Electrophilic Halogenation of 8-Methoxyquinoline[1]

HERMAN GERSHON* AND M. W. MCNEIL

Boyce Thompson Institute for Plant Research, Yonkers, New York 10701

STEPHEN G. SCHULMAN

College of Pharmacy, University of Florida, Gainesville, Florida 32601

Received April 11, 1972

Electrophilic halogenation of 8-methoxyquinoline with elemental halogen and *N*-halosuccinimide was studied and compared with that of 8-quinolinol. Monochlorination and monobromination took place in the 5 position under acidic and neutral conditions, whereas iodination took place in the 7 position. This paralleled the results with 8-quinolinol. Under basic conditions, 8-methoxyquinoline remained unhalogenated, whereas 8-quinolinol formed 7-chloro, 7-bromo, and 5-iodo derivatives with the respective halogenating agents. The inactivity of 8-methoxyquinoline to halogenation in strongly basic media is attributed to the absence of an anionic form of the compound. The importance of the anionic form of 8-quinolinol for electrophilic chlorination and bromination in the 7 position and iodination in the 5 position was established.

Recent studies of the electrophilic halogenation of 8-quinolinol and its bischelate with copper(II) revealed that, although chelation does not alter the electrophilic positions, it does influence the orientation of the incoming halogen.[2,3] Other factors which influence orientation in electrophilic monohalogenation are the prototropic form of the substrate, the nature of the halogenating agent, and the solvent employed.[4] It should also be mentioned that chlorination and bromination, under acidic conditions, favor the 5 position, and in basic media the 7 position is favored. Iodination is characterized by the reverse orientation and may take place by a different mechanism.[4]

Since the prototropic form of the substrate strongly influences the orientation of the incoming halogen in electrophilic substitution of 8-quinolinol, it is of interest to examine the electrophilic halogenation of 8-methoxyquinoline, which can form cationic and neutral species but no anions. Halogenations using *N*-chlorosuccinimide (NCS), *N*-bromosuccinimide (NBS), *N*-iodosuccinimide, chlorine, bromine, and iodine were carried out in 93% sulfuric acid, glacial acetic acid, chloroform, pyridine, diethylamine, and 10% sodium hydroxide. The reactions were carried out at ambient temperatures for 3 hr with the *N*-halosuccinimides and elemental halogens and also at 40–60° with the *N*-halosuccinimides. The molar ratios of halogenating agent to substrate were 1:1, 2:1, and 3:1, and the reaction mixtures were assayed by gas chromatography. A second portion of mixture was gas chromatographed after treatment with *N,O*-bis(trimethylsilyl)acetamide to detect demethylated compounds, when present. The rationale for this approach has been previously developed.[2-4]

The results obtained are summarized in Table I. A cursory examination of the data indicates that, on monohalogenation, chlorine and bromine were oriented to the 5 position and iodine to the 7 position. No 7-monochloro- or 7-monobromo-8-methoxyquinoline was detected under any of the conditions of halogenation employed, with the following three exceptions. When 8-methoxyquinoline was treated with 3 equiv of NCS in 93% sulfuric acid at 40–60°, 2% 7-chloro-8-methoxyquinoline was formed. Upon replacing the sulfuric acid with acetic acid and keeping the remaining conditions the same, only a trace of 7-chloro-8-methoxyquinoline was detected. When the chlorination was carried out in pyridine with 1 equiv of chlorine to 1 equiv of 8-methoxyquinoline, 3% 7-chloro-8-methoxyquinoline was produced. On the other hand, upon iodination under the same conditions as employed for chlorination and bromination, only 7-iodo-8-methoxyquinoline was found. It should also be noted that no halogenation occurred in solvents that were considerably more basic than the substrate, 8-methoxyquinoline. Thus it can be concluded that, on monohalogenation of 8-quinolinol in strong base, the orientation of chloro and bromo substituents to the 7 position and iodo to the 5 position is due to the influence of the anionic form of the substrate. Where the substrate cannot form an anion, as in 8-methoxyquinoline, no halogenation takes place under any of the strongly basic conditions studied. Polyhalogenation was also observed, but this occurred only under acidic and neutral conditions.

