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# SYNTHESIS AND BIOLOGICAL ACTIVITY OF 2-AMINO-1,3,4-OXADIAZOLE DERIVATIVES

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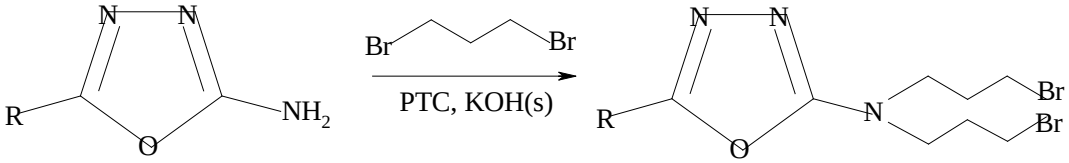
## Introduction

Substituted 1,3,4-oxadiazoles[1] have wide variety of uses, in particular as biologically active compounds in medicine and as dye stuff, fluorescent whitener, herbicides, fungicides, hypnotics and as sedatives. These compounds also showed antibacterial, analgesic, anti-malarial, anti-inflammatory, anticonvulsant and diuretic activity. In particular, 2-amino-1,3,4-oxadiazoles have been reported to possess promising anti-tumor activity[2].

Normally 2-amino-1,3,4-oxadiazoles alkylate at the amino group under alkaline condition. For instance , the anion derived from N-acetylamino-1,3,4-oxadiazole react with ethyl bromoacetate and phenacyl bromide to give N-alkyl derivatives[1]. Montgomery et.al[3] reported that N-mustards undergo ring closure to form strained ring systems, which subsequently act to alkylate a critical cell constituent on an NH, SH or OH functions and thereby blocks the function of such a cell constituent. biochemically, the alkylation could destroy the activity of an essential cell constituent. Prompted by these findings and in continuation of other studies on 1,3,4-oxadiazoles[4,5], a number of N-bromoalkylated 5-aryl-2-amino-1,3,4-oxadiazoles were prepared and were studied for their anti-mitotic activity.

## Methods and reagents

5-aryl-2-amino-1,3,4-oxadiazoles were prepared. It is alkylated to get alkylated derivative which showed antimitotic activity. A mixture of 5-aryl-2-amino-1,3,4-oxadiazole (A, 1 mmol), 1,3-dibromopropane (2 mmol)and tetrabutylammonium bromide (0.1 mmol) in THF were treated with powdered KOH (1 mmol) at room temperature and stirred for 15 hours. After 15 hours of stirring, TLC of the reaction mixture showed three spots corresponding to starting material, a minor spot due to allyl substituted product and the major spot due to expected product. The expected product is then isolated and later purified by column chromatography to get the desired N-mustard derivatives (B) in 70-80% yield. Structure proof for alkyl derivatives is provided by NMR studies. NMR showed the absence of NH protons in the region 3.3-3.35 ppm. $H^1$ NMR of all the bromoalkylated aminooxadiazoles showed peaks due to aromatic protons and other substitutents in the expected region. The substituted oxadiazoles gave significantly stable two molecular ion peaks with relative intensity ranging from 20-35% respectively. the two molecular ion peaks are due to the presence of bromine atom in the molecule. All underwent similar fragmentation pattern and gave aryl nitrile radical ion as the base peak.




(A) (B)

R a. Ph b. p(OMe)$C_6H_4$ c. m-($NO_2$)$C_6H_4$

**Table-1. Yield and physical data of 2-N,N-di(3'-bromopropyl)amino-1,3,4-oxadiazoles (B).**

| Product | Yield (%) | M.P ($^0$C) | Elemental analysis (found) | | | |
|---|---|---|---|---|---|---|
| | | | C (%) | H (%) | N (%) | Br (%) |
| B(a) | 75 | 216-217 | 41.7 (41.7) | 4.3 (4.2) | 10.4 (10.5) | 39.6 (39.7) |
| B(b) | 70 | 225-229 | 41.6 (41.5) | 4.4 (4.4) | 9.7 (9.73) | 36.9 (36.9) |
| B(c) | 70 | 144-146 | 37.5 (37.5) | 3.6 (3.5) | 12.5 (12.5) | 35.7 (35.7) |

