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Photo-induced Alkoxybromination of Olefins by *N,N'*-Dibromo-2,5-piperazinedione

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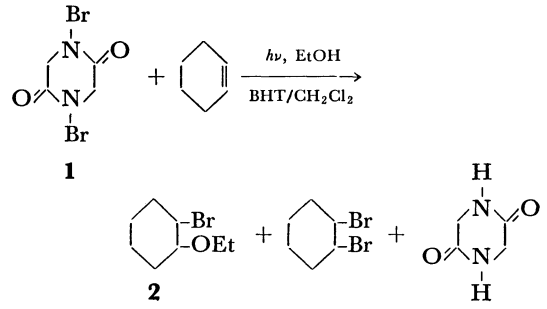
Irradiation of *N,N'*-dibromo-2,5-piperazinedione in dichloromethane in the presence of an alcohol induced alkoxybromination of cyclohexene to give *trans*-1-bromo-2-alkoxycyclohexane in a good yield. The reaction was thought to proceed through an ionic mechanism.

N-Bromosuccinimide(NBS) and related active *N*-halogeno compounds have been prepared and their reactivity has been thoroughly examined.[1] They have been employed as the versatile allylic brominating and oxidizing reagents in many organic syntheses. Although reactions of NBS with simple olefins in water or in acetic acid gave corresponding bromohydrins or bromoacetoxylated compounds, photoreactions of NBS with olefins in aprotic solvents gave exclusively allylic brominated products, 1,2-addition products, and in some instances rearranged products, which were all produced through the well established free radical reaction mechanism. Related reactions of *N*-halogenated amines or imides,[1] sulfoximides,[2,3] have been examined, however, nothing has been investigated on the reaction of *N*-halogeno derivatives of 2,5-piperazinedione, a cyclic anhydride of glycine. This paper concerns with some particular reactions of *N,N'*-dibromo-2,5-piperazinedione (NBP, **1**).

Results and Discussion

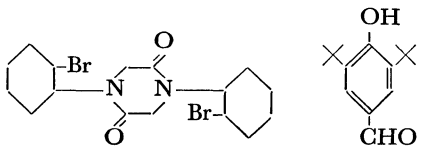
Bromination of 2,5-piperazinedione gave NBP in a good yield. NBP showed free radical reactivities similar to those of NBS. For example, a benzoyl peroxide induced reaction of NBP with cyclohexene in boiling carbon tetrachloride gave 3-bromocyclohexene (70—75%) and a small amount of 1,2-dibromocyclohexane. No *N*-(2-bromocyclohexyl)-2,5-piperazinedione was obtained in this case, while quite recently Skell[4] reported the formation of the corresponding free radical adducts,[5] *N*-(2-halocyclohexyl)succinimide, in a similar reaction of *N*-halosuccinimide with cyclohexene.

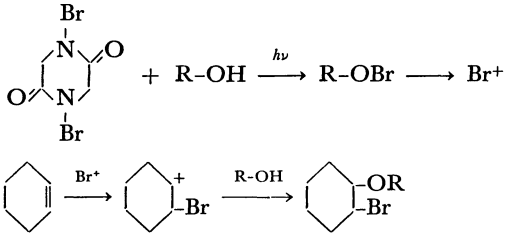
Irradiation of NBP with cyclohexene in dichloromethane[6] gave neither photo-decomposition product nor substitution product in an appreciable amount. In the presence of added ethanol (5 mol equivalent to NBP), however, the reaction gave 3-bromocyclohexene (12%) and *trans*-1-bromo-2-ethoxycyclohexane (37%, **2**). No *cis* isomer was detected (NMR). The stereochemistry of **2** was determined by comparison of its spectral characteristics with those of authentic specimen.[7] An increased yield of **2** was achieved by adding a small amount of a free radical inhibitor, 2,6-di-*t*-butyl-*p*-cresol (BHT, 0.1 mol equivalent to NBP). The free radical inhibitor depressed the formation of 3-bromocyclohexene which was thought to be produced by the free radical mechanism as was observed for the allylic bromination by NBS. Instead, 1,2-dibromocyclohexane was obtained in a considerable yield. This dibromide could be resulted from an addition of bromine which was produced from NBP through an ionic process.[8]



