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SOME OBSERVATIONS CONCERNING THE BROMINATION OF IMIDAZOLE DERIVATIVES IN CHLOROFORM

P. LINDA

Istituto di Chimica Organica, Università di Perugia, Perugia, Italy

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Abstract—The bromination of imidazole, N-methylimidazole, benzimidazole and N-methyl- benzimidazole in chloroform has been studied.

Imidazole gives with half mole of bromine a C-polybromoderivative together with imidazole hydrobromide which by treatment with additional bromine gives a red dicoordinate complex of unipositive bromine. N-methylimidazole gives a similar result.

Benzimidazole also gives a dicoordinate complex but, probably, the intermediate is the N-bromobenzimidazole hydrobromide: no C-bromination is detected in this case.

Under similar conditions N-methylbenzimidazole gives a 1:1 complex of the n-donor type.

The reasons for these differences are discussed.

THE halogenation of heteroaromatic compounds proceeds by different reaction paths depending on the nature of the heterocyclic substrate and the experimental conditions.[1]

In the bromination of imidazole[2] the latter was treated with an equimolecular amount of bromine in chloroform at room temperature and yielded after removing most of the solvent and boiling the residue with water 2,4,5-tribromoimidazole, imidazole hydrobromide, ammonium bromide and a very small amount of 4,5-dibromoimidazole.

Similar results were obtained with N-methylimidazole.[3] The bromination of the benzo derivatives has not been reported.

RESULTS

Imidazole and N-*Methylimidazole.* Imidazole has been brominated under conditions similar to those reported[2] and in the dark. A white precipitate formed almost immediately and if this was isolated when only half a mole of bromine had been added, the compound exhibited physical properties and analytical data corresponding to the imidazole hydrobromide.

Further addition of bromine converted the white precipitate into an orange crystalline solid **A**, m.p. 108–110° (dec), insoluble in the reaction mixture. Evaporation of the mother liquor led to a white residue, melting at 220–222° identical with 2,4,5-tribromoimidazole. Similar results were obtained using dichloroethane or carbon tetrachloride as solvent.

The empirical formula of the orange compound **A** was $C_3H_4Br_2N_2$. It did not give imidazole by treatment with sodium sulfite and was converted into 2,4,5-tribromoimidazole by treatment with hot water. The following structures were considered:

(a) A 1:1 imidazole–bromine molecular complex of the n-donor type similar to

that formed from interaction of quinoline with bromine in carbon tetrachloride solution.[4]

(b) A π-donor type complex formed by a charge-transfer process involving the π electrons of the ring

(c) A dicoordinate complex of unipositive bromine $Im_2Br^+Br_3^-$ similar to that formed by quinoline[5] and pyridine[6] Ag^+ complexes by treatment with bromine.

(d) The hydrobromide of N-bromoimidazole

If the structure is of type (a) or (b) all the bromine (calc. as Br_2) should be "available", i.e. reducible by iodide anions; if the structure is of type (c) the "available" bromine should be 50% of total bromine (calc. as Br_2) or 75% (50% as Br_2, 25% as Br^+) if also the unipositive bromine is reduced; if (d) is the formula 50% of bromine (calc. as Br^+) should be "available".

Experimentally it was found that only about 50% of bromine (as Br_2) or 25% (as Br^+) was "available". On this basis the structure (c) was tentatively assigned to compound **A**. Further experimental evidence is necessary but the very low solubility of this compound in inert solvents and its decomposition in highly polar solvents prevented determination of the mol. wt. and the electronic adsorption spectrum.

The behaviour of N-methylimidazole was similar but the analyses were less good since the derivatives are liquid or semisolid.

Benzimidazole. In this case no precipitation of a white hydrobromide was observed. The orange compound of empirical formula $C_7H_6N_2Br_2$ has properties similar to those of the analogous derivative of imidazole. The structure is probably also that of a dicoordinate complex of unipositive bromine, but an important difference was observed: after the evaporation of the mother liquors *no appreciable amount of either poly- or mono-C-bromo derivatives of benzimidazole were collected.*

N-*Methylbenzimidazole.* The orange crystalline compound formed by the interaction of N-methylbenzimidazole with bromine exhibits different chemical properties:

(a) Addition of sodium sulphite gives the free base;

(b) The iodide ions reduce all the bromine present.

These chemical properties suggest in this case a structure of the n-donor type.

DISCUSSION

The reported data indicate that imidazole (and its N-methyl derivate), benzimidazole and N-methylbenzimidazole react with bromine in three different ways.

The bromination of imidazole should proceed according to the following scheme:

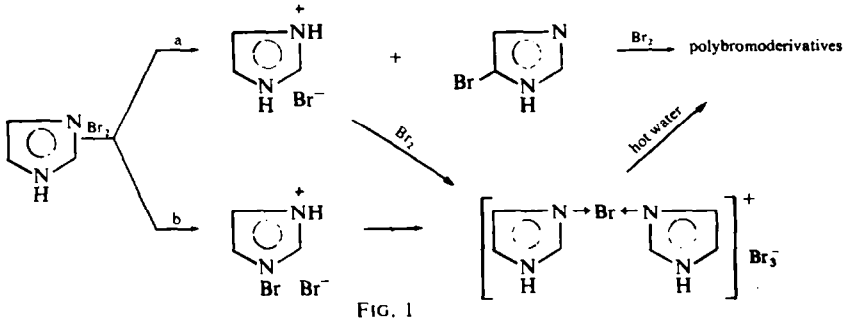

FIG. 1

Path(a) should be the preferred one since the position 4 is probably the one most subjected to an electrophilic attack.

