SYNTHESIS AND POLAROGRAPHIC BEHAVIOUR OF BENZOTHIAZOLYLAZOPYRIMIDINES

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The present paper deals with the synthesis and polarographic behaviour of some benzothiazolylazopyrimidines. Synthesis of these compounds have been achieved by the condensation of 2-ABT(s) with 4-methyl-2-thiouracil and 6-hydroxy-4-methyl-2-methylthiopyrimidine. Their structures have been established on the basis of IR and NMR spectral studies. Polarographic studies were carried out in N,N-dimethylformamide.

Recently benzothiazoles and pyrimidines have been the subject matter of various reviews [1-3]. Keeping in view the biological importance of these moieties, it was considered worthwhile to synthesise some new derivatives in which both benzothiazole as well as pyrimidine nuclei are linked by an azogroup. Also, in view of the fact that the physiological activity of a molecule is closely related to its redox behaviour [4] in the cell membrane, the polarographic behaviour of these benzothiazolylazopyrimidines was studied.

EXPERIMENTAL

Synthesis of Benzothiazolazopyrimidine

Synthesis of 2-mercapto-4-methyl-6-hydroxy-5-benzothiazolylazopyrimidiness (A) reported herein, have been achived by the condensation of 2-aminobenzothiazoles (2 ABT(s) [5] with 4-methyl-2-thiouracil and 6-hydroxy-4-methylthiopyrimidine.

2-ABT (3.75 gm, 0.025 mol) was dissolved in dilute hydrochloric acid (10 ml) and cooled to 0°C in an ice-bath. Sodium nitrite (0.69 gm, 0.01 mol) solution was then gradually added. The diazonium salt solution so obtained was filtered into a cold stirred solution of 4-methyl-2-thiouracil (1.42 gm, 0.01 mol) in 10 ml of 10% sodium hydroxide containing 2.3 gm of sodium acetate. The reaction mixture was held at 0°C for 4 hours and then left at room temperature for 2 days, when a reddish brown solid separated out. It was filtered, washed well with water and recrystallised from dimethylformamide. It was characterized by mpt, chemical analysis (Table 1) and also characterized by IR and NMR data.

The IR (in KBr pellet) and NMR data for $C_{11}H_9N_3S_2O$ as below.

$\nu_{max.}^{KBr}$: 1590 cm^{-1} (-N=N-), 3100 cm^{-1} (-NH)

1610 cm^{-1} (-C=C- or C=N), 3400-3500 cm^{-1} (-OH)
1190-1230 cm (-CS)

NMR : (DMSO, D_6) δ = 2.4 (3H, $-CH_3$),
4.32 (H, -OH). 7.0 (4H, $-C_6H_4$)

Similarly 2-methylthio-4-methyl-6-hydroxy-5-benzothiazolylazo pyrimidines were prepared by taking 6-hydroxy-4-methyl-2-methylthio pyrimidine in place of 4-methyl-2-thiouracil and their characteristics are given in Table 1. The structures of all the compounds have been established on the basis of IR and NMR spectral studies.

Polarographic Technique

Polarographic measurements were made on a ELICO-DC-CL-25 recording polarograph. The capillary had the characteristics m = 1.25 mg/sec, t = 2.66 S per drop at -0.0 V (SCE) in 1.0 M KCl solution at a height of 65 cm of mercury column. The polarograms were recorded at 25 ± 1.0°C. The pH measurements were made on ELICO LI-15 (India) expanded scale pH meter fitted with glass electrode. De-aeration of polarographic solutions was carried out by streaming Oxygen-free nitrogen for 10 minutes just prior to the polarographic examination.

