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Addition Reaction of 1,4-Dibromo-2,5-piperazinedione with 3,4-Dihydro-2*H*-pyran

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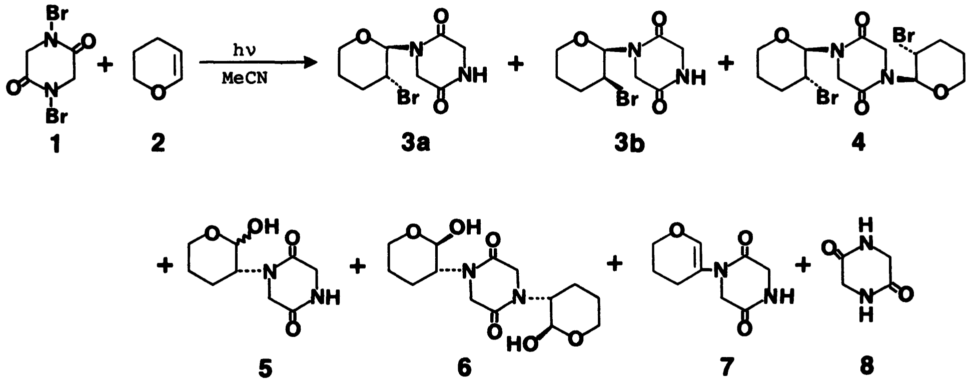
Reaction of 1,4-dibromo-2,5-piperazinedione (**1**) with 3,4-dihydro-2*H*-pyran (**2**) under irradiation gave 1 : 1- and 1 : 2-addition products (**3**,**4**) and corresponding secondary products (**5**—**7**). The adducts were considered to be produced separately by photoinduced free radical addition as well as concomitant ionic addition reactions.

Reactions of *N*-bromosuccinimide (NBS) with olefins are characterized as allylic brominations and additions to double bonds.[1] The majority of the NBS-reactions have been postulated to involve a free radical chain mechanisms, though different chain transfer species participate: a bromine atom[1] or a succinimidyl radical[2–4] according to the reaction conditions. Incremona and Martin[5] however, claimed that reactions of *N*-bromotetrafluorosuccinimide (NBTFS) with olefins were considerably different from those of NBS, and proposed an ionic reaction pathway for these reactions. The ionic reactivity of NBTFS was attributed to the electron-withdrawing inductive effect of the fluorine substituent of NBTFS. We have reported that irradiation of 1,4-dibromo-2,5-piperazinedione (**1**) with cyclohexene or 1-alkenes in acetonitrile gave addition products produced by a free radical mechanism. The reactions were rationalized by taking into account an initial attack of the 2,5-dioxo-1-piperazinyl radical in the olefinic double bonds to give stable radical intermediates.[6,7] However, minor intervention of a concomitant ionic addition mechanism could not be ruled out. In this paper, we describe the reaction of **1** with 3,4-dihydro-2*H*-pyran (**2**) which is more susceptible to ionic addition reactions than cyclohexene or 1-alkenes. The addition reaction of **1** to **2** was suggested to proceed by two pathways, a free radical and an ionic process, to give two types of addition products, respectively.

Results and Discussion

The photoreaction of 1,4-dibromo-2,5-piperazinedione (**1**) with 3,4-dihydro-2*H*-pyran (**2**) was carried out in acetonitrile using a high pressure mercury lamp. The photolysate was separated by silica-gel column



Scheme 1.

Table. Product Distribution of Addition of 1,4-Dibromo-2,5-piperazinedione (**1**) to 3,4-Dihydro-2*H*-pyran (**2**) in Acetonitrile under Irradiation[a)]

Entry	1,2-Epoxybutane	Temperature	Reaction	Yield/%[b)]						
	mmol		time/h	**3a**	**3b**	**4**	**5**	**6**	**7**	**8**
1	—	Room temp	3	Trace						44
2	40	Room temp	3	8	4	2	7	8	9	42
3[c)]	40	Room temp	3	9	5	2	3	4	5	51
4	40	0°C	3	7	4	4	12	12	15	32
5[d)]	40	Room temp	3	5	2	Trace			2	75[e)]
6[d)]	40	Room temp	24	15	7	6	2	2	4	55

a) A solution of **1** (10 mmol) and **2** (100 mmol) in acetonitrile (50 cm^3) was irradiated in the presence of the addendum given in the Table. b) Isolated yields are given as averages of three experiments, and on the basis of **1** employed. c) In the presence of hydroquinone (2 mmol). d) Under dark conditions. e) Contained a considerable amount of **1**.

