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BEHAVIOUR OF 2-SUBSTITUTED 6,8-DIBROMO-3,1-BENZOXAZIN-4-ONES TOWARDS o-PHENYLENEDIAMINE AND ANTHRANILIC ACID ; A CASE OF UNUSUAL CLEAVAGE OF 6,8-DIBROMO-2-METHYL-3,1-BENZOXAZIN-4-ONE

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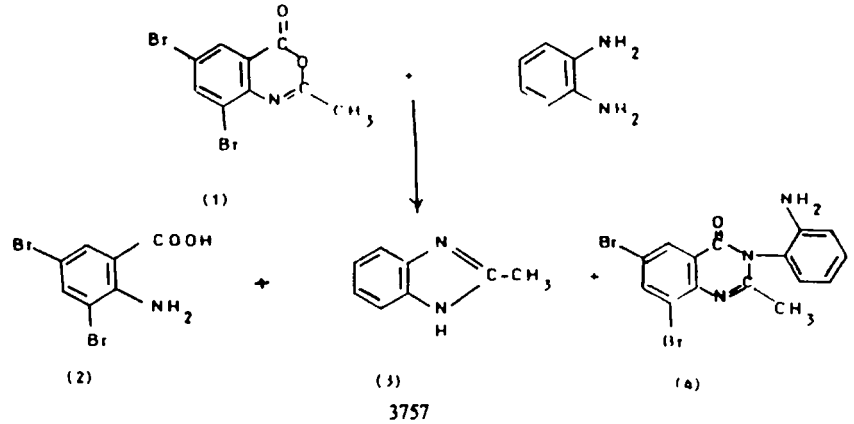
Abstract - 6,8-Dibromo-2-methyl-3,1-benzoxazin-4-one (1) reacts with o-phenylenediamine to give a mixture of 3,5-dibromoanthranilic acid (2), 2-methylbenzimidazole (3) and 3-(o-aminophenyl)-6,8-dibromo-2-methylquinazolin-4-one (4). However, when the reaction was conducted in ethanol or in the absence of solvent at elevated temperature, a mixture of (2) & (3) was obtained. A similar cleavage of (1) took place when it was allowed to react with anthranilic acid yielding a mixture of (2) and N-acetylanthranilic acid (6). The reaction of o-phenylenediamine with 6,8-dibromo-2-phenyl-3,1-benzoxazin-4-one (7) proceeded normally to give 3-(o-aminophenyl)-6,8-dibromo-2-phenylquinazolin-4-one (8) or 2-benzoylamino-3,5-dibromo-N-(o-aminophenyl)benzamide (9), depending upon the reaction conditions.

Recently,[1] we reported that 6,8-dibromo-2-methyl-3,1-benzoxazin-4-one (1) reacts with primary or secondary amines at room temperature via ring opening to give 2-acetylamino-3,5-dibromobenzamide derivatives. The reaction involved nucleophilic attack of the co-reactant amine at 4-position of the benzoxazin-4-one ring. These results contrast sharply with the recent generalisation made by Errede et al[2] for the reaction of 2-methylbenzoxazin-4-ones with simple amines. They claimed that the reaction in this case involves nucleophilic attack at position-2 forming intermediate amidine salts which lose water, in very short intervals, to form the quinazolin-4-one derivatives.