The reaction was examined using variable sets of alcohol–olefin or –vinyl ether pair. The reactivity of the photoalkoxybromination decreased in the order of primary, secondary, and tertiary alcohols (see Table 1). With an increased amount of added ethanol (or by the use of an ethanol as the solvent), **2** was obtained in a nearly quantitative yield. Although the alkoxybromination of olefins was observed in dark conditions,[9] the reaction was actually accelerated by a UV irradiation. A representative case was the bromo-*t*-butoxylation of cyclohexene by NBP–*t*-butyl alcohol, where the irradiation gave a nearly 20-fold yield of 1-bromo-2-*t*-butoxycyclohexane in comparison with that in the dark reaction.

In the cases of less reactive alcohols, isopropyl and *t*-butyl alcohols, small amounts of *N,N'*-bis(2-bromocyclohexyl)-2,5-piperadinedione (**3**) and 2,6-di-*t*-butyl-4-formylphenol (**4**) were isolated in addition to alkoxybromides. The former is one of the free radical reaction products,[10] while the latter is considered to be produced by the oxidation of the free radical inhibitor, BHT.





1-Hexene and 3,4-dihydro-2*H*-pyran were also ethoxy-

TABLE 1. ALKOXYBROMINATION OF OLEFINS BY NBP[a]

Olefins (2 mmol)	ROH, added mmol		Product yields/% Br OR -C-C-	Br Br -C-C-	Others
Cyclohexene		—	0	0	3-bromocyclohexene (trace)
Cyclohexene	EtOH	10[b]	37	trace	3-bromocyclohexene (12%)
Cyclohexene	MeOH	10	73	12	
Cyclohexene	MeOH	10	43	4	(dark reaction)
Cyclohexene	EtOH	10	73	13	
Cyclohexene	EtOH	10	20	0	(dark reaction)
Cyclohexene	EtOH	30	95	5	
Cyclohexene	*n*-BuOH	10	73	17	
Cyclohexene	*i*-PrOH	10	44	32	small amounts of **3** and **4**
Cyclohexene	*t*-BuOH	10	11	11	small amounts of **3** and **4**
Cyclohexene	*t*-BuOH	10	0.6	0	(dark reaction)
1-Hexene	EtOH	10	62[c]	29	
Dihydropyran	EtOH	10	100[d]	0	
t-Bu-CH=CH_2	EtOH	10	11[e]	20	
C_4H_9-O-CH=CH_2	EtOH	10	18[f]	5	small amounts of **3** and **4**

a) Irradiation with 1 mmol of NBP in 5 ml of dichloromethane containing 0.1 mmol of 2,6-di-*t*-butyl-*p*-cresol for 30 min. b) Without 2,6-di-*t*-butyl-*p*-cresol. c) 1-Bromo-2-ethoxyhexane. d) *trans*-3-Bromo-2-ethoxytetrahydropyran. e) 2-Bromo-1-ethoxy-3,3-dimethylbutane. f) 2-Bromo-1-ethoxy-1-butoxyethane.

brominated in the same conditions to give 1-bromo-2-ethoxyhexane and 3-bromo-2-ethoxytetrahydropyran, respectively. These two products were undoubtedly the Markovnikov addition products, and hence the formation of these two products indicated that the reaction should proceed through an ionic mechanism.[11] Accordingly one can assume that the photoreaction of NBP with an alcohol gives an alkyl hypobromite intermediate[12] which in turn decomposes to give bromine cation. An addition of bromine cation to cyclohexene yields a new carbon centered cation. Following reaction of the cation with alcohol finally produces the alkoxybrominated product. Intervention of the alkyl hypobromite or bromine cation in the reaction can rationalize the formation of **4** as a by-product, because Cohen[13] reported that **4** was obtained from 2,6-di-*t*-butyl-*p*-cresol by treatment with bromine in *t*-butyl alcohol or acetic acid. The photoethoxybromination of *t*-butylethylene gave 2-bromo-1-ethoxy-3,3-dimethylbutane which was seemingly an *anti*-Markovnikov adduct. However, this observation implied the intervention of an intermediate bridged bromonium cation[14] on which a nucleophilic attack of ethanol occurred from less hindered site.[15] Photoreactions with electron poor olefins (methyl acrylate, stilbene *etc.*) gave little or no alkoxybromides, but yielded dibromides exclusively. In the photo-induced ionic addition of alcohols, Marshall[16] reported that cyclohexenes and cycloheptenes showed marked reactivities to give Markovnikov addition products. As seen in the Table, cycloolefins (cyclohexene and 3,4-dihydro-2*H*-pyran) gave alkoxybromides in higher yield than corresponding acyclic olefins (1-hexene and vinyl ether) did. All of these results agree the proposed ionic addition mechanism where the electrophilic attack of bromine cation plays a key role in determining regioselectivity of the reaction.

