Both NMR spectra [$\delta=1.1$ (CH_3), 3.5 (CH_2 of ethoxyl group), 4.1 (CH_2 of ethoxycarbonyl group), 5.2 (CH), 7.8 and 8.0 (NH$_2$), and 9.1 (NH)] and IR absorptions [3380 and 3270 (NH) and 1760 and 1680 (C=O) cm^{-1}] supported the structure of **7** to be that depicted above. The amide protons of **7** resonated at δ=7.8 and 8.0 (DMSO-d_6) at ambient temperature. These two signals began to coalesce at around 100 °C, indicating the presence of restricted rotation around a formal single bond.[8]

Because the structure of **5** is composed of two glyoxalic acid units, **4** was thought to be produced from **5** in the course of the treatment of ethanol. Actually the ethanolysis of **5** in the presence of hydrochloric acid gave **4**. The same treatment of **6** also yielded **4** and ethyl glycinate hydrochloride. In addition, the treatment of **3a** with ethanol containing hydrogen bromide gave **4** and **5**. Thus **3a** was a key intermediate of the successive reactions of **2** giving **4** and **5**, where hydrogen bromide liberated from **2** played a catalytic role in the ethanolysis. The alcoholysis reactivity of **3a** seemed rather high, but one can anticipate that an addition of a hydrogen bromide scavenger can increase the yield of **3**. The yield of 3,6-dialkoxy derivative was found as follows. Reactions were carried out using methanol instead of ethanol: a 5% yield of 3,6-dimethoxy-2,5-piperazinedione (**3b**) was obtained by an irradiation of NBP in dichloromethane and a subsequent treatment of the remaining solid with methanol; 48% was obtained by the same irradiation followed by a treatment with methanol–pyridine. As expected, **2** reacted with other nucleophiles; water, acetic acid, and an azide ion.



3b; X=OMe
3c; X=OH
3d; X=OAc
3e; X=N$_3$

The whole reaction scheme will be represented as follows: the photoisomerization of NBP gave the intermediate **2**, which on ethanolysis yielded **3a**. A nucleophilic attack of ethanol to the carbonyl group of **3a** and a subsequent ring opening followed by transacetalization gave **5**, which in turn yielded **4** by ethanolysis. A part of NBP was converted to *N*-bromo-2,5-piperazinedione by the protodebromination with hydrogen bromide.[9] A similar photoisomerization-ethanolysis of this *N*-bromo compound could give 3-ethoxy-2,5-piperazinedione and the corresponding ring opening product (**6**). The formation mechanism of **7** is not determined at present.

One of characteristic features of the photoreaction of NBP is the absence of the photo ring opening reaction, which has been often encountered in reactions of NBS giving 3-bromopropionyl isocyanate in a variety of conditions.[1,10] Massive evidence exists that the succinimido radical isomerizes to ·CH$_2$CH$_2$CONCO by a photochemical α-cleavage-like reaction, and the latter radical abstracts a bromine atom of NBS to give 3-bromopropionyl isocyanate. However, in the case of NBP, this was not the case. This characteristic may arise from the structural feature of NBP, which is characterized as a bromide of cyclic diamide. Investigations are in progress to elucidate the dissimilarity of NBP to NBS in reactivity.

Experimental

Melting points were determined on a Yanagimoto hot stage and were uncorrected. NMR spectra were determined on a JEOL PMX-60 spectrometer using TMS as the internal standard. IR spectra were recorded on a JASCO IRA-1 spectrometer. Mass spectra were recorded on Hitachi RMU-6MG and JEOL JMS-01SG-2 spectrometers. All irradiations were carried out using Ushio UM 453B(450 w) and Halos EHB-WU(100 w) high pressure mercury arc lamps. Dichloromethane was washed with sulfuric acid to remove the contained ethanol, washed thoroughly with water, dried and distilled. *N,N'*-Dibromo-2,5-piperazinedione was prepared as described in the literature.[4]

Photoreaction of NBP. A suspension of NBP (**1**, 10 g) in 100 cm^3 of dichloromethane in a Pyrex vessel was irradiated by a high pressure Hg arc lamp for 8 h with stirring at ambient temperature. The mixture was filtered to give a pale yellow solid (**2**). In the filtrate, nothing was found but bromine. The solid **2** was quite unstable.[5] The color of **2** turned red, and meanwhile **2** decomposed spontaneously to a clear viscous liquid. Accordingly **2** was rinsed quickly with dichloromethane and was added into ethanol. The mixture was stirred overnight at room temperature, and was filtered to give white crystals. Recrystallization from ethanol gave 240 mg (3.3% based on NBP) of 3,6-diethoxy-2,5-piperazinedione (**3a**), mp 217 °C (dec). IR: 3230, 1680 cm^{-1}; NMR (DMSO-d_6): δ=1.1 (6H, t, J=7 Hz), 3.5 (4H, q, J=7 Hz), 4.5 (2H, dd, J=4 and 1.2 Hz), 8.9 (2H, broad d, J=4 Hz); MS (m/e)[6]: 174 (M$^+$), 131, 115, 72, 60. Found: C, 47.83; H, 6.98; N, 13.97%. Calcd for C$_8$H$_{14}$N$_2$O$_4$: C, 47.52; H, 6.93; N, 13.86%.