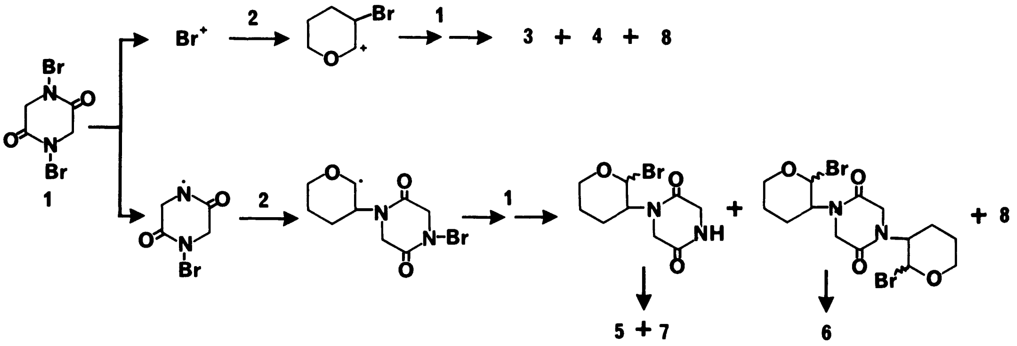
chromatography and the structures of the products were determined by elemental and spectroscopic analyses. The results are summarized in Table.

Irradiation of **1** with **2** in acetonitrile gave only 2,5-piperazinedione (**8**) as an isolable product accompanied by a large amount of polymeric products. The dione **8** was derived from **1** by either hydrogen abstraction of the 2,5-dioxo-1-piperazinyl radical intermediate or protonation on the corresponding anion.[6] The polymeric products may come from **2** via the well-known acid catalyzed polymerization. When the reaction was performed in the presence of 1,2-epoxybutane (a hydrogen bromide scavenger), the formation of the polymers was greatly depressed. In the presence of 1,2-epoxybutane, the reaction gave a considerable amount of addition products (Scheme 1). These adducts consisted of bromine-containing 1:1- and 1:2-adducts (**3** and **4**), hydroxyl group-containing 1:1- and 1:2-adducts (**5** and **6**). A substituted 3,4-dihydro-2*H*-pyran (**7**) was also produced. The bromine-containing 1:1-adduct (**3**) was rechromatographed to give isomers **3a** and **3b** (approx. 2:1).

Both **3a** and **3b** had a bromine substituent (MS), and an NH group (IR and NMR). They gave similar NMR and IR spectra which demonstrated the presence of a 2,5-dioxo-1-piperazinyl group at C_1 of the respective tetrahydropyran ring. That is, both adducts showed characteristic infrared absorptions (1690, 1445—1460, 1190—1215 cm^{-1}) of a 2,5-piperazinedione moiety, and their NMR spectra showed signals of protons on bromine-bearing carbon atoms (C_2 of the tetrahydropyran ring) [**3a**; δ=4.0—4.6, m, and **3b**; δ=4.56, br.], and those on C_1 of the tetrahydropyran ring [**3a**; δ=5.43, d, J=10 Hz (axial-H_1/axial-H_2), and **3b**; δ=5.19, J=2 Hz (axial-H_1/equatorial-H_2)]. Treatment of **3a** and **3b** with tributyltin hydride led to the same reduced product, 1-(2-tetrahydropyranyl)-2,5-piperazinedione. This observation indicated that these two 1:1-adducts are a pair of stereoisomers at the bromine-bearing carbon atom. From these results, the stereochemistry was deduced as trans for the major isomer **3a** and cis for the minor isomer **3b**.[8] The bromine containing 1:2-adduct (**4**) bore two bromine atoms (MS), and showed no NH absorption on its IR spectrum. The features of the NMR spectra of **4** were similar to those of **3a**. Thus the structure of **4** was determined as *trans,trans*-1,4-bis(3-bromo-2-tetrahydropyranyl)-2,5-piperazinedione. Neither the trans, cis, nor the cis, cis isomer was isolated.