Where direct comparisons of the halogenation of 8-quinolinol[3,4] with 8-methoxyquinoline can be made, the rate of halogenation of 8-quinolinol is greater than or equal to that for the methoxyquinoline under comparable conditions; however, the purity of the halogenomethoxy compounds was usually greater owing to the fact that only one monohalogenated isomer formed, and that dihalogenation did not occur until the monohalogenation reaction went to completion. Iodination of 8-methoxyquinoline with elemental iodine did not take place under any of the conditions employed. These results did not parallel those observed for 8-quinolinol.[3,4]

When the ratio of chlorine to 8-methoxyquinoline in 93% sulfuric acid was greater than 1:1, an unknown product was detected of which the retention time of the trimethylsilyl derivative was between that of 8-methoxyquinoline and 5-chloro-8-methoxyquinoline. It was not further characterized. The bromination of 1 equiv of 8-methoxyquinoline with 2 and 3 equiv of NBS in 93% sulfuric acid was also complicated by the appearance of side products. In the reaction of 1 equiv of 8-methoxyquinoline with 2 equiv of NBS in 93% sulfuric acid at ambient temperatures, 10% 5-bromo-8-methoxyquinoline, 30% 5,7-dibromo-8-methoxyquinoline, 45% 5-bromo-8-quinolinol, and 15% 5,7-dibromo-8-quinolinol were formed. The same re-

(1) This work was supported in part by the U. S. Public Health Service, Grant No. AI-05808.

(2) H. Gershon, M. W. McNeil, and A. T. Grefig, *J. Org. Chem.*, **34**, 3268 (1969).

(3) H. Gershon and M. W. McNeil, *ibid.*, **35**, 3993 (1970).

(4) H. Gershon, M. W. McNeil, and S. G. Schulman, *ibid.*, **36**, 1616 (1971).

action in the presence of 3 equiv of NBS yielded 57% 5,7-dibromo-8-methoxyquinoline, 11% 5-bromo-8-quinolinol, 22% 5,7-dibromo-8-quinolinol, and 7 and 11% of two uncharacterized hydroxyquinolines. When the temperature was kept at 40–60° using 2 equiv of NBS, the resulting mixture was composed of 6% 5-bromo-8-methoxyquinoline, 63% 5,7-dibromo-8-methoxyquinoline, 15% 5-bromo-8-quinolinol, and 16% 5,7-dibromo-8-quinolinol. At the same temperature, when 3 equiv of NBS was used, the products consisted of 57% 5,7-dibromo-8-methxyquinoline, 39% 5,7-dibromo-8-quinolinol, and 4% 5,6,7-tribromo-8-quinolinol.

To determine whether the demethylated products resulted from the conditions of the work-up of the sulfuric acid solutions, 5-bromo- and 5,7-dibromo-8-methoxyquinolines were treated in 93% sulfuric acid, in the absence of NBS, in the same manner as in a bromination reaction. Only starting materials were detected, and the mechanism of the demethylation reaction is not clear.

On comparing chlorine with NCS and bromine with NBS as halogenating agents in reactions with 8-methoxyquinoline, the elemental halogen reacted more rapidly and was more controllable than the *N*-halosuccinimides, as evidenced by the greater yields of products and fewer by-products. Increasing the reaction temperature increased the reaction rates, as expected. In addition, products were formed in certain instances which were not found when ambient temperatures were employed. The explanation of the greater reactivity of chlorine and bromine as compared with NCS and NBS may reside in the fact that chlorination and bromination with the elemental halogen are accompanied by the release of equivalent amounts of hydrogen halides. This aids in protonating the quinolines to enhance reactivity and control orientation, and may be especially significant where weakly acidic and weakly basic solvents as well as aprotic solvents are employed.