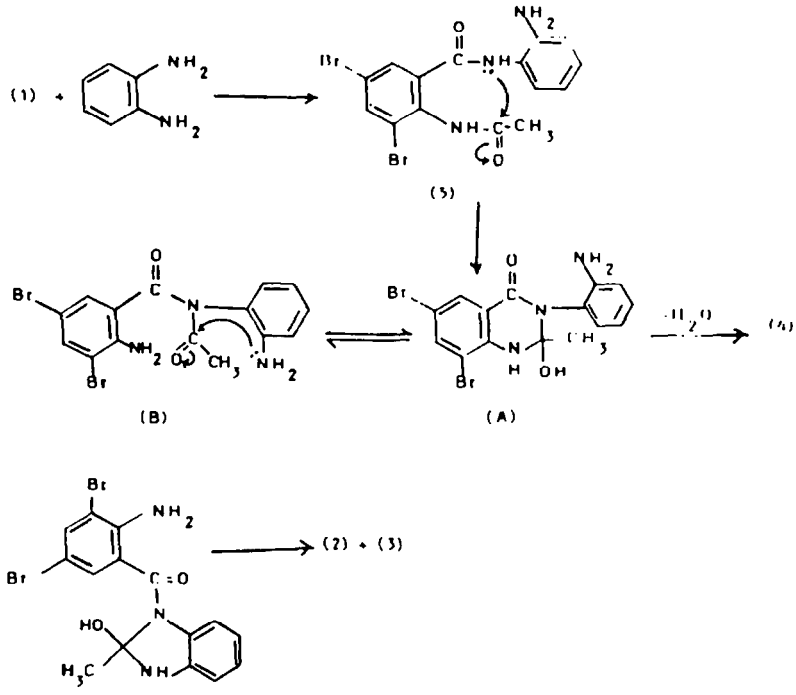
This investigation is an extension to our previous study in this field and deals with the behaviour of 6,8-dibromo-2-methyl-3,1-benzoxazin-4-one (1) towards o-phenylenediamine under different conditions. Thus, when (1) was allowed to react with o-phenylenediamine either in chloroform at room temperature or in refluxing benzene, an unusual cleavage took place yielding a mixture of 3,5-dibromoanthranilic acid (2), 2-methylbenzimidazole (3) and 3-(o-aminophenyl)-6,8-dibromo-2-methylquinazolin-4-one (4). However,



(1) (2) (3) (4)

when the reaction was conducted in refluxing ethanol or in the absence of solvent at high temperature (250°C), (2) and (3) were the only products isolated. 3,5-Dibromoanthranilic acid (2) and 2-methylbenzimidazole (3) were characterised by their identity with authentic sample.[3,4] The structure of 3-(o-aminophenyl)-6,8-dibromo-2-methylquinazolin-4-one (4) was substantiated from: (i) Microanalytical data, and (ii) Its infrared spectrum shows the stretching frequencies of NH and carbonyl groups of quinazolin-4-ones (cf. experimental).

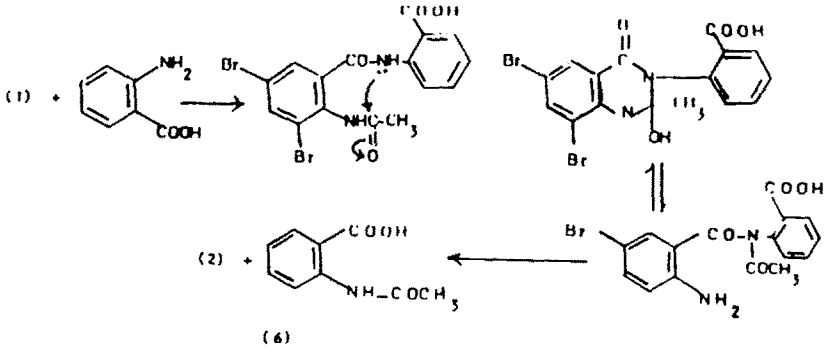
A possible explanation for the formation of the products (2-4) in the previous reaction could be outlined in scheme 1. The reaction evidently involves the initial formation of benzamide derivative (5) by nucleophilic attack at position-4. This benzamide derivative passes through the intermediate (A) which possibly exists in equilibrium with its isomeric compound (B) whose cleavage would give 3,5-dibromoanthranilic acid (2) and 2-methylbenzimidazole (3). Loss of water from the intermediate (A) gives the quinazolinone derivative (4). The second amino group of o-phenylenediamine seems to assist its partial existance in the isomeric structure (B) and consequently its cleavage. In favour of the proposed explanation is that similar cleavage reactions were observed previously in reactions of similar nature.[5]



(Scheme 1)

