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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE STATE UNIVERSITY OF IOWA]

The Addition of Bromine Chloride to Carbon–Carbon Double Bonds[1]

BY ROBERT E. BUCKLES AND JOHN W. LONG

A mixture of N-bromoacetamide and hydrogen chloride has been used as a source of the elements of bromine chloride for addition to ethylene, styrene, cinnamic acid, *cis*-stilbene and *trans*-stilbene. The structures of the chlorobromides which were obtained support the polar mechanism of addition in which positive bromine is transferred to the double bond to form a complex, *e.g.*, the bromonium ion, which is attacked by chloride ion to give the product. The direction of addition to unsymmetrically substituted double bonds is that predicted by this mechanism. The expected *trans*-addition has also been observed. The chlorobromides derived from styrene and *trans*-stilbene have also been prepared by the reactions of anhydrous stannic chloride with the corresponding dibromides. These displacement reactions presumably take place either by way of intermediates similar to those proposed for the addition reactions or by way of carbonium ion intermediates.

The physical evidence for the existence of bromine chloride is based mainly on thermodynamic and kinetic studies of the equilibrium of formation from bromine and chlorine.[2] Attempts to measure such properties as m.p.[3] and b.p.[3b] have led to the conclusion that bromine chloride is not a stable compound. The preparation of a sample of bromine chloride with a definite m.p. (−54°) and a characteristic vapor-pressure *vs.* temperature curve has been reported,[4] however.

Chemical evidence for the existence of bromine chloride in an equimolar mixture of bromine and chlorine is to be found in its action on ethylene to yield mostly 1-bromo-2-chloroethane[5] and in its action on diazodesoxybenzoin to give mostly α-bromo-α-chlorodesoxybenzoin.[6]

In the present work it has been found convenient to use a mixture of N-bromoacetamide and hydrogen chloride in a suitable solvent as a source of the elements of bromine chloride for addition to olefins. When aqueous hydrochloric acid was treated portionwise with N-bromo-acetamide while ethylene was bubbled through the solution, the product was 1-bromo-2-chloroethane just as when mixtures of chlorine and bromine were used.[5]

It has previously been shown[7] that even in relatively non-polar solvents N-bromoacetamide in the presence of an acid acts as a source of positive bromine for the polar mechanism of addition to double bonds. In this mechanism the positive bromine is transferred to the double bond to form a positively charged complex, *e.g.*, the bromonium ion, which is capable of maintaining its steric identity. The reaction of this complex with chloride ion leads to the bromochloride. The attack of chloride ion on the complex would be at the more positive carbon atom of an unsymmetrically substituted double bond so that Markovnikov's rule would hold for hydrocarbons. Also the attack would be on the side opposite to the attachment of the bromine in the complex; *i.e.*, *trans* addition would prevail.

Styrene, when treated with N-bromoacetamide and hydrochloric acid in water, yielded (36–44%) 2-bromo-1-chloro-1-phenylethane along with some dibromide. A similar addition reaction of *trans*-cinnamic acid in dimethylcellosolve gave a 56% yield of α-bromo-β-chlorohydrocinnamic acid. The structures of these products were established by dehydrohalogenation to known compounds. In either case the product is that predicted as the result of the addition of positive bromine and negative chlorine to the partially polarized double bond.

When an addition of bromine chloride in the reverse order (*i.e.*, N-chloroacetamide in the presence of hydrogen bromide) was carried out on styrene, the dibromide was the major product. When the reaction was carried out in water with excess hydrogen bromide, no bromochloride was isolated. With ether as a solvent and with a limited amount of hydrobromic acid, the reaction gave a 30% yield of impure 2-bromo-1-chloro-1-phenylethane. None of the isomer, 1-bromo-2-chloro-1-phenylethane, was obtained.

Although N-chloroacetamide would be considered as a source of positive chlorine the greater electronegativity of chlorine as compared to bromine would be expected to lead to an exchange of electrons so that a source of positive bromine would rapidly be formed.

$$\mathrm{AcNHCl} + \mathrm{HBr} \rightleftharpoons \mathrm{AcNH_2Cl^+} + \mathrm{Br^-}$$

$$\mathrm{AcNH_2Cl^+} + \mathrm{Br^-} \rightleftharpoons \mathrm{AcNH_2Br^+} + \mathrm{Cl^-}$$

$$\mathrm{AcNH_2Cl^+} + \mathrm{Br^-} \rightleftharpoons \mathrm{AcNH_2} + \mathrm{BrCl}$$

Such reactions are well known.[8] With such a source of positive bromine present the formation of dibromide with excess hydrobromic acid and the formation of 2-bromo-1-chloro-1-phenylethane with limited hydrobromic acid would be the results expected.