A striking difference between 8-quinolinol and 8-methoxyquinoline is the failure of 8-methoxyquinoline to form appreciable quantities of 7-chlorinated and 7-brominated derivatives with 1 equiv of halogenating agent per 1 equiv of substrate, even in solvents in which the neutral and protonated species derived from 8-quinolinol are halogenated in the 7 as well as in the 5 positions. This observation can be explained on the basis of the difference in hydrogen bonding properties between the 8-hydroxy and 8-methoxy compounds. In 8-quinolinol, the greatest amount of 7-chlorination and 7-bromination occurs in those species in which the amount of electronic charge released to the 7 position from the hydroxyl group is greatest. In the anions, the electron density is obviously substantial, and chlorination and bromination occur at these sites almost exclusively. However, in the neutral species derived from 8-quinolinol, substantial 7-halogenation also occurs, with the greatest ratio of 7-halogeno to 5-halogeno compound occurring in the most basic solvent, diethylamine, which is also the best hydrogen-bond acceptor. The lowest ratio of 7-halogenation to 5-halogenation occurs in the poorest hydrogen bond acceptor, chloroform. Even in the protonated species, some 7-halogenation occurs in acetic acid in which the carbonyl oxygen atom is a fair hydrogen bond acceptor, but in sulfuric acid, which is an extremely poor hydrogen bond acceptor solvent, no 7-chlorination or 7-bromination takes place. Apparently, there is a good degree of correlation between the degree of removal of the proton from the phenolic oxygen atom and the yield of 7-chlorinated and 7-brominated products. The effect of replacement of the phenolic proton of 8-quinolinol by a methyl group, as in 8-methoxyquinoline, is not only to prevent dissociation from the phenolic site, but also to eliminate hydrogen bonding of the phenolic proton with the solvent. Thus, the neutral 8-methoxyquinoline molecule does not have the appreciable excess π charge density at the 7 position which occurs in 8-quinolinol in hydrogen bond acceptor solvents, and electrophilic chlorination and bromination are directed exclusively to the 5 position. The lack of reactivity of 8-methoxyquinoline in the most basic solvents, aqueous NaOH and diethylamine, relative to that in pyridine and chloroform, is possibly due to the loss of hydrogen bonding with the by-product succinimide or hydrogen halide of the heterocyclic nitrogen. This hydrogen bonding interaction introduces positive charge into the quinoline ring, much the same as protonation does, and favors halogenation at the 5 position. In strongly basic, high-dielectric solvents, the hydrogen halide or succinimide formed as a result of the reaction is not constrained to the site of the heterocyclic nitrogen and probably reacts preferentially with the solvent.

It can be concluded that the single most important factor which influences electrophilic halogenation of both 8-quinolinol and its methyl ether is the prototropic form of the substrate. Both hydrogen bonding and dielectric properties of the solvent are of consequence in the orientation of chlorine and bromine, as a result of electrophilic halogenation of 8-quinolinol.

Experimental Section[5]

Halogenation of 8-Methoxyquinoline in Different Solvents with Elemental Halogen and *N*-Halosuccinimide.—8-Methoxyquinoline was halogenated in the same manner as described for 8-quinolinol in ref 3.

7-Chloro-8-methoxyquinoline.—To a solution of sodium (0.69 g, 0.03 g-atom) in 30 ml of mehanol was added 7-chloro-8-quinolinol[2] (5.4 g, 0.03 mol). Methyl iodide (5.7 g, 0.04 mol) was added dropwise with stirring at room temperature. Upon completion of addition of the methyl iodide, the temperature was raised slowly to 40–45° and stirring was continued overnight. The temperature was brought to boiling for 1 hr, after which the methanol was removed by flash evaporation, and the residue was dissolved in a mixture of chloroform and H_2O. After removal of the aqueous layer, the chloroform solution was washed three times with 5% aqueous KOH followed by H_2O until the washings were no longer alkaline. The chloroform was evaporated, and the residue was steam distilled. The product (3.0 g, 52%) was obtained by filtration and drying at 60° overnight, mp 73–75°. An analytical sample was crystallized from aqueous ethanol, mp 75°.

(5) Melting points were taken in a Thomas-Hoover capillary melting point apparatus and are uncorrected. Gas chromatography was performed on a Varian Aerograph Model 1200 gas chromatograph with a flame ionization detector to which was attached a Varian Aerograph Model 20 recorder. All of the compounds in this study (Table I) were separated on a 1% Apiezon L column under the conditions described previously.[2] Silylations were carried out according to the procedure of Klebe, *et al.*[6] 8-Methoxyquinoline and its 5-chloro, 5-bromo, 5-iodo, 5,7-dichloro, 5,7-dibromo, and 5,7-diiodo analogs were prepared by the method of Gershon and Parmegiani.[7]

(6) J. F. Klebe, H. Finkbeiner, and D. M. White, *J. Amer. Chem. Soc.*, **88**, 3390 (1966).