Experimental

The olefins used were dried over Molecular Sieves 4A and distilled over copper chloride(I) prior to use. Alcohols were dried over Molecular Sieves 4A and distilled. Dichloromethane was washed successively with sulfuric acid, sodium hydroxide solution and water, dried over calcium chloride and distilled. IR and NMR spectra were measured on a JASCO IRA-1 and a JEOL JNN-PMX 60 spectrometers, respectively. GLC analysis was carried out by a Hitachi Model 063; column (1 m×3 mm); A, 10% Carbowax 20 M on 60—80 mesh Shimalite W; B, 15% Diethylene Glycol Succinate Polyester on 60—80 mesh Chromosorb W. All irradiations were conducted through a Pyrex filter using an Ushio Model UI-501e high-pressure mercury lamp (500 W).

Preparation of NBP:[17] To a solution of 3.5 g of sodium carbonate in 100 ml of water was added 3.3 g of 2,5-piperazinedione. The mixture was stirred as bromine was added dropwise. After the reaction mixture had been stirred for 2 h, the pale yellow solid was collected by filtration, washed with water, and dried under vacuum. Yield, 5.7 g, white powder, recrystallizable from hot pyridine; insoluble in carbon tetrachloride, dichloromethane, acetone, benzene; slightly soluble in ethanol, acetonitrile, DMF and DMSO.

NBP–Cyclohexene–Ethanol Reaction. The typical experimental procedure employed in all the reactions is described. Irradiation of a mixture[6] containing 272 mg (1 mmol) of NBP, 164 mg (2 mmol) of cyclohexene, 461 mg (10 mmol) of ethanol, 22 mg (0.1 mmol) of BHT in 5 ml of dichloromethane was carried out under stirring at ambient temperature for 30 min. The products were determined by GLC using methyl benzoate as the internal standard. The reaction mixtures (3—4 runs) were combined, and after removal of solvent, the products were separated on a silica-gel column (benzene→benzene:ethyl acetate/4 : 1). 1,2-Dibromocyclohexane: liquid; NMR (CCl_4) δ=4.40 (2H, s), 1.0—2.8 ppm (8H, m); IR, ν_{C-Br} 680 cm^{-1}. *trans*-1-Bromo-2-ethoxycyclohexane: MS, *m/e*, 208 and 206 (M^+), 127, 81 57; NMR (CCl_4) δ=1.14 (3H, t), 3.48 (2H, q),

3.1—3.5 (1H, m), 3.6—4.1 (1H, m), 1.0—2.5 ppm (8H, m): IR, ν_{C-O} 1110, ν_{C-Br} 690 cm^{-1}. The stereochemistry of the products was determined to be *trans* judging from comparison with the authentic specimen.

