143. *The Action of Acids on* N-*Bromoacetanilides.*

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The object of the investigation was to determine whether the general acid-catalysed transformation of *N*-bromoacetanilide follows an intramolecular mechanism, as suggested by Bell and his co-workers, or whether acids produce an intermediate and free brominating agent. Evidence has been found for the latter view, acetic acid being used as catalyst, and bromous acetate has been suggested as the intermediate brominating agent.

THE extra-molecular nature of the transformation of *N*-chloroacetanilide under the influence of halogen acids, first demonstrated by Orton and Jones (P., 1909, **25**, 196, 233, 305; *Brit. Assoc. Reps.*, 1910, 85), has been confirmed by subsequent investigations (for summary to 1928, see Orton, Soper, and Williams, J., 1928, 998). The halogen or mixed halogen, XY, produced by the primary interaction of the *N*-chloro- or *N*-bromo-acetanilide with the halogen acid HY, NPhX·COR + HY = XY + NHPh·COR, reacts with any substance in the reaction medium which is capable of being halogenated. In the simple transformation the substance halogenated is mainly the anilide. Certain allied substituted anilines, *e.g.*, in which X = NO_2 (for summary of reactions, see Ingold and Kidd, J., 1933, 984), may, however, under the influence of acids, be transformed quite differently by intramolecular rearrangement.

The further study of the halogenoacylanilides in non-aqueous solvents (Bell, *Proc. Roy. Soc.*, 1934, *A*, **143**, 377; Bell and Levinge, *ibid.*, 1935, *A*, **151**, 211; Bell and Brown, J., 1936, 1520; Bell and Danckwerts, *ibid.*, 1939, 1774) has demonstrated their transformation not only by halogen acids but also by carboxylic acids and phenols. Bell (J., 1936, 1154) considers that under these conditions of general acid catalysis the migration of the halogen group is an intramolecular change, an idea partly based on the observation that the concentration of free bromine detected during the transformations could not account for the observed reaction rate.

This view of the change as intramolecular would appear to involve the setting up of an intermediate position of considerable strain, if the process is envisaged as one of direct transfer, for the bromine atom attached to nitrogen is well separated from the *p*-position to which it ultimately migrates. With hydrochloric acid, *N*-bromoacetanilide forms bromine chloride (Orton and Jones, *loc. cit.*, 1910), and it is conceivable that with other acids some reactive brominating agent may be formed as an intermediate. Two lines of enquiry have been pursued to test this possibility in the present work: (*a*) whether cross-bromination occurs when the transformation is carried out in the presence of another brominatable substance, and (*b*) the behaviour of *N* : 2 : 4 : 6-tetrabromoacetanilide (where self-bromination is impossible) when examined in the presence of a carboxylic acid.

If the change is truly intramolecular, addition of added substances, such as anisole or phenetole, should not affect the nature of the end-product, *p*-bromoacetanilide, provided that there be no direct interaction between these substances and *N*-bromoacetanilide. It was found that anisole and phenetole do not react appreciably with *N*-bromoacetanilide. Other anilides could be used in place of an ether, but the production of mixed *N*-bromo-derivatives formed by direct interchange of the bromine is difficult of detection, and additions of other anilides were not made. It was found that when anisole or phenetole was present, and acetic acid was added as catalyst, acetanilide could be isolated from the end-products in both cases (40—50% recovered), together with some *p*-bromoacetanilide.

By using anisole, an ether fraction rich in bromine was separated from which, after hydrolysis and benzoylation, *p*-bromophenyl benzoate was separated. Hence, in the presence of substances which are easily brominated, cross-bromination occurs during the transformation, indicating the formation of an intermediate and free brominating agent.

Experiments using *N* : 2 : 4 : 6-tetrabromoacetanilide showed that this substance was, as had been anticipated, stable in the presence of acetic acid in chloroform solution, in the sense that its iodine titre after addition to acidified potassium iodide solution did not decrease appreciably. The substance was also stable to anisole and to phenetole in the absence of acetic acid. The mixture of *N* : 2 : 4 : 6-tetrabromoacetanilide and acetic acid brominated the above ethers, however, at a speed dependent on the acid concentration and independent of that of the ether and of its nature. This indicates that a brominating agent is produced from a bromoamine when acid is added, which can brominate so rapidly that it is removed as fast as it is produced. The rate of fall of oxidising power of the solution is thus a measure of the rate of production of the brominating agent.