On the other hand, the adducts **5** and **6** were determined to be 3-substituted 2-hydroxytetrahydropyran derivatives by the following spectroscopic analysis. The presence of hydroxyl groups in **5** and **6** was characterized by their IR absorption (ν_{OH} 3400 cm^{-1}) and MS peaks (M^+-H_2O and M^+-2H_2O). The adduct **5** consisted of two isomers; which were hardly separated on TLC. The NMR spectra of **5** showed complex signals indicating that it contained two configurational isomers. That is, there were two hemiacetal hydroxylic groups at δ=6.29 (a doublet, coupled with an adjacent methine proton with J=4.5 Hz) and at δ=6.42 (another doublet, coupled with another adjacent methine proton with J=6 Hz). Two respective hemiacetal methine protons were also observed at δ=4.79 (dd, J=2 and 4.5 Hz) and at δ=4.57 (dd, J=6 and 8 Hz). The former was presumed to be an equatorial hemiacetal methine proton and the latter to be an axial hemiacetal methine proton, and their coupling constants indicated the presence of axial protons on C_2, to which an equatorial 2,5-piperadinedione moiety was attached. The NMR spectra also indicated a hemiacetal structure for the 1:2-adduct **6**. The methine protons resonated at δ=4.70 as a double doublet with J=6 and 12 Hz, which may be assigned to axial protons on C_1 with adjacent axial protons on C_2 as mentioned above. The spectra of **7** were also found to be consistant with the structure given in Scheme 1.

The position of the bromine substituent(s) of the bromine-containing adducts (**3** and **4**) suggested that a species to attack the double bond of **2** was either a bromine cation to give a 3-bromo-1-tetrahydropyranyl cation, or a bromine radical to give a corresponding radical. In the presence of hydroquinone, the reaction gave **3** and **4** in almost unchanged yields, while the yields of **5**—**7** were considerably depressed. In addition, the reactions in the dark[9] afforded **3** and **4** in increased yields, while **5**—



Scheme 2.

7 in highly decreased yields. These observations may rule out the radical addition mechanism for the formation of **3** and **4**. Thus the bromine cation produced by heterolysis of the N–Br bond of **1** added to **2** to give the 3-bromo-1-tetrahydropyranyl cation, which in turn reacted with the 2,5-dioxo-1-piperazinyl anion to afford the adducts **3** and **4**. In the reaction of **1** with cyclohexene in acetonitrile under similar conditions, 2-acetylamino-1-bromocyclohexane was isolated. This was thought to be derived by a Ritter-type addition of the 2-bromocyclohexyl cation to acetonitrile.[6] However, in the present reactions, no 2-acetylamino-3-bromotetrahydropyran, a corresponding Ritter-type product, was detected.

On the other hand, the hydroxyl group-containing adducts (**5** and **6**), and the dihydropyran derivative (**7**) were presumed to be secondary products derived from other bromine-containing adducts produced through a radical addition of **1** to **2**. We had previously shown that the radical reactions of **1** with cyclohexene and 1-alkenes revealed a solvent dependent product distributions.[6,7] In carbon tetrachloride, which is a poor solvent for **1** (under essentially heterogeneous conditions), allylic bromination and bromine addition to the double bonds were the dominant processes. Contrarily, in acetonitrile (a good solvent for **1**) the radical addition of **1** to the double bonds became the main reaction path, in which the 2,5-dioxo-1-piperazinyl radical added initially to the less substituted carbon atoms of the respective double bonds to give more stable radical intermediates.[7] Tedder and Walton[10] reported that addition of a radical to a vinyl ether gave preferentially a 1-alkoxy-1-alkyl radical. Accordingly, a primary radical expected from addition of the 2,5-dioxo-1-piperazinyl radical to **2** should be a 3-(4-bromo-2,5-dioxo-1-piperazinyl)-2-tetrahydropyranyl radical. The radical thus formed would abstract a bromine atom from **1** to give 1-(2-bromo-3-tetrahydropyranyl)-2,5-piperazinedione (not isolated). 1,4-Bis(2-bromo-3-tetrahydropyranyl)-2,5-piperazinedione (not isolated) woubd be produced in a similar manner. We had observed previously that 1- and 1,4-bis(2-bromoalkyl)-2,5-piperazinediones are spontaneously hydrolyzed during chromatographic separation to give corresponding 2-hydroxyalkyl derivatives.[7] Participation of the neighboring N-function was responsible for the observed ease of hydrolysis. In the present cases, the bromine substituents of the above mentioned bromotetrahydropyranyl-2,5-piperazinediones were undoubtedly more easily hydrolyzed to give **5** and **6**, because of the hemiacetal character of the bromine-bearing carbon atoms. The substituted 3,4-dihydro-2*H*-pyran (**7**) was considered to be formed by concomitant dehydrobromination of 1-(2-bromo-3-tetrahydropyranyl)-2,5-piperazinedione.