NBP–Cyclohexene–t-BuOH Reaction. Irradiation of a mixture[6] containing 272 mg (1 mmol) of NBP, 164 mg (2 mmol) of cyclohexene, 741 mg (10 mmol) of *t*-butyl alcohol, 22 mg (0.1 mmol) of BHT in 5 ml of dichloromethane was carried out as above. The products: 1-Bromo-2-*t*-butoxycyclohexane: NMR (CCl_4) δ=1.20 (9H, s), 3.1—3.5 (1H, m), 3.7—4.0 (1H, m), 1.0—2.5 ppm (8H, m); IR, ν_{C-O} 1100, ν_{C-Br} 690 cm^{-1}. *N,N'*-Bis(2-bromocyclohexyl)-2,5-piperadinedione: mp 211.2—211.5 °C; NMR ($CDCl_3$) δ= 1.1—2.6 (16H, m), 3.90 (4H, s), 3.9—4.5 (4H, m); IR, $\nu_{C=O}$ 1680, ν_{C-N} 1080, ν_{C-Br} 680 cm^{-1}. 2,6-Di-*t*-butyl-4-formylphenol: mp 191.5—192.5 °C (Ref.[18] mp 189—190 °C); NMR (CCl_4) δ=1.50 (18H, s), 5.72 (1H, s), 7.60 (2H, s), 9.71 (1H, s); IR, ν_{O-H} 3440, ν_{C-H} 2810 and 2730, $\nu_{C=O}$ 1665, ν_{C-O} 1100 cm^{-1}.

Products from Other Reactions: *trans*-1-Bromo-2-methoxycyclohexane: NMR (CCl_4) δ=3.35 (1H, s), 3.1—3.5 (1H, m), 3.7—4.1 (1H, m), 1.0—2.5 ppm (8H, m); IR, ν_{C-O} 1110, ν_{C-Br} 690 cm^{-1}.

trans-1-Bromo-2-isopropoxylcycloxane: NMR(CCl_4) δ= 1.12 (6H, dd), 3.67 (1H, m), 3.1—3.5 (1H, m), 3.7—4.0 (1H, m), 1.0—2.5 ppm (8H, m); IR, ν_{C-O} 1110, ν_{C-Br} 680 cm^{-1}.

trans-1-Bromo-2-butoxycyclohexane: NMR (CCl_4) δ=0.95 (3H, t), 1.0—2.5 (4H, m), 3.44 (3H, t), 3.1—3.5 (1H, m), 3.7—4.1 (1H, m), 1.0—2.5 ppm (8H, m); IR, ν_{C-O} 1110, ν_{C-Br} 690 cm^{-1}.

1-Bromo-2-ethoxyhexane: NMR (CCl_4) δ=1.13 (3H, t), 3.45 (2H, q), 3.2—3.4 (2H, m), 3.5—4.0 (1H, m), 1.03 (3H, t), 0.6—2.1 ppm (6H, m); IR, ν_{C-O} 1100, ν_{C-Br} 670 cm^{-1}.

trans-3-Bromo-2-ethoxytetrahydropyan: NMR (CCl_4) δ= 1.18 (3H, t), 3.63 (2H, q), 3.7—4.1 (1H, m), 4.50 (1H, d), 3.2—4.1 (2H, m), 1.2—2.7 ppm (4H, m); IR, ν_{C-O} 1100, ν_{C-Br} 670 cm^{-1}.

2-Bromo-1-ethoxy-3,3-dimethylbutane: NMR (CCl_4) δ= 1.17 (3H, t), 3.42 (2H, q), 3.62 (2H, dd), 3.82 (1H, t), 1.07 ppm (9H, s); IR, ν_{C-O} 1110, ν_{C-Br} 660 cm^{-1}.

(2-Bromo-1-ethoxyethyl)benzene: NMR (CCl_4) δ=1.16 (3H, t), 3.30 (2H, q), 3.28 (2H, d), 4.30 (1H, t), 7.08 ppm (5H, s); IR, ν_{C-O} 1120, ν_{C-Br} 690 cm^{-1}.

2-Bromo-1-ethoxy-1-butoxyethane: NMR (CCl_4) δ=1.16 (3H, t), 3.48 (2H, q), 3.22 (2H, d), 4.53 (1H, t), 1.06 (3H, t), 0.7—2.1 ppm (6H, m); IR, ν_{C-O} 1120, ν_{C-Br} 680 cm^{-1}.

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11) While the free radical addition of methyl hypobromite to 1-hexene gave 2-bromo-1-methoxyhexane as the main adduct (85%), the reaction under ionic condition gave 1-bromo-2-methoxyhexane in 71% yield; V. L. Heasley, C. L. Frye, G. E. Heasley, K. A. Martin, D. A. Redfield, and P. S. Wilday, *Tetrahedron Lett.*, **1970**, 1573.
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