Synthesis and antimicrobial activity of some bromo-benzothiazolo pyrazolines

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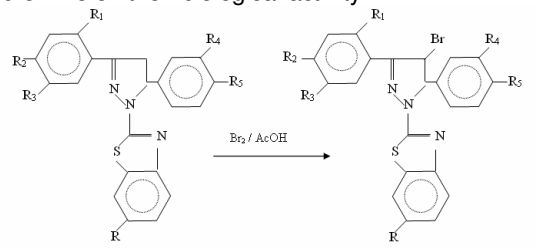
Abstract-The present investigation was carried out to study the effect of bromine on the biological activity of pyrazolines. Some previously synthesized substituted pyrazolines were brominated by bromine in acetic acid. The synthesized bromo-benzothiazolopyrazolines were characterized by elemental analysis, IR and PMR spectra. The synthesized bromo-benzothiazolopyrazolines were subjected to *in-vitro* antimicrobial activity against various pathogenic bacteria.

Introduction

Pyrazolines or di-hydro pyrazoles/Pyrazolines derivatives have been studied extensively because of their ready accessibility, diverse chemical reactivity and broad spectrum of biological activity. Literature survey reveals that several workers have synthesized pyrazolines by addition reactions of hydrazine [1], phenyl hydrazine [2] and 2, 4-dinitrophenylhydrazines [3] with chalcones. Antibacterial activity of some fluorine containing 2-Pyrazolines has been studied recently [4]. In view of the influence of halogen atoms on the biological activity of organic compounds [5], Ankhiwala [6] synthesized some nuclear halogenated pyrazolines and their derivatives and screened them for their biological activity. In continuation of our previously synthesized pyrazolines [7], we have now synthesized bromopyrazolines by the bromination of pyrazolines to study the effect of bromine on their biological activity.



Where,
R = CH_3, $R_1 = R_2 = R_3 = R_4 = R_5$ =H
R = OCH_3, R_1 = OH, $R_2 = R_3 = R_4$ = H, R_5 = Cl
R = OCH_3, R_1 = H, R_2 = Cl, $R_3 = R_4$ = H, R_5 = Cl
R = CH_3, R_1 = H, $R_2 = CH_3$, R_3 = H, $R_4 = R_5$ = OCH_3
R = OCH_3, R_1 = OH, $R_2 = R_3 = R_4 = R_5$ =H

Experimental procedure

All chemicals and solvents used in the present investigation were BDH products. Melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded in KBr on Perkin-Elmer 577 spectrophotometer and NMR spectra on an AC 300F spectrophotometer with $CDCl_3$ using TMS as internal references (chemical shift in δ ppm). Purity of the compounds was checked on TLC using silica gel-C.

Synthesis of 3, 5-diphenyl-1-(6-methylbenzothiazolo)-4-bromopyraxolines (I)

The 3, 5-Diphenyl-1-(6-methylbenzothiazolo) pyrazoline (0.62 g) was dissolved in hot acetic acid (40 ml). After cooling bromine (o.3 ml) in acetic acid (10 ml) was added drop wise with constant shaking in order to ensure thorough mixing. The reaction mixture was shaken occasionally and allowed to stand at room temperature for overnight. The solid mass obtained was separated by filtration, washed with water and dried. The white crystals obtained were crystallized from a mixture of chloroform and alcohol (2:1) (M.P. 215-216 ^{0}C).
Mol. Formula: $C_{23}H_{18}N_3SBr$
Observed: C = 61.34; H = 4.02; N = 9.4 %,
Calculated: C = ^1.60; H = 4.01; N = 9.37%
IR: ν_{max} (KBr): 2980, 1600, 1530, 1440, 1340, 1330, 1290, 1240, 1140, 1080, 1040,, 900, 870, 820, 750, 680 and 550 cm^{-1}.

