91.60; H, 5.49. Found: C, 91.80; H, 5.45.

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Registry No. 1, 7512-20-1; 2, 72948-52-8; 3a, 79916-87-3; 3b, 79916-88-4; 4a, 79916-89-5; 4b, 79916-90-8; 5a, 79916-91-9; 5b, 79916-92-0; 6a, 79916-93-1; 6b, 79916-94-2; 9-anthraldehyde, 642-31-9.

Bromine Chloride from *N*-Chlorosuccinimide Oxidation of Bromide Ion. Electrophilic Addition Reactions in Protic and Aprotic Solvents

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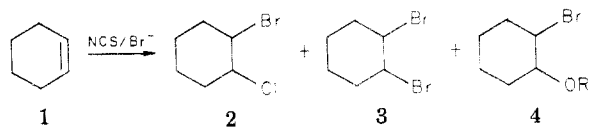
Bromine chloride can be prepared by condensing chlorine gas into liquid bromine.[2] However, applications of this method of bromine chloride formation to millimolar or smaller scale reactions is limited because of the difficulty in quantitating the amounts of each halide added. Bromine chloride may presumably by formed more conveniently from the reaction of compounds containing electrophilic halogens (Br^+ or Cl^+) and the appropriate halide ion.[3] Surprisingly, very few investigations of this method of bromine chloride formation have been reported in the literature.[4,5]

A desire to explore methods of generating electrophilic brominating agents in situ[6] led to an investigation of the formation of bromine chloride from *N*-chlorosuccinimide (NCS) and bromide ion. We now report on the reaction products obtained from the reaction of cyclohexene with what appears to be bromine chloride[7] formed from NCS and lithium bromide in a variety of solvents.

Results and Discussion

Reaction of cyclohexene 1 with NCS/Br^- in aprotic solvents at room temperature yielded two major addition products. These reaction products were shown to be 1-bromo-2-chlorocyclohexane (2) and 1,2-dibromocyclohexane (3) by gas chromatography/mass spectrometric analysis. Reaction of 1 in protic solvents also yielded 2 and 3; however, the major product was that of the addition of one bromine atom and a molecule of solvent, 4. As



1 2 3 4

Table I. Cyclohexene Addition Products[a]

	% composition[b]			
solvent	2	3	4	other
MeOH[c]	5.3	7.4	86.3	1.0
MeOH[d]	18.5	22.1	57.9	1.4
EtOH[c]	13.4	10.5	75.3	0.8
EtOH[d]	36.3	30.3	31.7	1.7
CH_3CN[c]	25.4	55.8		18.8
CH_3CN[d]	39.5	59.3		1.2
THF[c]	63.5	21.1		15.3
THF[d]	75.6	22.3		2.1
DME[c]	74.1	13.2		12.7
DME[c]	66.4	30.4		3.2

[a] Composition determined by GC analysis. [b] Values not corrected for FID response factors. [c] Concentration of NCS and $Br^- \cong 6 \times 10^{-2}$ M. [d] Concentration of NCS and $Br^- \cong 6 \times 10^{-1}$ M.

might be expected, a change in the concentration of reactants in solution changed the relative proportions of products observed (Table I). An increase in the concentration of reactants in protic solvents increased the percentage of 2 and 3 and decreased the percentage of 4. This is what might be expected for a reaction which involved a bromonium ion intermediate, where an increase in reactant concentration increases the availability of halogen anion for attack of the brominium ion. Likewise, an increase in the concentration of reactants in aprotic solvents also increased the percentage of 2 and 3 present. In these examples however, the increases observed were accompanied by a decrease in the amount of products other than 2 and 3.[8] Hageman and Havinga[4] have demonstrated that the reaction of bromine chloride with substituted cyclohexenes in methylene chloride yields the trans diaxial addition products. Although different solvents were used in this investigation, the same stereochemical and regiochemical reaction course would be expected.

None of the dichloride addition product was detected by GC/MS analysis of the product mixtures. In contrast to this, Beger and Thielmann[9] found that the reaction of cyclopentene with bromine chloride gave approximately equal quantities of dibromo adduct and dichloro adduct in both methylene chloride and methanol. the presence of equal quantities of dibromo and dichloro addition products in that investigation can be readily explained by the disproportionation of BrCl in solution (eq 1).[10] However, to explain the substantial amounts of dibromo adduct 3 and total absence of dichloro adduct observed in this investigation, it must be assumed that if BrCl is formed, it does not disproportionate under the reaction conditiions employed. Since BrCl is stabilized by an association of chloride ions in solution (eq 2),[11] it can be surmised that other anionic species such as bromide ions (eq 3) or the nitrogen anion of succinimide might also have the same effect. Evidence for such in situ stabilization of BrCl can be obtained from an investigation by de la Mare and Galandauer[12] where BrCl (from Br_2 and Cl_2) was added to propene in 1 M HCl. In their investigation they also observed no dichloro adduct. Additionally, Surles and Popov[13] have noted the stabilization of BrCl with nitrogen