The prevalence of *trans* addition was demonstrated by the addition of bromine chloride to *cis*- and *trans*-stilbene in dimethylcellosolve. A 67% yield of *erythro*-α-bromo-α′-chlorobibenzyl (III)

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(1) Taken from the Ph.D. thesis of John W. Long. Presented before the Organic Division of the American Chemical Society, Chicago, Illinois, September, 1950.

(2) C. M. Beeson and D. M. Yost, THIS JOURNAL, **61**, 1432 (1939); C. M. Blair and D. M. Yost, *ibid.*, **55**, 4489 (1933); H. G. Vesper and G. K. Rollefson, *ibid.*, **56**, 620 (1934); G. S. Forbes and R. M. Fuoss, *ibid.*, **49**, 142 (1927); G. Brauer and E. Victor, *Z. Elektrochem.*, **41**, 508 (1935).

(3) (a) P. Lebeau, *Compt. rend.*, **143**, 589 (1907); (b) B. J. Karsten, *Z. anorg. Chem.*, **53**, 365 (1907).

(4) H. Lux, *Ber.*, **63**, 1156 (1930).

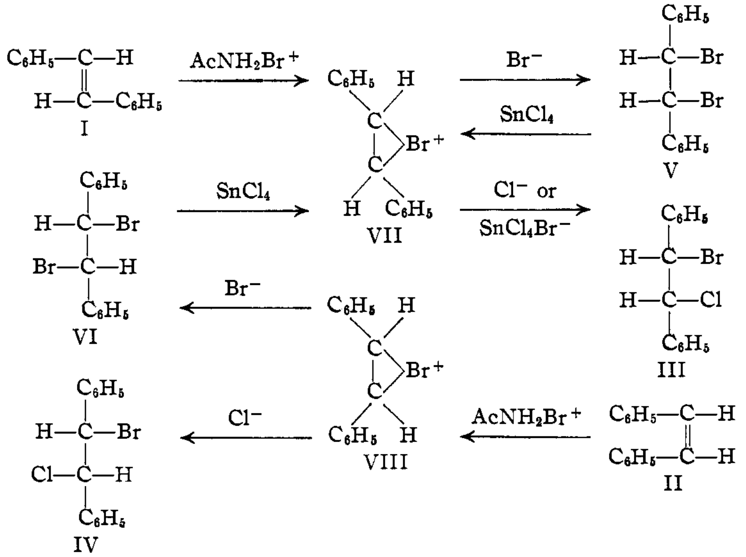
(5) M. Delépine and L. Ville, *Bull. soc. chim.*, [4] **27**, 673 (1920); J. W. James, *J. Chem. Soc.*, **43**, 37 (1883).

(6) T. W. J. Taylor and L. A. Forscey, *ibid.*, 2272 (1930).

(7) R. E. Buckles, THIS JOURNAL, **71**, 1157 (1949).

(8) L. Farkas, M. Lewin and R. Bloch, *ibid.*, **71**, 1988 (1949).

was obtained from *trans*-stilbene (I) while *cis*-stilbene (II) gave a 47% yield of *threo*-α-bromo-α'-chlorobibenzyl (IV) accompanied by a 14% yield of III. The structures of these compounds were assigned on the basis of the well known analogous additions of bromine to *trans*-stilbene to give *meso*-α,α'-dibromobibenzyl (V) and to *cis*-stilbene to yield mostly the *dl*-dibromide (VI) plus a little V. Again the bromonium ion intermediates, VII and VIII, are those most usually proposed to explain the *trans* addition.