Synthesis of 3-(2´-hydroxyphenyl)-5-(4-chlorophenyl)-1-(6-mrthoxybenzothiazolo)-4-bromopyrazoline (II)

The 3-(2´-hydroxyphenyl)-5-(4-chlorophenyl)-1-(6-methoxybenzothiazolo)-4-bromopyrazoline (0.73 g) was dissolved in hot acetic acid (40 ml). After cooling, bromine (0.3 ml) in acetic acid (10ml) was added drop wise with constant shaking to ensure thorough mixing. The reaction mixture was occasionally shaken and was allowed to stand at room temperature for overnight. The solid mass separated and filtered, washed with water and dried and recrystallization from the mixture of chloroform and alcohol (2:1) afforded pale yellow crystals (M.P. 240-242 ^{0}C).
Mol. Formula: $C_{23}H_{17}N_3SClBrO_2$
Observed: C = 61.34; H = 4.02; N = 8.10 %,
Calculated: C = 53.64; H = 3.30; N = 8.16 %

IR: ν_{max} (KBr): 3400, 2920, 1620, 1590, 1500, 1490, 1450, 1410, 1320, 1290, 1250, 1180, 1140, 1030,930, 900, 810, 760, 640, 550 and 500 cm^{-1}.

Synthesis of 3-(4´-chlorophenyl)-5-(4-chlorophenyl)-1-(6-methylbenzothiazolo)-4-bromopyrazoline (III)

The 3-(4´-Chlorophenyl)-5-(4-chlorophenyl)-1-(6-methoxybenzothiazolo)-4-bromopyrazoline (0.73 g) was dissolved in hot acetic acid (40 ml). After cooling bromine (0.3 ml) in acetic acid (10ml) was added drop wise with constant shaking to ensure thorough mixing. The reaction mixture was occasionally shaken and allowed to stand at room temperature for overnight. The solid mass separated, washed with water and dried. Crystallization from the mixture of chloroform and alcohol (2:1) afforded greenish yellow crystals (M.P. 204 ^{0}C).

Mol. Formula: $C_{23}H_{16}N_3SCl_2Br$

Observed: C = 61.34; H = 4.02; N = 8.08 %,

Calculated: C = 53.38; H = 3.09; N = 8.12 %

IR: ν_{max} (KBr): 2900, 1610, 1590, 1490, 140, 1340, 1310, 1200, 1160, 1070, 910,870, 830, 820, 750, 680 and 540 cm^{-1}.

Synthesis of 3-(4´-methylphenyl)-5-(3,4-dimethoxyphenyl)-1-(6-methylbenzothiazolo)-4-bromopyrazoline (IV)

The 3-(4´-methylphenyl)-5-(3, 4-dimethoxyphenyl)-1-(6-methoxybenzothiazolo) pyrazoline (1.49 g) was dissolved in hot acetic acid (40 ml). After cooling bromine (0.3 ml) in acetic acid (10ml) was added drop wise with constant shaking to ensure thorough mixing. The reaction mixture was occasionally shaken and allowed to stand at room temperature for overnight. The solid thus separated was filtered, washed with water and dried. Crystallization from the mixture of chloroform and alcohol (2:1) afforded white crystals (M.P. 175-176 ^{0}C).

Mol. Formula: $C_{26}H_{24}N_3SBrO_2$

Observed: C = 61.34; H = 4.02; N = 8.08 %,

Calculated: C = 59.77; H = 4.59; N = 8.04 %

IR: ν_{max} (KBr): 2920, 1600, 1570, 1530, 1490, 1440, 1320, 1260, 1240, 1100, 1020, 900,840, 820, 760, 730. 690, 630 and 550 cm^{-1}.