It was suggested that in the reaction of 1,4-dibromo-2,5-piperazinedione (**1**) with 3,4-dihydro-2*H*-pyran (**2**) the two processes, the radical addition and the ionic addition, were operating concurrently to give the corresponding adducts (Table). In dark conditions, the ionic addition predominated, but the radical addition was not completely depressed. Hydroquinone decreased the yields of the radical addition products, whereas those of the ionic addition products remained unchanged. Low temperature seemed to favor the radical addition process as described in the case of NBS.[4]

Experimental

3,4-Dihydro-2*H*-pyran and 1,2-epoxybutane were dried over Molecular Sieve 4A and distilled over copper(I) chloride prior to use. Acetonitrile was dried over calcium hydride and distilled. 1,4-Dibromo-2,5-piperazinedione was prepared according to the procedure reported earlier.[11] IR spectra (KBr) were recorded with JASCO IR-A-1 and -3 spectrometers. NMR spectra were measured on JEOL JMN-PMX-60 and-PS-100 specrometers using tetramethylsilane as the internal standard. Mass spectra were obtained by an ESCO EMD-05A spectrometer. Irradiation was carried out using a Halos EHB-WU high pressure mercury arc lamp (100 W).

Reaction of 1,4-Dibromo-2,5-piperazinedione (1) with 3,4-Dihydro-2*H*-pyran (2) in the Presence of 1,2-Epoxybutane. A typical experimental procedure is described. Irradiation of a mixture containing 2.72 g (10 mmol) of **1**, 8.41 g(100 mmol) of **2**, and 1,2-epoxybutane (2.88 g, 40 mmol) in acetonitrile (50 cm^3) was carried out for 3 h at room temperature with stirring. The resulted mixture was filtered to give 2,5-piperazinedione (**8**). The filtrate was evaporated to a syrup, which was separated on a silica-gel column using benzene–acetone (4:1) as eluant. Yields are given in Table as an average of three experiments on the basis of **1** employed. Physical constants of respective products are shown below.

***trans*-1-(3-Bromo-2-tetrahydropyranyl)-2,5-piperazinedione (3a):** Mp 195 °C (decomp). IR; 3200, 1690, 1450, 1330, 1215, 1060, and 720 cm^{-1}. ^{1}H NMR (DMSO-d_6); δ=1.4—2.3 (4H, m, -(CH$_2$)$_2$-), 3.4—4.3 (2H, m, O-CH$_2$-), 3.77 (4H, s, ring H), 4.0—4.6 (1H, m, -CHBr-), 5.43 (1H, d, *J*=10 Hz, O-CH-N), and 8.00 (1H, s, NH). MS (*m/z*); 278, 276(M$^+$), 197, 169, 115, and 114. Found: C, 39.04; H, 4.67%. Calcd for $C_9H_{13}BrN_2O_3$; C, 39.01; H, 4.73.

***cis*-1-(3-Bromo-2-tetrahydropyranyl)-2,5-piperazinedione (3b):** Mp 175 °C (decomp). IR; 3200, 1690, 1670, 1460, 1320, 1205, 1080, and 760 cm^{-1}. ^{1}H NMR (DMSO-d_6); δ=1.3—2.4 (4H, m, -(CH$_2$)$_2$-), 3.4—4.3 (2H, m, O-CH$_2$-), 3.79—3.91 (centers) (2H, AB-quartet, *J*=2 Hz, ring H), 4.56 (1H, broad, -CHBr-), 5.19 (1H, d, *J*=2Hz, O-CH-N), and 7.97 (1H, s, NH). MS (*m/z*); the same as those of **3a**. Found: C, 39.05; H, 4.84%. Calcd; see above.

1,4-Bis(3-bromo-2-tetrahydropyranyl)-2,5-piperazinedione (4): Mp 185 °C (decomp). IR; 1690, 1445, 1310, 1190, 1060, and 710 cm^{-1}. ^{1}H NMR (DMSO-d_6); δ=1.5—2.8 (8H, m, -(CH$_2$)$_2$-), 3.4—3.8 (4H, m, O-CH$_2$-), 3.95 (4H, s, ring H), 4.0—4.6 (2H, m, -CHBr-), and 5.42 (2H, d, *J*=9 Hz, O-CH-N). MS (*m/z*); 442, 440, 438(M$^+$), 361, 359, 240, 197, 165, 112, and 111. Found: C, 38.30; H, 4.86%. Calcd for $C_{14}H_{20}Br_2N_2O_4$; C, 38.21; H, 4.58%.