2-Bromo-1-chloro-1-phenylethane and *erythro*-α-bromo-α'-chlorobibenzyl[9] (III) were also synthesized by the action of anhydrous stannic chloride on the corresponding dibromides. Both *meso*- and *dl*-α,α'-dibromobibenzyl (V and VI, respectively) yielded the higher melting, *erythro*-bromochloride (III). Such a replacement of the S_N1-type[10] would be expected to take place with retention of configuration because of participation of the neighboring bromine atom to form a bromonium ion intermediate, VII or VIII, which maintains its configuration.[11] The case of the stilbene dihalides differs from the usual one, however, as has been reported[12] in the reaction of silver acetate with the stilbene dichlorides. The stilbene dibromides have been shown[13] by several methods to have preferred orientations about the central carbon–carbon single bond so that the phenyl groups are *trans* to each other. In the *meso*-isomer, then, the neighboring bromine atom is in position to participate in the reaction to form VII and bring about over-all retention of configuration whereas in the *dl*-isomer the neighboring bromine atom is not in position to form VIII and presumably forms VII instead. The formation of a carbonium ion with no participation by the neighboring bromine atom would also lead to the more stable *erythro*-bromochloride (III) from each dibromide. Either of these interpretations would also explain the formation of 2-bromo-1-chloro-1-phenylethane from styrene dibromide since the bromonium ion or the stabilized secondary carbonium ion would react with chloride ion to yield this product. Similar explanations apply to the reaction of cinnamic acid dibromide with mercuric chloride to yield a product described as α-bromo-β-chlorohydrocinnamic acid but for which no proof of structure was offered.[14]

Experimental

N-Bromoacetamide.[7,15]—This material was prepared from 3 moles of purified acetamide by the reaction with bromine and potassium hydroxide. A 58% yield of product of m.p. 105–106° (from purified chloroform) was obtained.

N-Chloroacetamide.—A solution of 236 g. (4 moles) of acetamide in 200 ml. of water was kept basic by the gradual addition of sodium hydroxide solution as chlorine was bubbled into the solution. The temperature of the reaction mixture was kept at 0–5° during the addition. In all, 160 g. (4 moles) of sodium hydroxide dissolved in 280 ml. of water was added. Crystallization of the product from benzene yielded 310 g. (83%) of N-chloroacetamide of m.p. 107–108°. The literature m.p. is 110°.[15]

Addition of Bromine Chloride to Ethylene.—To a stirred, cooled solution of 126 ml. of concentrated (37%) hydrochloric acid in 126 ml. of water, 71 g. (0.52 mole) of N-bromoacetamide was added portionwise as ethylene was bubbled into the mixture. Bromine color was observed only locally as the portions of N-bromoacetamide were added. The oily organic layer was separated from the aqueous layer which was then extracted with ether. The organic product was washed with 5% sodium bicarbonate and dried over calcium sulfate. Distillation yielded 23.6 g. (32%) of 1-bromo-2-chloroethane, b.p. 105–108° (746 mm.), $d^{20}{}_4$ 1.723, $n^{20}{}_D$ 1.4920. These values agree with those reported.[5]

Similar experiments in other solvents led to varying results. The simultaneous addition of ethylene and hydrogen chloride to a chloroform solution of N-bromoacetamide yielded impure 1-bromo-2-chlorethane whereas in ether the product was mostly 1,2-dibromoethane with no bromochloride being isolated. In glacial acetic acid containing N-bromoacetamide and excess lithium chloride ethylene reacted to yield small amounts of 1-bromo-2-chloroethane (b.p. 106–107°), 1,2-dibromoethane (b.p. 111–139°) and 1-bromo-2-acetoxyethane (b.p. 155–162°).

Addition of Bromine Chloride to Styrene.—In a manner similar to that described for the addition of bromine chloride to ethylene 156 g. (1.5 moles) of styrene and 207 g. (1.5 moles) of N-bromoacetamide were slowly added separately to a cooled solution (−5 to 0°) of 378 ml. of 37% hydrochloric acid in 378 ml. of water. Distillation of the product yielded 119–145 g. (36–44%) of 2-bromo-1-chloro-1-phenylethane, b.p. 95–99 (3.5 mm.) 110–114 (7 mm.), $n^{20}{}_D$ 1.5770, $d^{20}{}_4$ 1.497.

Anal. Calcd. for C_8H_8ClBr: C, 43.7; H, 3.67; total halogen, 52.6. Found: C, 43.8; H, 3.77; total halogen, 51.9.

A series of experiments analogous to the one described above were carried out with N-chloroacetamide and excess hydrobromic acid in water. In each case styrene dibromide was the product. When a limited amount of hydrobromic acid was added dropwise during the reaction a very small yield of the bromochloride was isolated along with the dibromide.

A solution 33.5 g. (0.25 mole) of N-chloroacetamide and 68 g. (0.65 mole) of styrene in 400 ml. of ether was stirred rapidly and cooled to −5°. A total of 25 ml. of 48% hydrobromic acid was added dropwise so that no accumula-

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[9] P. Pfeiffer and B. Eistert, *J. prakt. Chem.*, **124**, 168 (1930).

