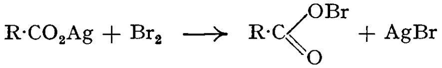
320. *The Reaction of Bromine with Silver (+)-α-Phenylpropionate. An Electrophilic Bimolecular Substitution.*

By C. L. Arcus, A. Campbell, and J. Kenyon.

The reaction of bromine in carbon tetrachloride solution with silver (+)-α-phenylpropionate yields (+)-α-phenylethyl bromide with inversion of configuration. It is considered that the positive-halogen compound, CHPhMe·CO·OBr, is first formed and that reaction subsequently proceeds according to equation (i) (below), with the similar reactions (ii) and (iii) as possible subsidiary reactions. All are bimolecular substitutions with inversion of configuration effected by the electrophilic reagent, positive bromine. The partial racemisation which occurs during this reaction is attributed to the experimentally-observed racemisation of (+)-α-phenylethyl bromide in solution in carbon tetrachloride by bromine in the presence of silver bromide.

Hell–Volhard bromination of (+)-α-phenylpropionic acid yields (±)-α-bromo-α-phenylpropionic acid.

Interaction of one equivalent of the silver salt of an aliphatic or substituted aliphatic carboxylic acid with two equivalents of bromine yields the alkyl bromide containing one carbon atom less than the original acid; numerous examples from the literature are cited by Kleinberg (*Chem. Reviews*, 1947, **40**, 386). The mechanism which has been generally accepted for this reaction (Birckenbach, Goubeau, and Berninger, *Ber.*, 1932, **65**, 1339; Bockemüller and Hoffmann, *Annalen*, 1935, **519**, 165; Kleinberg, *loc. cit.*) is that an intermediate positive-halogen compound R·CO·OBr, the acyl hypobromite, is formed:



$$R\cdot CO_2Ag + Br_2 \longrightarrow R\cdot C\begin{matrix}\diagup OBr \\ \diagdown\!\diagdown O\end{matrix} + AgBr$$

This undergoes decarboxylation to give the alkyl bromide, RBr.

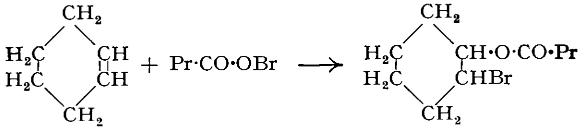
Bockemüller and Hoffman (*loc. cit.*) obtained the following evidence for the existence of the acyl hypobromites. Silver butyrate was shaken with bromine in carbon tetrachloride solution, and the product filtered. The yellowish-green filtrate, which was free from silver, liberated iodine from acidified potassium iodide solution, whereby its oxidising power was determined. The total bromine content was one-half of that of a solution of bromine of equal oxidising power,

$$Pr\cdot CO\cdot OBr + 2HI \longrightarrow Pr\cdot CO_2H + HBr + I_2$$

as compared with

$$Br_2 + 2HI \longrightarrow 2HBr + I_2.$$

Further, the butyryl hypobromite so prepared combined with *cyclo*hexene to give 2-bromo*cyclo*hexyl butyrate:



The use of a silver-free filtrate (as distinct from a suspension of the silver salt in bromine–carbon tetrachloride) precluded the possibility that the 2-bromo*cyclo*hexyl butyrate might be formed as follows:

$$-CH{:}CH- + Br_2 \longrightarrow -CHBr\cdot C^{\oplus}H- + Br^{\ominus}$$

$$-CHBr\cdot C^{\oplus}H- + Pr\cdot CO_2{}^{\ominus}Ag^{\oplus} \longrightarrow -CHBr\cdot CH(O\cdot CO\cdot Pr)- + AgBr.$$

Birckenbach *et al.* (*loc. cit.*) had earlier effected the reaction of silver acetate and iodine in ether at −80° and by adding *cyclo*hexene to the filtrate had obtained 2-iodo*cyclo*hexyl acetate.

Determinations of oxidising power and of bromine content, and addition to *cyclo*hexene, gave analogous results with a solution of benzoyl hypobromite, which was similarly prepared.