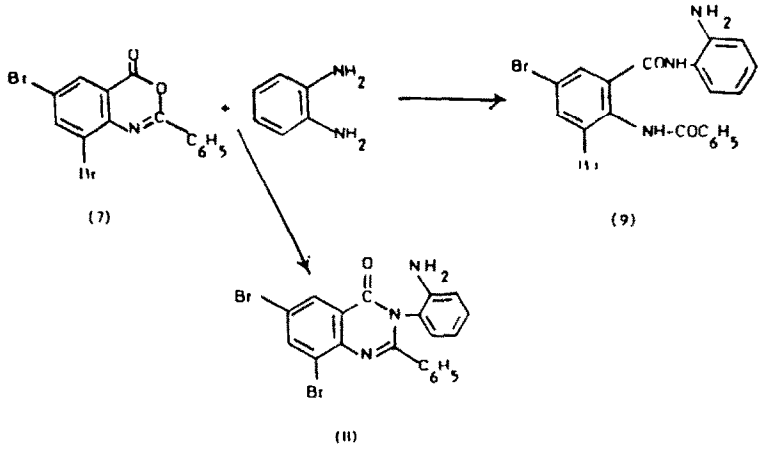
The unusual behaviour of 3,1-benzoxazin-4-ones towards o-phenylenediamine tempted us to investigate the reaction of (1) with anthranilic acid in which an ortho carboxy group replaces the basic ortho amino group of o-phenylenediamine. Errede et al[6] reported that the reaction of anthranilic acid with 2-methyl-3,1-benzoxazin-4-one proceeded normally by the attack either at position-4 to give the benzamide derivative or at position-2 affording the quinazolinone derivatives, depending upon the polarity of the solvent. However, when 6,8-dibromo-2-methylbenzoxazin-4-one (1) was allowed to react with anthranilic acid in benzene or in ethanol as examples of non polar and polar solvent, respectively, cleavage of the benzoxazinone ring took place giving a mixture of 3,5-dibromoanthranilic acid (2) and N-acetylanthranilic acid (6). It was not possible to isolated any benzamide or quinazolinone derivatives. The products of the reaction were characterised by their identity with authentic samples.

The formation of these cleavage products favours the proposed postulation for the cleavage reactions involved in case of reaction of o-phenylenediamine with (1) and could be accounted for by similar representation as follows :



(6)

The reaction of o-phenylenediamine with 6,8-dibromo-2-phenyl-3,1-benzoxazin-4-one (7), on the other hand, proceeded normally. Thus, when the reaction was carried out either in chloroform at room temperature, in refluxing benzene, or in the absence of solvent at elevated temperature, 3(o-aminophenyl)-6,8-dibromo-2-phenylquinazolin-4-one (8) was formed. However, when the reaction was carried out in refluxing ethanol, 2-benzoylamino-3,5-dibromo-N-o-aminophenylbenzamide (9) was formed.



(7) (9)

(II)

The structures of (8) & (9) were established, other than from analytical data, from a study of their infrared spectra. The infrared spectrum of (8) shows the carbonyl stretching frequency of quinazolinones in addition to νNH of primary amines while that of (9) show the carbonyl stretching frequency of amides and the NH stretching frequency of both amides and primary amines (cf. experimental).

EXPERIMENTAL

All melting points are uncorrected. Infrared spectra were measured on PYE UNICUM Sp 1200 spectrophotometer, using KBr wafer technique.

Reaction of 6,8-dibromo-2-methyl-3,1-benzoxazin-4-one (1) with o-phenylenediamine:

(A) In chloroform

The solution of 6,8-dibromo-2-methyl-3,1-benzoxazin-4-one (1) (0.01 mole) in chloroform (20 ml) was treated with o-phenylenediamine (0.01 mole) and the reaction mixture was left overnight at room temperature with occasional shaking. The solid formed was filtered off, treated with an aqueous sodium carbonate solution and filtered. The alkaline filtrate was acidified by conc. hydrochloric acid to give a colourless solid which was crystallised from benzene-ethanol mixture to give 3,5-dibromoanthranilic acid (2), m.p. 230-2°C, yield 25 %, undepressed on admixture with an authentic sample. The insoluble solid was boiled with water and filtered while hot. The solid formed after cooling of the aqueous extract was filtered off and crystallised from benzene-light petroleum (b.p. 60-80°) mixture to give 2-methylbenzimidazole (3), m.p. 173-5°C, yield 25 %. The product showed no depression with an authentic sample. Found: C, 72.53; H, 6.0; N, 20.95, $C_8H_8N_2$ requires: C, 72.72; H, 6.06; N, 21.21 %. The remaining water - insoluble solid product was crystallised from ethanol to give 3-(o-aminophenyl)-6,8-dibromo-2-methylquinazolin-4-one (4), as colourless crystals, m.p. 220-1°C, yield 20 %. Found: C, 43.8; H,3.0; N, 10.0; Br, 39.2, $C_{15}H_{11}N_3OBr_2$ requires: C, 44.00; H, 2.68; N, 10.26; Br, 39.11 %.