The ethanolic filtrate was evaporated up to a syrup (11.5 g) which was separated on siliga-gel column to afford products in the following order. Yields are given on the basis of NBP employed.

Elution with benzene–ether (9:1) gave 530 mg (4.2%) of ethyl diethoxyacetate (**4**), a colorless liquid. IR: 1760 cm^{-1}; NMR (CCl$_4$): δ=1.1 (9H, m), 3.5 (4H, q, J=7 Hz), 4.0 (2H, q, J=7 Hz), 4.6 (1H, s). Found: C, 53.88; H, 9.10%. Calcd for C$_8$H$_{16}$O$_4$: C, 54.55; H, 9.11%. The IR and NMR spectra of this compound were found to be identical to those of an authentic sample prepared by a recorded method.[7]

Further elution gave 2.48 g (24.8%) of ethyl 2-(diethoxyacetylamino)-2-ethoxyacetate (**5**) as a colorless liquid. IR: 3400, 1760, 1710 cm^{-1}; NMR (CCl$_4$): δ=1.2 (12H, m), 3.5 (6H, q, J=7 Hz), 4.1 (2H, q, J=7 Hz), 4.7 (1H, s), 5.3 (1H, d, J=9 Hz), 7.3 (1H, broad d, J=7 Hz); MS (m/e): no M$^+$, 131, 130. Found: C, 51.25; H, 8.41; N, 4.79%. Calcd for C$_{12}$H$_{23}$NO$_6$: C, 51.95; H, 8.31; N, 5.05%.

Next the column was eluted with benzene-acetone (4:1) to give 128 mg (1.6%) of *N*-(1-ethoxy-1-ethoxycarbonylmethyl)oxamide (**7**) as white crystals, mp 163—165 °C. IR: 3380, 3270, 1760, 1690 cm^{-1}; NMR (DMSO-d_6): δ=1.1 (6H, m), 3.5 (2H, q, J=7 Hz), 4.1 (2H, q, J=7 Hz), 5.2 (1H, d, J=8 Hz), 7.8 and 8.0 (2H, rotation restricted NH$_2$), 9.1 (1H, broad d, J=8 Hz); MS (m/e): 218 (M$^+$), 173, 145, 116. Found: C, 44.06; H, 6.60; N, 12.80%. Calcd for C$_8$H$_{14}$N$_2$O$_5$: C, 44.04; H, 6.42; N, 12.84%.

Elution with benzene–ethanol (9:1) afforded 1.11 g (13%) of ethyl *N*-(diethoxyacetyl)glycinate (**6**) as a yellow liquid.

IR: 3350, 1760, 1690 cm^{-1}; NMR (CCl_4): δ=1.2 (9H, m), 3.6 (4H, q, *J*=7 Hz), 3.9 (2H, d, *J*=6 Hz), 4.1 (2H, q, *J*=7 Hz), 4.7 (1H, s), 7.0 (1H, broad t, *J*=6 Hz); MS (*m/e*): no M$^+$, 174, 131, 130. Found: C, 51.38; H, 8.11; N, 5.77%. Calcd for $C_{10}H_{19}NO_5$: C, 51.50; H, 8.15; N, 6.01%.

Elution was continued using benzene–ethanol (4:1) and a compound was isolated. The structure of this compound has not been determined yet. Final elution with ethanol afforded ammonium bromide (2.3 g, 28%).

*Ethanolysis of 3,6-Diethoxy-2,5-piperazinedione (**3a**).* Compound **3a** (1 g) was refluxed in a 0.5 mol dm^{-3} ethanolic hydrogen bromide solution for 1.5 h. After the usual work-up and column chromatography, 270 mg (31%) of **4** and 230 mg (42%) of **5** were obtained.

*Ethanolysis of Ethyl 2-(Diethoxyacetylamino)-2-ethoxyacetate (**5**).* Compound **5** (1 g) was refluxed in an ethanol solution containing 0.5 mol dm^{-3} hydrochloric acid for 3 h. After the usual work-up and column chromatography, 570 mg (39%) of **4** and unchanged **5** (280 mg, 28%) were obtained.