[10] L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, pp. 173–174.

[11] S. Winstein and H. J. Lucas, THIS JOURNAL, **61**, 1576, 2845 (1939); S. Winstein and R. E. Buckles, *ibid.*, **64**, 2780 (1942); S. Winstein and E. Grunwald, *ibid.*, **70**, 828 (1948).

[12] S. Winstein and D. Seymour, *ibid.*, **68**, 119 (1946).

[13] A. Weisberger, *ibid.*, **67**, 778 (1945); J. D. McCullough, *ibid.*, **62**, 480 (1940); W. G. Young, D. Pressman and C. D. Coryell, *ibid.*, **61**, 1640 (1939).

[14] P. Pfeiffer and W. Praetorius, *J. prakt. Chem.*, **137**, 27 (1933).

[15] C. Mauguin, *Ann. chim.*, [8] **22**, 302 (1911).

tion of bromine color was allowed during the addition. Distillation yielded 16.5 g. (30%) of 2-bromo-1-chloro-1-phenylethane, b.p. 111–115° (7 mm.), $n^{20}\mathrm{D}$ 1.5660. The reaction mixture also yielded 11% of the dibromide. The analysis of the bromochloride for total halogen was quite low. This result as well as the lowered index of refraction points to the chlorohydrin, b.p. 110–111° (6 mm.), $n^{20}\mathrm{D}$ 1.5400[16] as a possible contaminant. The product when dehydrohalogenated as described below gave a 56% yield of α-chlorostyrene.

Dehydrohalogenation of 2-Bromo-1-chloro-1-phenylethane.—A solution of 7.3 g. (0.19 mole) of sodium hydroxide in 38 ml. of 70% ethanol was treated with 31 g. (0.14 mole) of the bromochloride according to the directions of Emerson and Agnew[17] for the dehydrochlorination of styrene dichloride. A 15.0 g. (78%) yield of α-chlorostyrene, b.p. 80–83° (20–22 mm.), $n^{20}\mathrm{D}$ 1.5578, was obtained. No bromine could be detected in the product. The α-chlorostyrene gave a precipitate with hot alcoholic silver nitrate whereas β-bromostyrene did not. The α-position of the chlorine was also checked by conversion of the compound to acetophenone by the action of 80% sulfuric acid.[17]

Addition of Bromine Chloride to *trans*-Cinnamic Acid.—To a solution of 20 g. (0.135 mole) of cinnamic acid and 59 ml. of 37% hydrochloric acid in 200 ml. of dimethylcellosolve 28.3 g. (0.205 mole) of N-bromoacetamide was added portionwise so that the temperature remained between 25 and 30°. Dilution with water led to two liquid phases. Both were separated and cooled to give samples of the product. Crystallization twice from aqueous ethanol yielded 19.8 g. (56%) of α-bromo-β-chlorohydrocinnamic acid, m.p. 180–181° (dec.). Pfeiffer and Praetorius[14] report m.p. 183–184° for a sample whose analysis indicated dibromide as a contaminant. It has been our experience that such mixtures melt higher than the pure bromochloride. These authors did not dehydrohalogenate their product.

Anal. Calcd. for $C_9H_8O_2ClBr$: C, 41.0; H, 3.04. Found: C, 40.9; H, 3.02.

Dehydrohalogenation of α-Bromo-β-chlorohydrocinnamic Acid.—A 6.0 g. (0.023 mole) sample of the bromochloride was treated with 2.1 g. (0.050 mole) of sodium hydroxide in 28 ml. of 60% ethanol in the same way as styrene bromochloride was. The reaction mixture was diluted with 500 ml. of water and neutralized to congo red with hydrochloric acid to form 2.8 g. (54%) of α-bromocinnamic acid, m.p. 130–133°. Crystallization from water gave a sample of m.p. 131–132° which checked with an authentic sample.

Addition of Bromine Chloride to the Stilbenes.—A solution of 1.0 g. (0.0055 mole) of the stilbene and 1 ml. of 37% hydrochloric acid in 30 ml. of dimethylcellosolve was treated with 0.83 g. (0.0060 mole) of N-bromoacetamide as described for cinnamic acid. The product from *trans*-stilbene separated on cooling. Crystallization from ligroin (b.p. 85–100°) yielded 1.09 g. (67%) of *erythro*-α-bromo-α′-chlorobibenzyl[9] (III), m.p. 222–224° (dec.). The product from *cis*-stilbene was obtained after the reaction mixture was concentrated to about 5 ml. Crystallizations from 95% ethanol and then from ligroin (b.p. 85–100°) yielded 0.22 g. (14%) of the *erythro* isomer, m.p. 222–224° (dec.) and 0.76 g. (47%) of *threo*-α-bromo-α′-chlorobibenzyl (IV), m.p. 99–101°.