1-(2-Hydroxy-3-tetrahydropyranyl)-2,5-piperazinedione (5): Mp 162—164 °C. IR; 3400, 3200, 1635, 1460, 1325, and 1060 cm^{-1}. ^{1}H NMR (DMSO-d_6); δ=1.2—2.1 (4H, m, -(CH$_2$)$_2$-), 3.2—4.3 (2H, m, O-CH$_2$-), 3.69 (2H, s, ring H), 3.74 (2H, AB quartet, J=4 Hz, ring H), 4.0—4.3 (1H, m, -CH-N), 4.57 and 4.79 (1H, two dd, J=6 and 8 Hz; 2 and 4.5 Hz, -CH-OH), 6.29 and 6.42 (1H, two d, J=4.5 and 6 Hz, OH), and 7.85 (1H, s, NH).. MS (m/z); 196 (M$^+$—H$_2$O), 166, 112, 84, and 56. Found: C, 50.36; H, 6.74%. Calcd for $C_9H_{14}N_2O_4$; C, 50.46; H, 6.59%.

1,4-Bis(2-hydroxy-3-tetrahydropyranyl)-2,5-piperazinedione (6): Mp 185 °C (decomp). IR; 3400, 3230, 1670, 1460, 1325, and 1060 cm^{-1}. ^{1}H NMR (DMSO-d_6); δ=1.1—2.2 (8H, m, -(CH$_2$)$_2$-), 3.3—4.3 (4H, m, O-CH$_2$-), 3.83 (4H, s, ring H), 4.0—4.3 (2H, m, -CH-N), and 4.70 (2H, dd, J=6 and 12 Hz, -CH-OH). MS (m/z); 296 (M$^+$—H$_2$O), 278 (M$^+$—2H$_2$O), 196, 166, 112, 84, 56. Found: C, 53.19; H, 6.75%. Calcd for $C_{14}H_{22}N_2O_6$; C, 53.49; H, 7.05%.

1-(3,4-Dihydro-2*H*-pyran-5-yl)-2,5-piperazinedione (7): Mp 210 °C (decomp). IR; 3220, 1660, 1460, 1325, and 1090 cm^{-1}. ^{1}H NMR (DMSO-d_6); δ=1.5—2.4 (4H, m, -(CH$_2$)$_2$-), 3.73 (2H, d, J=1 Hz, ring H), 3.90 (2H, s, ring H), 3.7—4.0 (2H, m, O-CH$_2$-), 6.49 (1H, t, J=1 Hz, O-CH=), and 7.49 (1H, s, NH). MS (m/z), 196(M$^+$), 166, 112, and 84. Found; C, 54.83; H, 6.25%. Calcd for $C_9H_{12}N_2O_3$; C, 55.09; H, 6.16%.

Reduction of 1,4-Bis(3-bromo-2-tetrahydropyranyl)-2,5-piperazinedione (4) with Tributyltin Hydride. The compound **4** (108 mg, 0.24 mmol), tributyltin hydride (180 mg, 0.62 mmol), and AIBN (20 mg) were dissolved in 50 cm^3 of benzene, and the mixture was kept in an atmosphere of nitrogen at 80 °C for 3 h. The solvent was evaporated off and the residue was chromatographed on a silica-gel column using benzene-acetone (4:1) to give 1,4-bis(2-tetrahydropyranyl)-2,5-piperazinedione in 75% yield: Mp 138—140 °C. IR: 1670, 1470, 1330, 1200, 1180, and 1080 cm^{-1}. ^{1}H NMR (CDCl$_3$); δ=1.3—2.1 (12H, m, -(CH$_2$)$_3$-), 3.3—4.3 (4H, m, O-CH$_2$-), 3.92 (4H, d, J=3 Hz, ring H), and 5.40 (2H, t, J=6 Hz, O-CH-N). MS (m/z); 282(M$^+$), 199, 115, 114, and 85. Found: C, 59.20; H, 8.00%. Calcd for $C_{14}H_{22}N_2O_4$; C, 59.56; H, 7.85%.

From 1-(3-bromo-2-tetrahydropyranyl)-2,5-piperazinedione (**3a** and **3b**) 1-(2-tetrahydropyranyl)-2,5-piperazinedione was produced. Mp 183—185 °C. IR; 3220, 1700, 1660, 1320, 1200, 1050, and 730 cm^{-1}. ^{1}H NMR (CDCl$_3$); δ=1.2—2.2 (6H, m, -(CH$_2$)$_3$-), 3,5—4.4 (2H, m, O-CH$_2$-), 3.95 (4H, s, ring H), 5.45 (1H, t, J=5 Hz, O-CH-N), and 7.20 (1H, s, NH). MS (m/z); 198(M$^+$), 169, 115, 114, and 85. Found: C, 54.40; H, 7.18%. Calcd for $C_9H_{14}N_2O_3$; C, 54.53; H, 7.12%.

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