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SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF SOME SUBSTITUTED PHENOTHIAZIN-3-ONES

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ABSTRACT

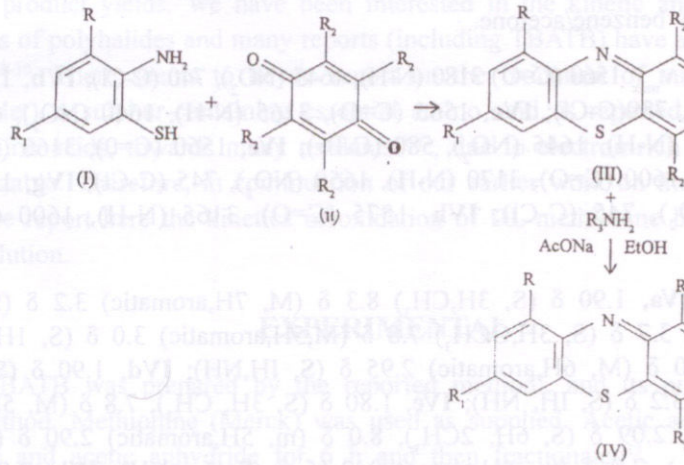
1,2,4-Trihalophenothiazin-3-ones **(III)** were prepared by condensing 2-aminobenzenethiols with chloranil/bromanil in 1:1 molar ratio. These compounds on refluxing with aryl amine and anhydrous sodium acetate in ethanol result in formation of substituted 2-arylamino phenothiazin-3-ones **(IV)**.

Key words : Phenothianzine-3-ones, Antibacterial activity.

INTRODUCTION

Various phenothiazine derivatives have been found to be associated with diverse pharmacological activities, such as antiinflammatory[1], anticancer[2, 3] bactericidal[4-6] and antiparasitic activities[7]. In continuation of our interest in the synthesis and usages of these compounds, we wish to report the synthesis of some new phenothiazinone derivatives.

In the present work, 1,2,4-trihalophenothiazin-3-ones **(III)** were prepared by the reaction of substituted 2-aminobenzenthiols **(I)** and chloranil/bromanil **(II)**. The compounds **(III)** were further refluxed with aryl amine and anhydrous sodium acetate in ethanol, which afforded substituted 2-arylamino phenothiazin-3-ones **(IV)** **(Scheme-I).**



(I) (II) (III) (IV)

Scheme I

EXPERIMENTAL

Melting points of all the compounds were determined in open capillaries and are uncorrected. The purity of the compounds was checked on thin layers of silica gel in various non-aqueous solvent systems. Structures of systhesised compounds were supported by their IR and NMR spectral data.

Bromanil was prepared by the method described by Tony and Hunter[8].

(i) Preparation of substituted 2-aminobenzenthiols (I).

Substituted 2-aminobenzenthiols were prepared by the method reported earlier[9-11]

(ii) Preparation of substituted l,2,4-trihalophenothiazin-3-ones (III).

To a suspension of chloranil/bromanil (**II**, 0.01 mole) in ethanol (20 mL) was added a solution of substituted 2-aminobenzenthiol (**I**, 0.01 mole) in ethanol (10 mL) and anhydrous sodium acetate (0.05 mole). The reaction mixture was refluxed for six hours. After cooling to room temperature, the solid separated was filtered, washed with water and finally with 30% ethanol. The products were recrystallised from benzene.

(Yields 55-70%); **IIIa**, ν_{max} 1600 (C==N), 1635 (C=O), 750 cm^{-1} (C-Cl) 1355 (NO_2) 1425 (-CH_3); ν_{max} 580 (C-Br); 1590(C=N), 1600 (C=O), 1350 (NO_2), 1420 (CH_3). 1_HNMR (DMSO); 1.8-2.09 δ (S,3H,CH_3), 7.8-8.3 δ (S,2H, aromatic).

(iii) Preparation of substituted 2-arylamino phenothiazin-3-ones (IV)

l,2,4-Trihalophenothiazin-3-ones (0.01 mole) in ethanol was mixed with arylamine (0.01 mole) and anhydrous sodium acetate (0.05 mole). The mixture was refluxed for four hours, the solid separated after cooling was filtered and washed with water and 30% alcohol. The products were recrystallised from benzene/acetone.