*Ethanolysis of Ethyl N-(Diethoxyacetyl)glycinate (**6**).* A similar treatment of **6** (450 mg) gave **4** (138 mg, 38%), unchanged **6** (240 mg, 53%), and ethyl glycinate hydrochloride (100 mg, 35%): mp 133—135 °C; IR: 3400, 1750 cm^{-1}; NMR (DMSO-d_6): δ=1.1 (3H, t, *J*=7 Hz), 3.7 (2H, s), 4.1 (2H, q, *J*=7 Hz), 8.4 (2H, s).

*Reaction of the Primary Photoproduct (**2**) with Other Nucleophiles.* The reaction of **2** with methanol (or methanol–pyridine) for 6 h at room temperature gave 3,6-dimethoxy-2,5-piperazinedione (**3b**) in 5% (or 48%) yield; mp 226 °C (dec); IR: 3250, 3180, 1680 cm^{-1}; NMR (DMSO-d_6): δ=3.3 (6H, s), 4.5 (2H, dd, *J*=4 and 1.2 Hz), 8.9 (2H, broad d, *J*=4 Hz); Found: C, 41.38; H, 6.02; N, 16.30%. Calcd for $C_6H_{10}N_2O_4$: C, 41.38; H, 5.75; N, 16.09%.

Similar treatment of **2** with aqueous acetone, acetic acid–triethylamine, and sodium azide yielded 3,6-dihydroxy-, 3,6-diacetoxy-, and 3,6-diazido-2,5-piperazinediones, respectively. 3,6-Dihydroxy-2,5-piperazinedione (**3c**); 22% yield; mp 260 °C (dec); IR: 3380, 3200, 1690 cm^{-1}; NMR (DMSO-d_6): δ=4.6—4.8 (2H, dd, *J*=4 and 1.2 Hz and d, *J*=2 Hz), 5.9 (2H, broad s), 8.3 (1H, broad s), 8.4 (1H, broad d, *J*=4 Hz); Found: C, 32.73; H, 4.29; N, 19.19%. Calcd for $C_4H_6N_2O_4$: C, 32.88, H, 4.11; N, 19.18%. 3,6-Diacetoxy-2,5-piperazinedione (**3d**); 44% yield; mp 185 °C (dec); IR: 3200, 3120, 1760, 1720 cm^{-1}; NMR (DMSO-d_6): δ=2.1 (6H, s), 5.8 (2H, dd, *J*=5 and 1.2 Hz), 9.3 (2H, broad d, *J*=5 Hz), Found: C, 41.77; H, 4.63; N, 11.99%. Calcd for $C_8H_{10}N_2O_4$: C, 41.74; H, 4.35; N, 12.17%. 3,6-Diazido-2,5-piperazinedione (**3e**); 32% yield; mp 168 °C; IR: 3250, 2150, 1700 cm^{-1}; NMR (DMSO-d_6): δ=5.2—5.4 (2H, dd, *J*=4 and 1.2 Hz, and d, *J*=2 Hz), 9.1 (2H, broad s); Found: C, 24.57; H, 2.25; N, 57.08%. Calcd for $C_4H_4N_8O_2$: C, 24.49; H, 2.04; N, 57.14%.

References

1) P. S. Skell and J. C. Day, *Acc. Chem. Res.*, **11**, 381 (1978).

2) P. S. Skell and J. C. Day, *J. Am. Chem. Soc.*, **100**, 1951 (1978).

3) F-L. Lu, Y. M. A. Naguib, M. Kitadani, and Y. L. Chow, *Can. J. Chem.*, **57**, 1967 (1979).

4) A. Sera, H. Yamada, and K. Itoh, *Bull. Chem. Soc. Jpn.*, **53**, 219 (1980).

5) The bromine analysis of **2** (70% purity determined by NMR) showed the presence of two bromine atoms in one molecule of **2** (Found, Br, 50.3%; Calcd, Br, 49.5%). NMR (DMSO-d_6); δ=5.0 (2H, broad s), 8.8 (2H, broad s).

6) For MS analysis, 3,6-dimethoxy-2,5-piperazinedione (**3b**) was employed.

7) *Org. Synth.*, Coll. Vol. IV, 427 (1963).

8) J. A. Pople, W. G. Sneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill, New York (1959), p. 365.

9) J. S. Pizey, "Synthetic Reagents," (1974), Vol. II, p. 1.

10) J. C. Martin and P. D. Bartlett, *J. Am. Chem. Soc.*, **79**, 2533 (1957).