Synthesis of 3-(2´-hydroxylphenyl)-5-phenyl-1-(6-methoxybenzothiazolo)-4-bromopyrazoline(V)

The 3-(2´-Hydroxylphenyl)-5-phenyl-1-(6-methoxybenzothiazolo) pyrazoline (0.67 g) was dissolved in hot acetic acid (40 ml). After cooling bromine (0.3 ml) in acetic acid (10ml) was added drop wise with constant shaking to ensure thorough mixing. The reaction mixture was occasionally shaken and was allowed to stand at room temperature overnight. The solid mass separated, washed with water and dried. Crystallization from the mixture of chloroform and alcohol (2:1) afforded yellow crystals (M.P. 241-242 ^{0}C).

Mol. Formula: $C_{23}H_{18}N_3SO_2Br$

Observed: C = 61.34; H = 4.02; N = 8.08 % ,

Calculated: C = 57.50; H = 8.75; N = 16.66 %

IR: ν_{max} (KBr): 3360, 2900, 1620, 1590, 1520, 1460, 1330, 1270, 1250, 1180, 1160, 1040, 930, 900, 810, 760, and 530 cm^{-1}.

($CDCL_3$): δ 3.30 (1H, dd,C-H), δ 3.80 (3H, s, OCH_3), δ 5.70 (1H, dd, C-H), δ 6.90 to 7.7 (12H, m, Ar), δ 10.70 (1H, s, OH).

Results and Discussion

The structures of these products have been established by spectral and analytical studies. The PMR spectra of pyrazolines showed doublets for each $-CH_2$ proton between δ2.25 and δ3.60 and δ3.90 and δ4.00, and double doublet between δ5.25 and δ6.20 for –CH- protons. However in PMR spectra of bromo-benzothiazolopyrazolines, the signal between δ3.90 to δ4.00 is absent, which provides the conclusive evidence that electrophilic attack of bromine takes place at C-4 of the pyrazoline nucleus. The mass spectrum of 3-(2´-hydroxylphenyl)-5-phenyl-1-(6-methoxybenzothiazolo)-4-bromopyrazoline exhibits the molecular ion peak at m/z 480, which is the molecular weight of the compound.:

Antibacterial Activity

The synthesized compounds were assayed against human pathogens like gram positive *S.aureus* and *B. subtilis* and gram negative *E.coli* and *S.typhi* by agar cup plate method [8] at concentration of 40 µg/ml in solvent DMF using nutrient agar medium. The zone of inhibition was measured in mm. Under similar conditions control experiment was carried out using Streptomycin, Chloramphenicol and Penicillin. It was found that most of these compounds were found active against all bacteria except gram negative *E. coli*.

References

[1] Holla B. S., Shivnanda M. K., Akberali P. M. and Shenoy M. S. (2000) *Indian J. Chem.*, 39B, 440.

[2] Sorathia S. D., Patel V. B. and Parikh A. R. (1997) *Indian J. Chem.*, 36B, 630.

[3] Desai J. K. and Ankhiwala M. D. (1997) *J. Inst. Chem. (India)*, 69, 27.

[4] Desai M. D. and Desai K. K. (2002) *Asian J. Chem.*, 14(2), 995.

[5] Ankhiwala M. D. and Naik H. B. (1990) *J. Indian Chem. Soc.*, 67, 258.

[6] Ankhiwala M. D. (1990) *J. Indian Chem. Soc.*, 67, 514.

[7] Pathak Vishal, Kumar Bharat and Tiwari I. C. (2009) *J. Chemtracks*, 11(2), 469.

[8] Simoncini F., Rangone R. and Calani C., Formaco. Ed., Pract. 23, 559 (1968) *Chem Abstr.*, 1968, 69, 109851d.

Table 1- Comparable antimicrobial activity with known chosen standard drugs

Standard drugs	Compd.	Gram positive		Gram negative	
		S.aures	*B. subtilis*	*E. coli*	*S. typhi*
	I	10	14	NA	11
	II	13	9	NA	12
	III	11	12	NA	!0
	IV	14	12	10	13
	V	19	16	12	14
Norfloxacin		27	25	20	25
Ampicillin		22	23	24	18
Chloronphenicol		20	27	20	20