**Table-2. Spectral data of aminooxadiazoles.**

| Product | $H^1$ NMR ($CDCl_3$) ppm (δ) | Mass spectra m/z (relative intensity) | Molecular formula |
|---|---|---|---|
| B(a) | 1.8-1.92 (m, 4H, $CH_2Br$)<br>7.5-7.8 (m, 5H, ArH) | 405 (M+1, 20)<br>401 (M+, 20)<br>302 (8), 103 (100),<br>77 (2) | $C_{14}H_{17}N_3OBr_2$ |
| B(b) | 1.8-1.9 (m, 4H, $CH_2$)<br>3.5-3.6 (t, 4H, $NCH_2$)<br>3.95 (s, 3H, $OCH_3$)<br>4.75-4.95 (t, 4H, $CH_2Br$)<br>7.1-7.12 (d, 2H, ArH)<br>7.7-7.72 (d, 2H, ArH) | 435 (M+1, 25)<br>431 (M+, 26),<br>302 (11), 298 (11),<br>133 (100), 107 (5) | $C_{15}H_{19}N_3O_2Br_2$ |
| B(c) | 1.8-1.9 (m, 4H, $CH_2$)<br>3.6-3.65 (t, 4H, $NCH_2$)<br>4.72=4.95 ($CH_2Br$)<br>7.45-7.5 (d, 2H, ArH)<br>7.7-7.8 (d, 2H, ArH) | 450 (M+1, 21)<br>446 (M+, 20)<br>302 (6), 298 (6),<br>148 (100), 122 (4) | $C_{14}H_{16}N_4O_3Br_2$ |

**Experimental procedure**

Melting point is determined. Elements present are also determined. (Table-1). NMR spectra were recorded on a Bruker MHz spectrometer in $CDCl_3$ solution. $H^1$ NMR spectra were measured at 300 MHz, TMS was used as an internal standard and chemical shifts are expressed in ppm (δ scale). Mass spectra were obtained on a Finnigan mass spectrometer (Table-2). TLC plates coated with silica gel were used and the spots were developed with iodine.

**Preparation of 2-N,N-di-(3'-bromopropyl)amino-1.3.4-oxadiazoles (B)**

Freshly powdered KOH (0.28g, 5 mmol) is added to the mixture of 2-amino-5-phenyl-1,3,4-oxadiazole (A, 0.81g, 5 mmol), 1,3-dibromopropane (2.4g, 9.9 mmol) and tetrabutyl ammonium bromide (0.32g, 1 mmol) in THF (15 mL) and stirred for 15 hours. Then the solvent is evaporated under reduced pressure and extracted with ether. The organic layer is washed with brine solution, dried over anhydrous sodium sulphate and evaporated. The residue is then dissolved in minimum quantity of chloroform and diluted with petroleum ether. The alkylated derivative (B) crysallises as a white crystalline solid. The yield and other parameters are shown in Table-1.

**Anti-mitotic activity:**

The anti-mitotic activity of the synthesised products were studied by Onion Root Tip method[6]. The $ID_{50}$ (concentration for 50% inhibition of mitosis) is determined as follows. After germinating the onion root tips for 2 days by immersing the onion to an extent of about 0.5 cm in a sample tube containing a test solution (prepared by dissolving known weight of synthetic derivative in 3 mL of ethanol and diluted with distilled water to 250 mL in a standard flask), germinated root tips were then removed and placed on the tube containing fixing solvent (ethanol-acetic acid 3:1 v/v) for 24 hours. It is then kept in the preservating solvent (70% ethanol). Root tios were placed in microslide, a drop of stain solution (orcein in acetic acid:0.2N HCl 7:1 v/v) is added and the root tips were squashed by a blade. The slide is then mounted for observation under the microscope. The total number of cells and the number of dividing cells were counted. The percent of the number of dividing cells were compared to the control and the percent inhibition of mitosis bu the test anti-mitotic agent at a given concentration against a control were calculated. The concentration needed for 50% inhibition ($ID_{50}$) values for the synthetic derivatives for anti-mitotic activity are shown in Table-3.

Table-3: Anti-mitotic activity of 5-aryl-2-N,N-dialkylamino-1,3,4-oxadiazoles

| Compound | Conc.in $10^{-6}$ mol | No. of dividing cells | Total no. of cells | % of dividing cells | % of dividing cells when compared to control | % of inhibition when compared to control | $ID_{50}$ ($mol^{-1}$) ($x10^{-6}$) |
|---|---|---|---|---|---|---|---|
| B(a) | 4.963, 9.926, 24.814 | 93, 88, 86 | 695, 822, 993 | 13.38, 10.7, 8.66 | 75.17, 60.13, 48.65 | 12.31, 27.19, 35.51 | 24.0 |
| B(b) | 4.619, 9.238, 23.095 | 113, 113, 85 | 931, 960, 1021 | 12.14, 11.77, 8.33 | 68.2, 66.12, 46.8 | 31.8, 33.88, 53.2 | 20.0 |
| B(c) | 2.232, 4.464, 11.161 | 154, 144, 154 | 912, 895, 1068 | 16.88, 16.08, 14.42 | 94.89, 90.34, 81.01 | 5.11, 9.66, 18.99 | 24.0 |

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