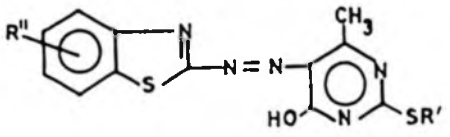
Procedure

Stock solution 1 mM of each of the benzothia-

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TABLE 1

CHARACTERISTICS OF SOME
SUBSTITUTED 2-MERCAPTO-4-METHYL-6-HYDROXY-5-BENXOTHIAZOLYLAZOPYRIMIDINES



Where - R' = -H , $-CH_3$

R" = -H , $-CH_3$, -Cl , $-OCH_3$, $-ONO_2$

Sl No.	R"	R'	M.P. °C	Yield	Molecular formula	Analytical data N%	S%
1.	-H	-H	250	70	$C_{12}H_9N_5S_2O$	24.00 24.05	21.85 21.99*
2.	4" - CH_3	-H	240	65	$C_{13}H_{11}N_5S_2O$	22.90 22.95	20.95 20.98*
3.	4" - Cl	-H	260	70	$C_{12}H_8N_5S_2OCl$	21.40 21.53	19.50 19.65*
4.	4" - OCH_3	-H	254	55	$C_{13}H_{11}N_5S_2O_2$	21.75 21.80	19.85 19.93*
5.	4" - NO_2	-H	245	60	$C_{12}H_8N_6S_2O_3$	20.50 20.83	19.00 19.04*
6.	-H	$-CH_3$	235	65	$C_{13}H_{11}N_5S_2O$	22.85 22.95	20.85 20.98*
7.	4" - CH_3	$-CH_3$	280	60	$C_{14}H_{13}N_5S_2O$	21.95 21.94	20.04 20.06*
8.	4" - Cl	$-CH_3$	250	55	$C_{13}H_{10}N_5S_2OCl$	20.54 20.64	18.85 18.87*
9.	4" - OCH_3	$-CH_3$	230	60	$C_{14}H_{13}N_5S_2O_2$	20.78 20.00	19.05 19.10*
10.	4" - NO_2	$-CH_3$	243	60	$C_{13}H_{10}N_6S_2O_3$	20.02 20.00	18.02 18.28*

All the melting points are uncorrected. * Calculated values.

zolylazo pyrimidines was preapred in dimethylformamide (A.R). B.R. Buffer [7] solutions of varying pH viz., pH 2.5,3.8,4.3, 6.5,8.8,10.5, 12.0 and 1 M KCl were prepared in distilled water from AnalaR grade Chemicals.

The polarographic behaviour of all these compounds was studied in B.R. buffers. The solutions to be polarographed were prepared by taking 1.0 ml aliquot of stock solution mixed with 2.0 ml of DMF, 1.0 ml of KCl (1M) and 6.0 ml of buffer solution of desired pH value. The necessary corrections for the residual current were made in all cases.

RESULTS AND DISCUSSION

All the benzothiazolylazopyrimidines (Table-1) were reduced in a single, two electron wave over the entire pH range studied. Some recorded typical polarograms are depicted in Fig. 1. The heights of the waves showed a linear dependence on concentration of depolarizer and $\sqrt{h}$, but independent of the pH of the solution (Table 3) indicating the diffusion-controlled nature of the waves. The electrode process was found to be irreversible [8] as half-wave patntial shifted towards more negative values with increase in concentra-

tion of depolarizer (Table 4). Irreversible nature of the waves was further confirmed by log plots [8-10].

The possible reduction sites in these pyrimidines are cyclic -C=C-, -C=N- and exocyclic -N=N-. Out of these, the latter site is more susceptible to reduction since -C=N-, and -C=C- requires much higher potential for reduction. This was verified by recording the polarograms of 6-hydroxy-2-mercapto-4-methyl-pyrimidine and benzothiazole separately under similar experimental conditions. No wave was observed in these cases.

The number of electrons involved in the reduction process was determined by millicoulometry and found to be two, which was also verified by comparing the test compounds with compounds of known 'n' values (e.g. azobenzene) under similar experimental conditions. Analogy in the limiting currents indicated that all the compounds are reduced involving the same number of electrons.

The shifting of half-wave potential cathodically with the increase in pH indicates the dependence of potential on pH. It is deduced from this behaviour that protonation precedes the first electron uptake. This dependence of half-wave potential on pH was also supported by other workers [11-13]. The plots (Fig.2) of $E_{1/2}$ vs pH are linear upto pH 8.0 with a slope value lying between 30 to 50 mV. The dependence of half-wave potential on pH for the parent compound be represented by the equation -

$$-E_{1/2} \quad (\text{pH } 2.0\text{-}8.0) = 0.040\ \text{pH} + 0.19\ \text{V}$$

The plots of $-E_{1/2}$ vs pH showed a break at $\sim$ pH 8.0 (Fig.2). Polarographic characteristics are summarized in Table 2. The values of αn_a (product of transfer coefficient and number of electrons involved per molecule of the reactant) and of p (no. of protons involved per molecule of the reactant in the rate determining step) was calculated involving the Tome's criteria by the following equation :

$$\alpha n_a = -0.0517/(E_{3/4} - E_{1/4})$$

$$p = (dE_{1/2}/dpH)(\alpha n_a/0.0591)$$

Since, all the compounds reduced in a single, two electron wave and involved one proton in the rate determining step, the following general mechanism can be proposed for the reduction of these compounds.