(7) H. Gershon and R. Parmegiani, *Contrib. Boyce Thompson Inst.*, **24**, 33 (1968).

TABLE I

ELECTROPHILIC HALOGENATION OF 8-METHOXYQUINOLINE WITH *N*-HALOSUCCINIMIDE AND WITH ELEMENTAL HALOGEN IN DIFFERENT SOLVENTS AT AMBIENT TEMPERATURES AND AT 40–60°[a]

Halogenating medium	Molecular ratio of halogen/substrate	Temp, °C	Products, %: *N*-Chlorosuccinimide 8-MeOx[b]	5-Cl-8-MeOx	7-Cl-8-MeOx	5,7-Cl_2-8-MeOx	Chlorine 8-MeOx	5-Cl-8-MeOx	7-Cl-8-MeOx	5,7-Cl_2-8-MeOx
H_2SO_4, 93%	1	Ambient	83	17	0	0	3	97	0	0
	2	Ambient	0	96	0	4	0	10	0	90[d]
	3	Ambient	0	90	0	10	0	0	0	95[e]
	1	40–60	0	100	0	0				
	2	40–60	0	80	0	20				
	3	40–60	0	33	2	65				
Acetic acid, glacial	1	Ambient	100	0	0	0	1	99	0	0
	2	Ambient	100	0	0	0	0	100	0	0
	3	Ambient	100	0	0	0	0	100	0	0
	1	40–60	100	Trace[c]	0	0				
	2	40–60	0	100	0	Trace				
	3	40–60	0	45	Trace	55				
Chloroform	1	Ambient	100	0	0	0	75	25	0	0
	2	Ambient	100	0	0	0	72	28	0	0
	3	Ambient	100	0	0	0	65	35	0	0
	1	40–60	100	0	0	0				
	2	40–60	77	23	0	0				
	3	40–60	65	35	0	0				
Pyridine	1	Ambient	100	0	0	0	0	97	3	Trace
	2	Ambient	100	0	0	0	0	27	0	73
	3	Ambient	100	0	0	0	0	0	0	100
	1	40–60	95	5	0	0				
	2	40–60	Trace	100	0	0				
	3	40–60	0	95	0	5				
Diethylamine	1	Ambient	100	0	0	0	100	0	0	0
	2	Ambient	100	0	0	0	100	0	0	0
	3	Ambient	100	0	0	0	100	0	0	0
	1	40–60	100	0	0	0				
	2	40–60	100	0	0	0				
	3	40–60	100	0	0	0				
NaOH, 10%	1	Ambient	100	0	0	0	100	0	0	0
	2	Ambient	100	0	0	0	100	0	0	0
	3	Ambient	100	0	0	0	100	0	0	0
	1	40–60	100	0	0	0				
	2	40–60	100	0	0	0				
	3	40–60	100	0	0	0				
			N-Bromosuccinimide 8-MeOx	5-Br-8-MeOx	7-Br-8-MeOx	5,7-Br-8-MeOx	Bromine 8-MeOx	5-Br-8-MeOx	7-Br-8-MeOx	5,7-Br_2-8-MeOx
H_2SO_4, 93%	1	Ambient	Trace	100	0	0	0	100	0	0
	2	Ambient	0	10	0	30[f]	0	100	0	0
	3	Ambient	0	0	0	57[g]	0	100	0	0
	1	40–60	0	100	0	0				
	2	40–60	0	6	0	63[h]				
	3	40–60	0	0	0	57[i]				
Acetic acid, glacial	1	Ambient	12	88	0	0	5	95	0	0
	2	Ambient	0	100	0	0	0	100	0	0
	3	Ambient	0	100	0	0	0	100	0	0
	1	40–60	9	91	0	0				
	2	40–60	0	90	0	10				
	3	40–60	0	10	0	90				
Chloroform	1	Ambient	100	0	0	0	0	100	0	0
	2	Ambient	0	100	0	0	0	100	0	0
	3	Ambient	0	100	0	0	0	100	0	0
	1	40–60	36	64	0	0				
	2	40–60	0	100	0	0				
	3	40–60	0	100	0	0				
Pyridine	1	Ambient	85	15	0	0	0	100	0	0
	2	Ambient	10	90	0	0	0	100	0	0
	3	Ambient	0	100	0	0	0	100	0	Trace