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(4) Hageman, H. J.; Havinga, E. *Recl. Trav. Chim. Pays-Bas* **1966**, *85*, 1141-1150.
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(6) Our interest was in finding methods which could be applied to radiobrominations. Radiobromine is obtained as bromide, and its conversion to an electrophilic brominating agent in situ is the most convenient and yields the highest radiochemical yields.
(7) It can only be presumed that bromine chloride is formed in situ. However, the fact that the reaction solution turns to a deep yellow-orange color when NCS and bromide are mixed might be taken as evidence for the presence of dihalide.
(8) Several minor peaks were observed in most chromatograms. Although these peaks were not identified, they had retention times identical with those observed in the reaciton of NCS and cyclohexene.
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Table II. Variance of Reactant Ratios[a]

reactants	ratio	% composition[b] 2	3	4
(MeOH)				
NCS/LiBr	1:1	18.8	22.4	58.8
NCS/LiBr	1.5:1	17.2	28.4	54.4
NCS/LiBr	1:1.5	17.7	42.7	39.6
NCS/LiBr/LiCl	1:1:1	32.1	17.2	50.7
(THF)				
NCS/LiBr	1:1	75.6	22.3	
NCS/LiBr	1.5:1	79.2	20.8	
NCS/LiBr	1:1.5	44.2	55.8	
NCS/LiBr/LiCl	1:1:1	85.9	14.1	

[a] All reactions are with cyclohexene at concentration of $\sim 6 \times 10^{-1}$ M. [b] Only percent of 2:3:4 is shown here for comparison purposes; some starting material remained and some unidentified products were present.

heterocycles. An association of bromide ion with BrCl could potentially produce Br_2 in solution (eq 4), but irre-

$$2BrCl \rightleftarrows Br_2 + Cl_2 \quad (1)$$

$$BrCl + Cl^- \rightleftarrows BrCl_2^- \quad (2)$$

$$BrCl + Br^- \rightleftarrows Br_2Cl^- \quad (3)$$

$$Br_2Cl^- \rightleftarrows Br_2 + Cl^- \quad (4)$$

spective of the electrophilic brominating species the most likely reaction path for the formation of dibromide product is attack of bromide ion on a bromonium ion intermediate. The amount of dibromide product 3 observed should therefore be dependent upon the concentration of bromide ion in solution.

To further investigate the participation of halide ions in the product ratios obtained, we carried out several reactions in which the stoichiometry of reagents was no longer unity and in which 1 equiv of lithium chloride had been added (Table II). The results of these experiments clearly indicate that the anion concentration can drastically alter the product composition. Importantly, no significant change in the ratio of products was observed when the amount of NCS was increased, while additional LiBr increased the amount of dibromo product, 3, and addition of LiCl increased the quantity of bromine chloride adduct 2.

Experimental Section

All chemicals used were at least analytical reagent grade and were used as obtained. Reaction mixtures were analyzed by GLC performed on a Varian 3700 gas chromatograph using FID detection coupled to a Spectra Physics 4100 integrator/plotter. Separations were accomplished on a 50-m SE-30 capillary column (J&W), using a temperature program of 40 °C (3 min) to 210 °C at 20 °C/min. Analysis of peak composition was accomplished on a Hewlett-Packard 5984 GC/MS DS system with a 30-m SE-30 capillary column (J&W) using a temperature program of 80 °C (2 min) to 250 °C at 16 °C/min. The following m/e values were observed: 2, 196 (1.2), 198 (1.4), 200 (0.3); for 3, 240 (0.7), 242 (1.5), 244 (0.7); for 4 (MeOH), 192 (11.2), 194 (11.4); and for 4 (EtOH), 206 (11.4), 208 (11.3).

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Registry No. 1, 110-83-8; bromine chloride, 13863-41-7; NCS, 128-09-6; Br^-, 24959-67-9.

A-Ring Bromination of Estradiol and 17α-Ethynylestradiol with *N*-Chlorosuccinimide and Bromide Ion. Possible Evidence for Hypobromite Intermediates

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A-ring radiobrominated estrogens may have applications in the detection and/or choice of therapy for some types of tumors.[1,2] A preliminary evaluation of radiobrominated steroids can be obtained through competitive receptor-binding studies,[3] using the stable brominated compounds. We, therefore, sought to obtain purified samples of two different estrogens brominated in the A ring. Although methods of brominating in the A ring of estrogens[4-6] have been described in the literature, we chose to employ a method that would convert bromide ion directly to an electrophilic brominating agent in situ. Such a method could be used for subsequent radiobrominations of these compounds.[7] Studies in this laboratory have demonstrated that mixing *N*-chlorosuccinimide (NCS) and bromide ion forms an electrophilic brominating species in situ.[8] We now report on the bromination of estradiol 1 and 17α-ethynylestradiol 5 with this combination of reagents.

Results and Discussions

Reaction of estradiol 1 with NCS/NaBr in ethanol at room temperature yielded a mixture of three brominated compounds. The brominated products were separated and purified by preparative high-performance LC (HPLC) and subsequently identified (Table III) as 2-bromoestradiol (2), 4-bromoestradiol (3), and 2,4-dibromoestradiol (4). Reaction of 17α-ethynylestradiol 5 with NCS/NaBr under the same reaction conditions also yielded three brominated products. The brominated products, 2-bromo-17α-ethynylestradiol (6), 4-bromo-17α-ethynylestradiol (7), and 2,4-dibromo-17α-ethynylestradiol (8), were subsequently separated, purified, and characterized (Table IV).

The A-ring bromination of estradiol 1 with NCS/Br^- was compared to brominations with *N*-bromoacetamide (NBA), *N*-bromosuccinimide (NBS), pyridinium bromide perbromide (PBPB), and Br_2 to see if the ratios of brominated products, 2–4, were the same (Table I). Indeed, all brominations carried out in ethanol gave nearly identical ratios of products by analytical HPLC. However, it was interesting to note that changing the solvent had a dramatic change in the ratio of 2:3 for PBPB but apparently not for NCS/Br^-.

When the reactions of 1 and 5 with NCS/Br were followed by reverse-phase HPLC, a transient species was observed.[9] Within a 40-min reaction time essentially all

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