Anal. Calcd. for $C_{14}H_{12}BrCl$: C, 56.8; H, 4.06. Found: C, 56.7; H, 4.09.

Preparation of Bromochlorides from Dibromides.—The method followed was that described by Pfeiffer and Eistert[9] for *meso*-stilbene dibromide. A solution of 30 g. (0.113 mole) of styrene dibromide in 400 ml. of benzene was treated with 400 ml. of anhydrous stannic chloride to yield 20.0 g. (80%) of 2-bromo-1-chloro-1-phenylethane, b.p. 106–107° (6 mm.), $n^{20}\mathrm{D}$ 1.5770, $d^{20}{}_4$ 1.500. This product was converted to α-chlorostyrene in 63% yield as described above. In a similar fashion 0.55 g. (0.0016 mole) of either *meso*- or *dl*-stilbene dibromide was treated with excess stannic chloride to yield 0.38 g. (80%) of *erythro*-α-bromo-α′-chlorobibenzyl (III), m.p. 222–224° (dec.).

IOWA CITY, IOWA

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[16] E. H. Huntress, "Organic Chlorine Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948, p. 1319.

[17] W. S. Emerson and E. P. Agnew, THIS JOURNAL, **67**, 518 (1945).

[CONTRIBUTION FROM THE ORGANIC RESEARCH LABORATORY, TRACERLAB, INC.]

The Synthesis of Ethyl Acetamidocyanoacetate, DL-Lysine, DL-Ornithine and DL-Tyrosine Labeled with Isotopic Carbon[1]

BY MELVIN FIELDS, DORIS E. WALZ AND SEYMOUR ROTHCHILD

The reductive acetylation of ethyl isonitrosocyanoacetate has been achieved in excellent yield by selective catalytic hydrogenation. New syntheses of *dl*-lysine, *dl*-ornithine and *dl*-tyrosine have been devised which have been utilized for the preparation of these compounds labeled with isotopic carbon.

The preparation of ethyl acetamidocyanoacetate (I) labeled with carbon-14 assumes special significance because of the versatility of this reagent in the synthesis of amino acids.[2] In our investigation of this route to a number of labeled amino acids, we have effected an improved preparation of I suitable for small scale work, and have devised satisfactory syntheses of *dl*-lysine, *dl*-ornithine and *dl*-tyrosine labeled at C-2 with carbon-14.

The preparation of ethyl isonitrosocyanoacetate (II) was accomplished in 90% yield by the nitrosation of ethyl cyanoacetate as described by Snyder and Smith for the preparation of ethyl isonitrosomalonate.[3] Previously published methods for the reductive acetylation of II have employed a variety of reagents such as aluminum amalgam,[4] zinc dust[5] and sodium hydrosulfite.[6] We investigated the selective catalytic hydrogenation of II at room temperature and atmospheric pressure in acetic anhydride solution with the results summarized in Table I. With 5% platinum–charcoal, as well as with Adams catalyst, hydrogenation practically ceased after two moles of gas had been absorbed, although the supported catalyst is obviously the more satisfactory under the conditions employed. Under similar conditions with 5% palladium–charcoal catalyst or with Raney nickel, four moles of gas were rapidly consumed with no apparent diminution of rate after two moles had been absorbed; interruption of the reaction after consumption of two moles of gas afforded I in variable yield with the palladium

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[1] This research was carried out under Contract AT-(40-1)-279 with the U. S. Atomic Energy Commission.

[2] N. F. Albertson and B. F. Tullar, THIS JOURNAL, **67**, 502 (1945); N. F. Albertson, *ibid.*, **68**, 450 (1946).

[3] H. L. Snyder and C. W. Smith, *ibid.*, **66**, 350 (1944).

[4] V. Cerchez and C. Colesiu, *Compt. rend.*, **194**, 1954 (1932).

[5] L. Light and Company, Ltd., British Patent 583,307; *C. A.*, **41**, 2747 (1947).

[6] B. F. Tullar, U. S. Patent 2,393,723; *C. A.*, **40**, 2465 (1946).