TABLE I
(*Continued*)

Halogenating medium	Molecular ratio of halogen/substrate		Products, %: *N*-Bromosuccinimide 8-MeOx	5-Br-8-MeOx	7-Br-8-MeOx	5,7-Br-8-MeOx	Bromine 8-MeOx	5-Br-8-MeOx	7-Br-8-MeOx	5,7-Br_2-8-MeOx
Pyridine	1	40–60	85	15	0	0				
	2	40–60	0	100	0	0				
	3	40–60	0	100	0	0				
Diethylamine	1	Ambient	100	0	0	0	100	0	0	0
	2	Ambient	100	0	0	0	100	0	0	0
	3	Ambient	100	0	0	0	100	0	0	0
	1	40- 60	100	0	0	0				
	2	40 60	100	0	0	0				
	3	40–60	100	0	0	0				
NaOH, 10%	1	Ambient	100	0	0	0	100	0	0	0
	2	Ambient	100	0	0	0	100	0	0	0
	3	Ambient	100	0	0		100	0	0	0
	1	40–60	100	0	0	0				
	2	40–60	100	0	0	0				
	3	40–60	100	0	0	0				
			N-Iodosuccinimide 8-MeOx	5-I-8-MeOx	7-I-8-MeOx	5,7-I_2-6-MeOx	Iodine 8-MeOx	5-I-8-MeOx	7-I-8-MeOx	5,7-I_2-8-MeOx
H_2SO_4, 93%	1	Ambient	2	0	98	0	100	0	0	0
	2	Ambient	0	0	65	35	100	0	0	0
	3	Ambient	0	0	20	80	100	0	0	0
	1	40–60	0	0	100	0				
	2	40–60	0	0	40	60				
	3	40–60	0	0	5	95				
Acetic acid, glacial	1	Ambient	40	0	60	0	100	0	0	0
	2	Ambient	0	0	100	0	100	0	0	0
	3	Ambient	0	0	100	0	100	0	0	0
	1	40–60	17	0	83	0				
	2	40–60	Trace	0	100	0				
	3	40–60	0	0	100	0				
Chloroform	1	Ambient	100	0	0	0	100	0	0	0
	2	Ambient	100	0	0	0	100	0	0	0
	3	Ambient	100	0	0	0	100	0	0	0
	1	40–60	100	0	0	0				
	2	40–60	70	0	30	0				
	3	40- 60	65	0	35	0				
Pyridine	1	Ambient	100	0	0	0	100	0	0	0
	2	Ambient	100	0	0	0	100	0	0	0
	3	Ambient	100	0	0	0	100	0	0	0
	1	40–60	100	0	0	0				
	2	40–60	100	0	0	0				
	3	40–60	100	0	0	0				
Diethylamine	1	Ambient	100	0	0	0	100	0	0	0
	2	Ambient	100	0	0	0	100	0	0	0
	3	Ambient	100	0	0	0	100	0	0	0
	1	40–60	100	0	0	0				
	2	40–60	100	0	0	0				
	3	40–60	100	0	0	0				
NaOH, 10%	1	Ambient	100	0	0	0	100	0	0	0
	2	Ambient	100	0	0	0	100	0	0	0
	3	Ambient	100	0	0	0	100	0	0	0
	1	40–60	100	0	0	0				
	2	40–60	100	0	0	0				
	3	40–60	100	0	0	0				

[a] All results are the average of three runs with an average deviation of ±10%. [b] 8-MeOx = 8-methoxyquinoline. [c] <1%. [d] Trace of unknown compound, the trimethylsilyl derivative of which had a retention time between that of 8-methoxyquinoline and 5-chloro-8-methoxyquinoline. [e] The unknown compound of *d* was 5% of the total. [f] The mixture also contained 45% 5-bromo-8-quinolinol and 15% 5,7-dibromo-8-quinolinol. [g] The mixture also contained 7% of an unknown compound, the trimethylsilyl derivative of which had a retention time shorter than that of the trimethylsilyl derivative of 8-quinolinol; 11% 5-bromo-8-quinolinol; 3% of a second unknown compound, the trimethylsilyl derivative of which had a retention time between that of the trimethylsilyl derivative of 5-bromo-8-quinolinol and 5,7-dibromo-8-methoxyquinoline; and 22% 5,7-dibromo-8-quinolinol. [h] The mixture also contained 15% 5-bromo-8-quinolinol and 16% 5,7-dibromo-8-quinolinol. [i] The mixture also contained 39% 5,7-dibromo-8-quinolinol and 4% 5,6,7-tribromo-8-quinolinol.