(B) In Benzene:

A mixture of (1) (0.01 mole) and o-phenylenediamine (0.01 mole) in benzene (20 ml) was heated under reflux for 6 hrs., and left to cool. The solid reaction product was worked out as described in the previous

experiment to give 3,5-dibromoanthranilic acid (2), (30 % yield), 2-methylbenzimidazole (3) (30 % yield), and 2-(o-aminophenyl)-6,8-dibromo-2-methylquinazolin-4-one (4) (35 % yield).

(C) In ethanol:

A mixture of (1) (0.01 mole) and o-phenylenediamine (0.01 mole) in ethanol (20 ml) was heated under reflux for 6 hrs., then left overnight. The solid formed was filtered off and worked out as described previously to give 3,5-dibromoanthranilic acid (2) (35 % yield), and 2-methylbenzimidazole (3), (35 % yield).

(D) In the absence of solvent:

An equimolecular mixture of (1) and o-phenylenediamine was heated for 1 hr. at 250°C and left to cool. The product was found to be a mixture of 3,5-dibromoanthranilic acid (2) (28 % yield) and 2-methylbenzimidazole (3), (28 % yield).

Reaction of 6,8-dibromo-2-methyl-3,1-benzoxazin-4-one (1) with anthranilic acid.

A mixture of (1) and anthranilic acid (0.01 mole) in benzene (20 ml) was heated under reflux for 7 hrs. and left overnight at room temperature. The solid formed was filtered off, extracted with boiling water and filtered while hot. The water-soluble part, precipitated after cooling of water extract, was filtered off and crystallised from benzene-ethanol mixture to give N-acetylanthranilic acid (6), as colourless crystals, m.p. 175-7°C, yield 48 %, undepressed when admixed with the authentic sample. Found: C, 60.30; H, 5.2; N, 7.6, $C_9H_9NO_3$ requires: C, 60.33; H, 5.02; N, 7.82 %.

The water insoluble part was crystallised from benzene-ethanol mixture to give 3,5-dibromoanthranilic acid (2), as colourless crystals m.p. 230-2°C; yield 40 %, undepressed when admixed authentic sample.

The same reaction products were obtained by using ethanol as a solvent instead of benzene under the same reaction conditioins and in nearly the same yields.

Reactions of 6,8-dibromo-2-phenyl-3,1-benzoxazin-4-one (7) with o-phenylenediamine

(A) In chloroform:

The solution of (0.01 mole) of 6,8-dibromo-2-phenyl-3,1-benzoxazin-4-one (7) in chloroform (20 ml) was treated with o-phenylenediamine (0.01 mole) and the reaction was left overnight at room temperature with occasional shaking. The solid formed was filtered off and crystallised from n-butanol to give 3-(o-aminophenyl)-6,8-dibromo-2-phenylquinazolin-4-one (8), as colourless crystals, m.p. 318-20°C, yield 35 %. Found: C, 51.30; H, 2.75; N, 8.73; Br, 34.23, $C_{20}H_{13}N_3OBr$ requires: C, 50.95; H, 2.76; N, 8.91; Br, 33.97 (νNH 3365, 3470 cm^{-1}; νCO 1685 cm^{-1}).

(B) In benzene:

A mixture of (7) (0.01 mole) and o-phenylenediamine (0.01 mole) in benzene (20 ml) was heated under reflux for 6 hrs., and left to cool. The solid reaction product was characterised as 3-(o-aminophenyl)-6,8-dibromo-2-phenylquinazolin-4-one (8) (50 % yield).

(C) In the absence of solvent:

Heating equimolecular amounts of (7) and o-phenylenediamine at 250°C for 1 hr., gave (8) in 30 % yield.

(D) In ethanol:

The mixture resulting from the addition of o-phenylenediamine (0.01 mole) to a solution of (7) (0.01 mole) in ethanol (20 ml) was heated under reflux for 6 hrs., then left overnight at room temperature. The solid formed was filtered off and crystallised from n-butanol to give 2-benzoylamino-3,5-dibromo-N-o-aminophenylbenzamide (9), as colourless crystals, m.p. 249-51°C, yield 50 %. Found: C, 49.38; H, 3.11; N, 8.6; Br, 33.0, $C_{20}H_{15}N_3O_2Br_2$ requires: C, 49.08; H, 3.07; N, 8.58; Br, 32.71. (νNH 3270, 3400, 3500 cm^{-1}, νC=O, 1635, 1650 cm^{-1}).

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