Two possibilities as to the nature of this brominating agent have been considered. Hypobromous acid is known to be a very effective brominating agent (cf. its estimation; Biilman and Rimbert, *Bull. Soc. chim.*, 1923, **33**, 1465) and might be produced by the reaction NPhBrAc + R·CO_2H = NPh(CO·R)Ac + HOBr, followed by bromination, production of water, and hydrolysis of the diacyl derivative. Although this might explain the action of carboxylic acids, picric acid, which is a strong catalyst (Bell, 1934, *loc. cit.*), should give an acetyl derivative of a secondary amine which would not be hydrolysed: NPh[$C_6H_2(NO_2)_3$]Ac. Nevertheless, only *p*-bromoacetanilide was isolated when picric acid was used as a catalyst. The brominating agent cannot, therefore, be hypobromous acid.

An alternative view is that the bromine of the *N*-bromo-derivative forms with a carboxylic acid or a phenol, a bromous salt, analogous to the iodous salts (Masson and Argument, J., 1938, 1702): NPhBrAc + R·CO_2H = NHPhAc + R·CO_2Br, followed by R·CO_2Br + NHPhAc $\longrightarrow$ C_6H_4Br·NHAc + R·CO_2H, for the simple transformation in the absence of other easily brominatable substances. Bell and his co-workers found that the order of general acid catalysis is greatest for the *N*-iodo- and least for the *N*-chloro-acylanilides. This order of general acid catalysis is paralleled by the increasing basicity of the halogens with increasing atomic number, and by the increasing ease of formation of halogen salts of the kind postulated for bromine in the above mechanism.

EXPERIMENTAL.

Preparation of Materials.—*N*-Bromoacetanilide, prepared by the method of Slosson (*Ber.*, 1895, **28**, 3266), had a purity of 98% by titration with thiosulphate after addition to acidified potassium iodide. *N* : 2 : 4 : 6-Tetrabromoacetanilide was prepared by adding 6 g. of tribromoanilide to 20 c.c. of chloroform and 3 g. of bromine in 100 c.c. of 5% potassium bicarbonate at 0°, with good stirring. When solution was complete, the chloroform layer was separated, dried, and evaporated in a vacuum. Yellow prisms were obtained of purity 89—93·5% by titration. Recrystallisation from chloroform did not increase the purity but all samples gave the same reaction rates. Acetic acid was purified by Bradfield and Orton's method (J., 1927, 983), giving an acid, m. p. 16·2°, stable to bromine. Chlorobenzene was dried over anhydrous potassium carbonate and fractionally distilled; b. p. 130·6° (uncorr.)/760 mm., $n_{\rm D}^{15^\circ}$ 1·5271. Chloroform, treated as above for chlorobenzene, was neutral to bromothymol-blue; b. p. 61·7°/779 mm., $n_{\rm D}^{15^\circ}$ 1·4491. Anisole and phenetole were shaken with ferrous sulphate, dried, and distilled.

Cross-bromination.—Three runs were carried out, of which the following is typical. 5·35 G. of *N*-bromoacetanilide were dissolved in chloroform, anisole or phenetole added (1 or 2 mols.), together with 50 c.c. of glacial acetic acid, and the solution made up to 500 c.c. This was kept at 25·0° in the dark until the reaction was complete (3—5 days). During this time the iodine titre of a similar mixture of *N*-bromoacetanilide and anisole or phenetole fell by less than 2%. This fall may be due to direct interaction of the phenolic ether and the *N*-bromoacetanilide. Cross-bromination may therefore occur to the extent of 2% without its affording evidence that an intermediate and free brominating agent is produced when acid is present.