The formation of polybromo derivatives is due probably to the fact that unprotonated bromoimidazole may undergo further bromination faster than imidazole hydrobromide.

In the case of benzimidazole the reactive positions 4 and 5 are blocked by the anellation and the bromination on the N atom is the observed reaction path b; the hydrobromide of the N-bromobenzimidazole probably, is then converted into the orange dicoordinate complex of unipositive bromine.

Finally in N-methylbenzimidazole there are no reactive positions and as substitution does not occur on the C or N atoms, a n-donor type complex is formed.

EXPERIMENTAL

Materials. Imidazole (Aldrich) was recrystallized from benzene, m.p. 89–90°. N-Methylimidazole b.p. 200–202°,[7] benzimidazole m.p. 171–172°[8] n-methylbenzimidazole m.p. 59–60°,[9] and 2,4,5-tribromoimidazole m.p. 220–221°[2] were synthesized according to the literature. Imidazole hydrobromide was prepared by the general method[10]. AnalaR bromine was used without further purification. The solvents were commercial products dried on Drierite and distilled.

"Available" bromine. Analyses were carried out by treating a weighed sample (0·05–0·1 g) in 20 ml glacial AcOH with 3 ml 40% KI aq., diluting with 20 ml water and titrating the liberated I_2 with standard $Na_2S_2O_3$ soln.

Reaction of imidazole with bromine (1:1). Bromine 1·6 g (0·01 mole) in 15 ml $CHCl_3$ was added dropwise in the dark to a soln of 0·7 g (0·01 mole) imidazole in 50 ml $CHCl_3$. The orange crystalline solid **A** (1 g; m.p. 108–110°, dec), insoluble in the reaction mixture was washed with pure solvent, collected and analysed. (Found: C, 15·84; H, 1·71; N, 13·04; Br, 69·44; available Br 34·95); required for $C_3H_4Br_2N_2$: C, 15·81; H, 1·77; N, 12·29; Br, 70·12%). Mother-liquor evaporation gave a colourless solid 0·4 g m.p. 220–222° which analysed for $C_3HBr_3N_2$. (Found: C, 12·06; H, 0·53; N, 9·27; Br, 78·03; Calc.: C, 11·82; H, 0·33; N, 9·19; Br, 78·66%).

Reaction of imidazole with bromine (1:0·5). Operating as in the previous experiment, a colourless deliquescent solid (1 g) was collected. (Found: C, 23·48; H, 2·97; N, 17·90; Br^-, 53·11); $C_3H_4N_2 \cdot HBr$ requires: C, 24·18; H, 3·38; N, 18·80; Br^-, 53·63%. A suspension of this compound in $CHCl_3$ treated with 0·80 g (0·005 mole) Br_2 gave an orange crystalline solid (1·3 g) m.p. 105–108°, identical with solid **A**. (Found: C, 15·46; H, 1·76; N, 12·46; Br, 69·85; Available Br, 34·95%).

Reaction of imidazole hydrobromide with bromine. The slow addition of 1 g Br_2 in $CHCl_3$ to a 0·5 g suspension Im·HBr gave an orange crystalline solid (0·7 g) m.p. 105–107° identical with solid **A**. (Found: C, 15·41; H, 1·76; N, 12·46; Br, 70·01; Available Br, 35·04%).

Decomposition of solid **A** *in hot water.* As the solid **A** (7 g) was added to boiling water, the orange color immediately disappeared and white ppt was formed m.p. 220–221° (2 g), admixed with authentic 2,4,5-tribromoimidazole the m.p. was not depressed. (Found: C, 11·35; H, 0·20; N, 9·08; $C_3HBr_3N_2$ requires: C, 11·82; H, 0·33; N, 9·19%).

Reaction of benzimidazole with bromine (1:1). Bromine 0·80 g (0·005 mole) in 20 ml $CHCl_3$ was added dropwise in the dark to a soln of 0·45 g (0·005 mole) benzimidazole in 100 ml $CHCl_3$. The orange crystalline solid (1·2 g) m.p. 240–245° was washed with pure solvent and analysed. (Found: C, 30·74; H, 2·42; N, 10·02; Br, 57·50; Available Br, 27·80; Calcd. For $C_7H_6N_2Br_2$; C, 30·24; H, 2·18; N, 10·08; Br, 57·62%). The same results were obtained with various bromine amount (20, 50, 70%). No appreciable residue was collected from the mother liquor of the 1:1 experiment.

Reaction of N*-methylbenzimidazole with bromine* (1:1). N—CH_3 Benzimidazole (2 g, 0·015 mole) in 20ml $CHCl_3$ and Br_2 (2·4 g, 0·015 mole) were mixed slowly at room temp in the dark. The orange ppt, m.p. 110–112° (4·2 g) was collected, washed with fresh solvent and dried in a vacuum dessicator over P_2O_5. (Found: C, 32·91; H, 2·51; N, 9·60; "available" Br, 54·99; $C_8H_8N_2 \cdot Br_2$ requires: C, 32·87; H, 2·76; N, 9·60; Br, 54·74%).

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