Anal. Calcd for $C_{10}H_8ClNO$: C, 62.03; H, 4.16; Cl, 18.31; N, 7.23. Found: C, 62.11; H, 4.19; Cl, 18.31; N, 7.40.

7-Bromo-8-methoxyquinoline was prepared in 56% yield in the same manner as the chloro analog, mp 79.5–80.5°. The analytical sample (aqueous ethanol) melted at 80–81°.

Anal. Calcd for $C_{10}H_8BrNO$: C, 50.45; H, 3.39; Br, 33.56; N, 5.88. Found: C, 50.45; H, 3.38; Br, 33.57; N, 5.83.

7-Iodo-8-methoxyquinoline was prepared in 88% yield in the same manner as the chloro analog, mp 112–113°. The analytical sample (aqueous ethanol) melted at 113°.

Anal. Calcd for $C_{10}H_8INO$: C, 42.13; H, 2.85; I, 44.52; N, 4.91. Found: C, 42.34; H, 2.79; I, 44.24; N, 5.07.

2-Acetamido-4-bromophenyl Acetate.—A mixture of 2-acetamidophenyl acetate[8] (32.7 g, 0.3 mol), NBS (53.4 g, 0.3 mol), and 1000 ml of chloroform was heated under reflux with stirring until a clear solution was formed. After cooling, the chloroform solution was washed several times with a dilute $NaHSO_3$ solution, and the chloroform was removed by flash evaporation. The product (31.5 g, 56%) was recrystallized from benzene twice and melted at 148–150°.[9]

Anal. Calcd for $C_{10}H_{10}BrNO_3$: C, 44.14; H, 3.70; Br, 29.37; N, 5.15. Found: C, 44.02; H, 3.75; Br, 29.31; N, 5.22.

6-Bromo-8-quinolinol.—A mixture of 2-acetamido-4-bromophenyl acetate (39 g, 0.14 mol), 30 ml of concentrated sulfuric acid, arsenic oxide (30 g, 0.13 mol), and glycerol (50 g, 0.54 mol) was heated under reflux for 3 hr. After cooling, it was diluted with H_2O and adjusted to pH 6 with concentrated NH_4OH. The suspension was steam distilled and yielded 10.5 g (33%) of product, mp 143–145° (lit.[10a] mp 138–139°).

5,6,7-Tribromo-8-quinolinol.—6-Bromo-8-quinolinol (2.24 g, 0.01 mol) was dissolved in 50 ml of acetic acid. A solution of 3.3 g (0.02 mol) of bromine in 25 ml of acetic acid was added dropwise with stirring. The reaction was complete when the color of the bromine persisted for 10 min. The solution was poured into 1000 ml of H_2O, decolorized with $NaHSO_3$, and brought to pH 7 with Na_2CO_3, and $NaHCO_3$. The product was removed by filtration and washed with H_2O. A yield of 3.5 g (92%) of compound, mp 182–185°, was obtained. Recrystallization from aqueous alcohol raised the melting point to 188–190° (lit.[10b] mp 192°).

Registry No.—8-Methoxyquinoline, 938-33-0; 7-chloro-8-methoxyquinoline, 36748-98-8; 7-bromo-8-methoxyquinoline, 36748-99-9; 7-iodo-8-methoxyquinoline, 36749-00-5; 2-acetamido-4-bromophenyl acetate, 36749-01-6; *N*-chlorosuccinimide, 128-09-6; *N*-bromosuccinimide, 128-08-5; *N*-iodosuccinimide, 516-12-1; 5-Cl-8-MeOx, 17012-44-1; 5,7-Cl_2-8-MeOx, 17012-48-5; 5-Br-8-MeOx, 10522-47-1; 5,7-Br_2-8-MeOx, 17012-49-6; 5-I-8-MeOx, 17012-46-3; 5,7-I_2-8-MeOx, 17012-50-9.

(8) W. Theilacker, *Chem. Ber.*, **71**, 2065 (1938).