These findings demonstrate the existence in solution of compounds of the structure R·CO·OBr and indicate the bromine to be a " positive " halogen such as exists in hypobromous acid and the *N*-bromoamides and in contrast with the bromine of alkyl and acyl bromides.

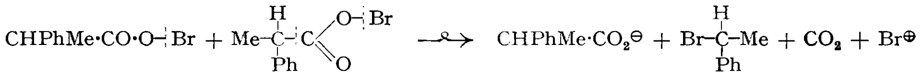
In order to elucidate further the mechanism of the substitution of carboxyl by bromine, silver α-phenylpropionate, prepared from the acid having $\alpha^{15^\circ}_{5893}$ +42·3° (*l*, 0·5) (optical purity, 81·7%), was treated in boiling carbon tetrachloride suspension with two equivalents of bromine;

it gave, in good yield, α-phenylethyl bromide, $\alpha_{5893}^{16^\circ}$ +46·2° (*l*, 1·0) [optical purity, 35·2%, by comparison with the highest recorded rotatory power of this compound, $\alpha_{5893}^{18^\circ}$ +131·4° (*l*, 1·0); Gerrard, *J.*, 1946, 741].

The retention of asymmetry during this substitution is thus 43·1%, and the following data permit comparison of the configurations of the acid and the bromide. (+)-α-Phenylpropionic acid has been converted, with retention of configuration, into (−)-α-phenylethylamine by the Hofmann, and other, rearrangements (Arcus and Kenyon, *J.*, 1939, 916; Kenyon and Young, *J.*, 1941, 263; Campbell and Kenyon, *J.*, 1946, 25). With nitrous acid the (−)-amine has been found (Campbell, unpublished results) to yield (+)-α-phenylethyl alcohol with 14·8% retention of asymmetry; it is concluded that during this reaction the diazonium ion $CHMePh{\cdot}N_2^{\oplus}$ dissociated into nitrogen and the ion $^{\oplus}CHPhMe$, and that the latter reacts with water to form the alcohol with a preponderance of the inverted configuration, due to shielding of the original point of attachment by the released nitrogen molecule. Finally, (+)-α-phenylethyl alcohol and (+)-α-phenylethyl bromide have the same configuration (Hughes, Ingold, and Scott, *J.*, 1937, 1201). Thus (+)-α-phenylpropionic acid and (+)-α-phenylethyl bromide have opposite configurations, and the silver salt–bromine reaction proceeds with inversion of configuration.

The following mechanism for the reaction is put forward. α-Phenylpropionyl hypobromite, CHPhMe·CO·OBr, is first formed, and two molecules of this compound react according to equation (i) to yield α-phenylethyl bromide, carbon dioxide, and two ions which combine to regenerate one molecule of α-phenylpropionyl hypobromite :

(i)



$$CHPhMe{\cdot}CO{\cdot}O{-}\!\vdots Br + Me{-}\overset{H}{\underset{Ph}{C}}{-}\!\vdots C\begin{matrix}\nearrow O{-}\!\vdots Br\\ \searrow O\end{matrix} \rightsquigarrow CHPhMe{\cdot}CO_2^{\ominus} + Br{-}\overset{H}{\underset{Ph}{C}}{-}Me + CO_2 + Br^{\oplus}$$

followed by

$$CHPhMe{\cdot}CO_2^{\ominus} + Br^{\oplus} \longrightarrow CHPhMe{\cdot}CO{\cdot}OBr$$

(ii) $$Br{-}\!\vdots Br + CHPhMe{-}\!\vdots CO{\cdot}O{-}\!\vdots Br \rightsquigarrow Br^{\ominus} + Br{-}CHPhMe + CO_2 + Br^{\oplus}$$

followed by

$$Br^{\ominus} + Br^{\oplus} \longrightarrow Br_2$$

(iii) $$Br^{\oplus} + CHPhMe{-}\!\vdots CO{\cdot}O{-}\!\vdots Br \rightsquigarrow Br{-}CHPhMe + CO_2 + Br^{\oplus}$$

It is possible that molecular bromine may react by a similar mechanism (ii) to yield α-phenylethyl bromide, carbon dioxide, and ions which combine to regenerate bromine. Finally, a small concentration of bromine cations may be either set up by reactions (i) and (ii) or may exist in equilibrium with CHPhMe·CO·OBr or with Br_2, and reaction may then proceed by (iii) in which α-phenylethyl bromide and carbon dioxide are formed and bromine cation is regenerated. All the reactions (i), (ii), and (iii) yield α-phenylethyl bromide with inversion of configuration and in each of them the attacking reagent is positive bromine, *i.e.*, bromine which tends to separate or which has separated with a sextet of electrons.