(Yields 60-70%); **IVa**, ν_{max} 1560 (C=O) 3180 (N-H), 1645 (NO_2), 740 (C-Cl); **IVb**, 1575 (C=O), 3170 (N-H), 1635(NO_2), 739(C-Cl); **IVc**, 1565 (C=O), 3165 (N-H), 1640 (NO_2), 682 (C-Br); **IVd**, 1675 (C=O), 3180 (N-H), 1645 (NO_2), 580 (C-Br); **IVe**, 1560 (C=0), 3160 (N-H), 1640 (NO_2), 750 (C-Cl); **IVf**, 1600 (C=O), 3170 (N-H), 1650 (NO_2), 745 (C-Cl); **IVg**, 1565 (C=O), 3170 (N-H), 1640 (NO_2), 745 (C-Cl); **IVh**, 1575 (C=O), 3165 (N-H), 1600 (NO_2), 582 (C-Br).

^{1}H NMR (DMSO); **IVa,** 1.90 δ (S, 3H,CH_3) 8.3 δ (M, 7H,aromatic) 3.2 δ (S, 1H,NH); **IVb**; 2.0 δ (S, 3H,CH_3) 3.7 δ (S, 3H,OCH_3) 7.8 δ (M,5H,aromatic) 3.0 δ (S, 1H,NH); **IVc**, 2.09 δ (S, 3H,CH_3) 7.90 δ (M, 6H,aromatic) 2.95 δ (S, IH,NH); **IVd**, 1.90 δ (S 3H, CH_3) 8.4 δ (M, 7H,aromatic) 3.2 δ (S, IH, NH); **IVe**, 1.80 δ (S, 3H, CH_3), 7.8 δ (M, 5H,aromatic) 3.1 δ (S, 1_H, NH); **IVf,** 2.09 δ (S, 6H, 2CH_3), 8.0 δ (m, 5H,aromatic) 2.90 δ (S, 1_H,NH); **IVg,** 2.05 δ (S, 3H,CH_3), 7.9 δ (m, 6H,aromatic) 3.15 δ (S, 1_H, NH); **IVh,** 2.09 δ (S, H, CH_3), 8.2 δ (m, 6H,aromatic), 3.0 δ (1H, NH)

Antibacterial activity

Compounds were screened for antibacterial activity by employing filter paper disc[12] method and tested against β-hemolytic streptococci, coguleus +ve, coaguleus -ve and Escherichia coli.

Table 1. Antibacterial activity of synthesised compounds (IV a-h).

S.No.	R	R_1	R_2	R_3	M.P. (°C)	Zone of inhibition			
						B-hemolytic streptococci	Coaguleus +ve	Coaguleus -ve	E. coli
IV a	CH_3	NO_2	Cl	C_6H_5NH	121	-	-	++	++
IV b	CH_3	NO_2	Cl	(o-CH_3)-C_5H_3NNH	121	++++	+++	++	-
IV c	CH_3	NO_2	Br	(o-NO_2)-C_5H_3NH	156	++	-	++	-
IV d	CH_3	NO_2	Br	(o-F)-C_6H_4NH	248	+++	-	+++	-
IV e	CH_3	NO_2	Cl	(o-NO_2)-C_6H_4NH	162	+++	-	+++	-
IV f	NO_2	CH_3	Cl	(o-CH_3)-C_5H_3NNH	118	++++	-	++++	++
IV g	NO_2	CH_3	Cl	(p-NO_2)-C_6H_4NH	176	+++	++	++++	-
IV h	NO_2	CH_3	Br	(m-NO_2)-C_6H_4NH	129	++++	++	++++	+++

The activity of compounds is represented by (+), (++), (+++) and (++++) depending upon the diameter and clarity of the zones of inhibition. Each (+) indicates a difference of 4 mm in the diameter of the zone of inhibition.Where there are no zones of inhibition, the result have been indicated by (–).

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