(9) R. K. Smalley and H. Suschitzky, *J. Chem. Soc.*, 5571 (1963). This compound was mentioned but not characterized.

(10) (a) A. R. Pinnington, Ph.D. Thesis, Oxford, 1954, in R. G. W. Hollingshead, "Oxine and Its Derivatives," Vol. III, Butterworths, London, 1956, p 674; (b) p 751.

The Electrophilic Addition of Bromine to *cis*- and *trans*-1,2-Dimethylcyclopropane

JOSEPH B. LAMBERT*[1] AND BOHDAN A. IWANETZ

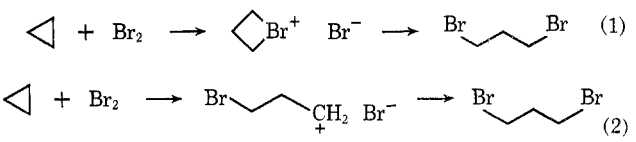
Department of Chemistry, Northwestern University, Evanston, Illinois 60201

Received June 6, 1972

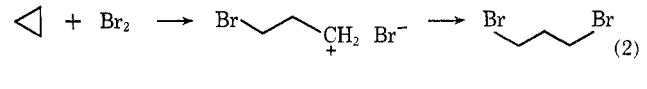
Under polar conditions, the major pathway for bromination of both *cis*- and *trans*-1,2-dimethylcyclopropane opens the less substituted carbon–carbon bond nonstereospecifically. Addition to the more substituted bond, also nonstereospecific, occurs to the extent of about 8% in both cases. A major component of the cis, but not the trans, reaction mixture is the hydride-shift product, 1,2-dibromo-2-methylbutane. The intermediates responsible for product formation are best described as nonbridged, secondary carbonium ions, because of the nonstereospecific nature of the reaction. The distribution of products is discussed in terms of steric and stereoelectronic effects.

Stereochemistry[2,3] and regiochemistry[4] have only recently been brought to bear on the mechanistic problems offered by the addition of electrophiles to cyclopropane rings. The bulk of the work to date has consisted in the addition of electrophiles to polycyclic compounds that contain a three-membered ring, and examination of the diastereomeric products in order to deduce the stereochemistry of the reaction. No single preferred stereochemical path has emerged from these studies, although individual cases have been thoroughly examined. No simple monocyclic cyclopropane has yet been studied with the view of determining the stereochemistry of the reaction.[5] To this end, we have studied the bromination of *cis*- and *trans*-1,2-dimethylcyclopropane. The products of this reaction offer a simple handle on the stereochemistry of the halogen addition. This study supplies the cyclopropane analog of the bromination of *cis*- and *trans*-2-butene. Conformational constraints on the conceivable acyclic carbonium ion intermediates produced from these monocyclic systems are much less important than those on the ions produced from the previously studied polycyclic compounds,[2,3] since the residual rings present in these latter ions prohibit free rotation. The structure of the monocyclic systems therefore has little bias on the stereochemical outcome. Furthermore, the availability of both the cis and the trans isomers enables the reaction to be studied from two diastereomeric directions. Such a comparison is not possible in polycyclic systems without using trans-fused rings.

The primary objective of these stereochemical studies is to distinguish between mechanistic pathways that involve cyclic bromonium ions (eq 1, analogous to



(1)



(2)

(1) This work was supported by the Petroleum Research Fund, administered by the American Chemical Society (Grant 2970-AC4,5) and by the National Science Foundation (Grant GP-22942).

(2) S. J. Cristol, W. Y. Lim, and A. R. Dahl, *J. Amer. Chem. Soc.*, **92**, 4013 (1970); S. J. Cristol, J. K. Harrington, T. C. Morrill, and B. E. Greenwald, *J. Org. Chem.*, **36**, 2773 (1971), and references cited therein.

(3) J. B. Lambert, R. D. H. Black, J. H. Shaw, and J. J. Papay, *J. Org. Chem.*, **35**, 3214 (1970), and references cited therein.

(4) N. C. Deno and W. E. Billups, *Chem. Commun.*, 1387 (1970).

(5) Since the preparation of this manuscript, the addition of bromine to the 1,2-diphenylcyclopropanes has been described; see R. T. LaLonde, P. B. Ferrara, and A. D. Debboli, Jr., *J. Org. Chem.*, **37**, 1094 (1972).