The configuration of the α-phenylethyl bromide resulting from these reactions would be completely inverted; the bromide obtained experimentally was inverted, but also partly racemised. The possibility that there may be a subsidiary mechanism of reaction in which a planar α-phenylethyl fragment is formed at one stage or which proceeds with retention of configuration is not excluded, but it appears most probable that the racemisation is due to the action of bromine and silver bromide on the fully inverted (+)-α-phenylethyl bromide during the period elapsing between its formation and the completion of the experiment. Experimental results leading to this explanation are described below.

It is concluded that the silver α-phenylpropionate–bromine reaction is mainly or entirely a bimolecular substitution with inversion of configuration effected by the electrophilic reagent, positive bromine. It appears to be the first established example of this class of replacement reaction.

The following experiments were carried out in order to elucidate the cause of the partial racemisation which occurred during the silver salt reaction. (+)-α-Phenylethyl bromide was dissolved in carbon tetrachloride and heated under reflux for 1 hour with silver bromide and bromine (0·7 equivalent); the recovered α-phenylethyl bromide was 99·8% racemised. During this experiment some hydrogen bromide was evolved, indicating the occurrence of bromination. From a similar experiment, in which silver bromide but no bromine was used, there was obtained, after heating for 3 hours, α-phenylethyl bromide which was racemised only to the extent of 0·6%. A similar experiment in which bromine (2·0 equivalents) but no silver bromide was used gave, after 3 and 19 hours, respectively, 38·4 and 99·0% racemisation. Thus racemisation is rapid when bromine and silver bromide are present together, slower with bromine alone, and slight with silver bromide alone.

The mechanism of racemisation of α-phenylethyl bromide by bromine, with catalysis by silver bromide, is uncertain. It may be due to bimolecular halogen exchange, which has been shown (Hughes, Juliusberger, Scott, Topley, and Weiss, *J.*, 1936, 1173) to be the mechanism of the racemisation of α-phenylethyl bromide by lithium bromide in solution in acetone. Alternatively, it may be due to a free radical reaction, $RBr + Br_2 \longrightarrow R^\bullet + Br_2 + Br^\bullet$, followed by $R^\bullet + Br^\bullet \longrightarrow RBr$.

Further work bearing on the mechanism of this racemisation is in progress.

A Hell–Volhard bromination of (+)-α-phenylpropionic acid has been carried out by converting the acid into the acid bromide and heating the latter with bromine; the resultant bromo-acid bromide with water gave optically inactive α-bromo-α-phenylpropionic acid. The isolation of the acid involved a crystallisation, so that the optically active acid, had it been present in small proportion, might have been removed; further, the reaction conditions might have caused racemisation of the optically active acid after its formation. With these reservations, the formation of optically-inactive α-bromo-α-phenylpropionic acid is consistent with bromination *via* the (symmetrical) enolic form of α-phenylpropionyl bromide, a mechanism of reaction which has been discussed by Watson (" Modern Theories of Organic Chemistry," 2nd edition, Oxford, 1941, p. 166).

EXPERIMENTAL.

(±)-α-Phenylpropionic acid was prepared by the method of Campbell and Kenyon (*loc. cit.*) and resolved according to Arcus and Kenyon (*loc. cit.*).