The chloroform and acetic acid were then distilled off under diminished pressure, and the residue extracted with ligroin (b. p. 50—60°). This dissolves the ethers and precipitates the anilides. The latter were recrystallised, and 45% of the *N*-bromoacetanilide was recovered as acetanilide (1·55 g.) and only 10% as *p*-bromoacetanilide (0·53 g.). The isolation of acetanilide as the main anilide shows that cross-bromination has occurred to the extent of over 40%. This percentage is probably greater, for in the absence of anisole or phenetole, 95% of the *N*-bromoacetanilide can be recovered as *p*-bromoacetanilide as against 10% when the phenolic ether is present.

Anisole (1 mol.) being used as the added substance, the ligroin extract containing the phenolic ethers gave on distillation a fraction distilling at 190—214° (Found, by Carius's method: Br, 34·6%) (*p*-bromoanisole has b.p. 215°; Br, 42·75%). This distillate was hydrolysed with hydrochloric acid at 170—200° for 3 hours to convert the anisoles into phenols. The product was dissolved in sodium hydroxide, benzoylated, and *p*-bromophenyl benzoate separated; m. p. 102° (uncorr.) (Beilstein gives 104°).

40—50% of acetanilide was separated in each case when phenolic ether was present, and this, together with the high percentage of bromine in the ethereal fraction from the ligroin extract, in which solvent anilides are insoluble, and the separation of a derivative of *p*-bromoanisole, is clear evidence of cross-bromination.

Behaviour of N : 2 : 4 : 6-*Tetrabromoacetanilide.*—The stability of this substance to anisole in chlorobenzene solution in the absence of added acid is shown in the first table, and its stability in chlorobenzene solution in the presence of acetic acid is shown in the second table.

[Anisole] = 0·5M; [:NBr] = 0·025M; temp. = 25·0°.

Time, mins.	7	27	47	70	113
Titre, c.c. of $Na_2S_2O_3$	9·62	9·68	9·65	9·62	9·60

[Acetic acid] = 1·67M; [:NBr] = 0·025M; temp. = 25·0°.

Time, mins.	6·1	20	52	210
Titre, c.c. of $Na_2S_2O_3$	9·55	9·52	9·52	9·46

In the presence of both anisole and acetic acid, the titre of the solution fell, and crystals of tribromoacetanilide separated, thus affording additional evidence of cross-bromination. The rate of fall of titre conforms to that of a unimolecular reaction and a typical experiment is given in Table I. Table II summarises the results obtained.

TABLE I.

[Acetic acid] = 1·67M; [Phenetole] = 0·1M; [:NBr] = 0·025M.

Time, mins.	0	5	10	34	51	70
Titre, c.c. of $Na_2S_2O_3$	9·31	9·11	8·90	7·97	7·45	6·72
$k_1 \times 10^3$	—	4·32	4·59	4·57	4·37	4·65

Mean $k_1 = 4·50 \times 10^{-3}$

TABLE II.

Phenolic ether.	Acetic acid.	Mean values of $k_1 \times 10^3$.	Phenolic ether.	Acetic acid.	Mean values of $k_1 \times 10^3$.
Anisole, 0·5M	1·67M	4·40, 4·51, 4·28	Phenetole, 0·2M	1·67M	4·35, 4·43
Anisole, 0·1M	1·67M	4·42, 4·45, 4·26	Phenetole, 0·1M	1·67M	4·59, 4·50
Anisole, 0·05M	1·67M	4·35	*p*-Tolyl methyl ether, 0·2M	1·67M	4·37, 4·28
Anisole, 0·2M	1·67M	4·11, 4·28	*p*-Tolyl methyl ether, 0·1M	1·67M	4·54, 4·62
Anisole, 0·2M	0·835M	2·33, 2·26			

p-Tolyl methyl ether at 0·2M concentration showed a 4·1% fall in titre with the bromo-amine in the absence of acid in the course of 1 hour, and the titres in the acid-catalysed reaction have been corrected for this spontaneous reaction. An increase in the concentration of anisole from 0·05M to 0·5M does not affect the speed appreciably, nor does the substitution of anisole by phenetole or *p*-tolyl methyl ether. Decrease of the acid concentration from 1·67M to half this value reduces k_1 to approximately half its previous value. The values of k_1 recorded thus have reference to the rate at which a brominating agent, considered to be bromous acetate, is produced from *N* : 2 : 4 : 6-tetrabromoacetanilide and acetic acid.

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