Silver-salt–Bromine Reaction.—α-Phenylpropionic acid having $\alpha_{5893}^{15^\circ}$ +42·3° (*l*, 0·5) (11·2 g.) was dissolved in one equivalent of N-NaOH (75 ml.), and to this solution was added silver nitrate solution until no further precipitate resulted. The grey precipitate was filtered off, washed, and dried *in vacuo* (yield, 18·0 g.). This silver salt was suspended with stirring in boiling, dry carbon tetrachloride (100 ml.), to which was added dry bromine (11·1 g., 2·0 equivs.). The solution was heated under reflux until all the colour had disappeared and then for a further hour. It was filtered from silver bromide, washed with sodium hydrogen carbonate solution and then with water, and dried (Na_2SO_4). Fractionation gave (+)-α-phenylethyl bromide, b. p. 98—99°/20 mm. (7·1 g.), having $\alpha_{5893}^{16^\circ}$ +46·2° (*l*, 1·0).

Racemisation of (+)-α-Phenylethyl Bromide.—A specimen of α-phenylethyl bromide, kindly supplied by Dr. W. Gerrard, had b. p. 80·5—83·5°/8 mm. and $\alpha_{5893}^{18^\circ}$ +96·6° (*l*, 1·0). This (3·3 g.) was dissolved in dry carbon tetrachloride (48 ml.), the solution having $\alpha_{5893}^{13^\circ}$ +8·89° (*l*, 2·0). Silver bromide (7·4 g.) and bromine (0·95 g., 0·7 equiv.) were added, and the mixture was boiled under reflux for 1 hour; acid fumes were evolved. The solution was washed with, successively, water, sodium thiosulphate solution, and water, and dried (Na_2SO_4); it had $\alpha_{5893}^{15^\circ}$ +0·03° (*l*, 2·0). Fractionation gave α-phenylethyl bromide (1·1 g.), b. p. 86°/7 mm., $\alpha_{5893}^{18^\circ}$ +0·21° (*l*, 1·0), and a fraction, b. p. 126°/8 mm., which solidified. The solid was dissolved in carbon tetrachloride, and light petroleum added; crystals (0·3 g.), m. p. 73—74°, separated, unchanged by further crystallisation from light petroleum. α-Phenylethyl bromide having $\alpha_{5893}^{18^\circ}$ +104·7° (*l*, 1·0) was prepared by the method of Gerrard (*loc. cit.*). It (7 g.) was dissolved in dry carbon tetrachloride (40 ml.) and heated under reflux with powdered silver bromide (5 g.) for three hours. Fractionation gave α-phenylethyl bromide (5·4 g.), b. p. 96°/18 mm., $\alpha_{5893}^{18^\circ}$ +104·1°. α-Phenylethyl bromide (6·5 g.) having $\alpha_{5893}^{18^\circ}$ +104·2° (*l*, 1·0) was dissolved in carbon tetrachloride (37 ml.), bromine (5·7 g., 2·0 equivs.) was added, and the solution boiled under reflux for three hours. A portion (13 ml.) was then removed, washed with aqueous sodium thiosulphate, dried (Na_2SO_4), and fractionated; it yielded α-phenylethyl bromide (2·0 g.), b. p. 96—97°/18 mm., $\alpha_{5893}^{17^\circ}$ +32·1° (*l*, 0·5). The remaining solution was boiled under reflux for a further sixteen hours, giving, after purification as before, α-phenylethyl bromide (3·1 g.), b. p. 96—97°/20 mm., $\alpha_{5893}^{18^\circ}$ +0·5° (*l*, 0·5).

Hell–Volhard Bromination of (+)-α-Phenylpropionic Acid.—α-Phenylpropionic acid having $\alpha_{5893}^{15^\circ}$ +42·3° (*l*, 0·5) (7·5 g.) was warmed to 60° for ½ hour with phosphorus tribromide (13·5 g.). The upper mobile layer was decanted and heated with bromine (8 g.) under reflux in an oil-bath at 140—150° for four hours. The resultant liquid was poured into water and then set aside overnight. An oil was produced which dissolved completely in sodium hydroxide solution. This solution was acidified and extracted with ether, and the extract was dried (Na_2SO_4) and distilled, to yield a fraction, b. p. 175—180°/25 mm. (5 g.), which partly solidified. Crystallisation from carbon disulphide by addition of light petroleum gave optically inactive α-bromo-α-phenylpropionic acid (4 g.), m. p. 91—93° (Fittig and Kast, *Annalen*, 1880, **206**, 28, record m. p. 93°).

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