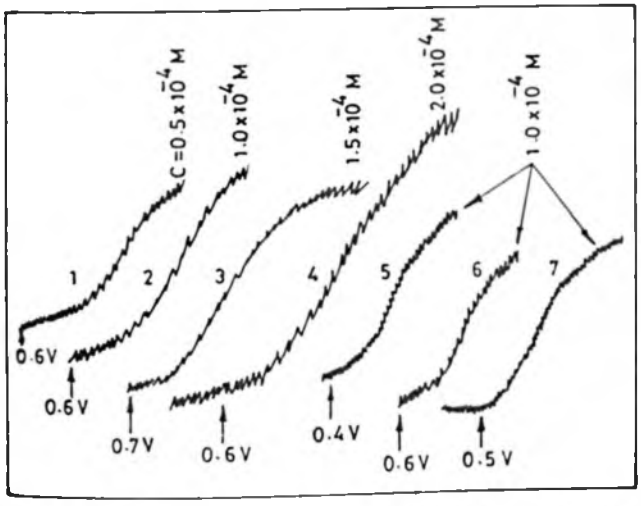
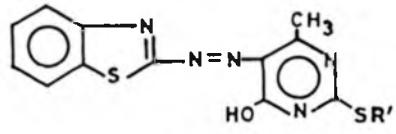


Fig. 1 Polarograms of 2-methylthio-4-methyl -6 Hydroxy-5-benzothiazolylazopyrimidine at different concentrations and various pH (1)-(4) at pH 4.5; (5) at pH 2.5; (6) at pH 3.8; (7) at pH 6.5

TABLE 2

POLAROGRAPHIC CHARACTERISTICS OF 2-MERCAPTO-4-METHYL-6-HYDROXY-5-BENZOTHIAZOLYLAZOPYRIMIDINE AT pH 4.5, C = 0.1 mM



Sl No.	Polarographic Characteristics	R' = H	R' = CH_3
1.	$-E_{1/2}$,(V)	0.82	0.75
2.	i_d , μA	0.36	0.36
3.	$E_{3/4} - E_{1/4}$, (V)	0.03	0.04
4.	αn_a	1.64	1.08
5.	I	2.6	2.6
6.	$k^{\circ}_{f,h}$ (cm./Sec)	6.49×10^{-10}	7.67×10^{-9}
7.	p	1.16	0.85
8.	$dE_{1/2}$ /dpH, (V/pH)	0.040	0.030
9.	$RT/\alpha n_a$, V	1.440	1.920

TABLE 3

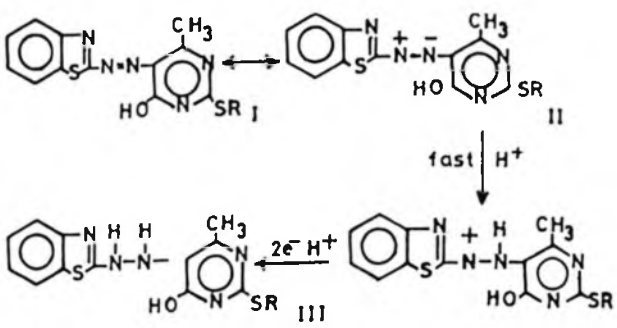
POLAROGRAPHIC CHARACTERSTICS OF SOME BENZOTHIOZOLYL PYRIMIDINES AT VARIOUS pH, C = 0.1 mM

S. No.	pH	$E_{1/2}$, V	i_d, μA	αn_a	I
2-mercapto-4-methyl-6-hydroxy-5-benzothiozolyl pyrimidine					
1.	2.5	0.68	0.33	2.08	2.4
2.	3.8	0.78	0.36	1.74	2.6
3.	4.5	0.82	0.36	1.64	2.6
4.	6.5	0.88	0.39	1.54	2.8
5.	8.8	0.96	0.39	1.64	2.8
6.	10.5	0.98	0.39	1.20	2.8
7.	12.0	1.00	0.39	1.74	2.8
2-methylthio-4-methyl-6-hydroxy-5-benzothiazolylazo pyrimidine					
1.	2.5	0.56	0.30	2.08	2.1
2.	3.8	0.71	0.33	1.08	2.4
3.	4.5	0.75	0.36	1.08	2.6
4.	6.5	0.81	0.33	0.90	2.4
5.	8.8	0.86	0.36	1.08	2.6
6.	10.5	0.87	0.36	1.35	2.6
7.	12.0	0.88	0.33	1.14	2.4

TABLE 4

EFFECT OF CONCENTRATION ON POLAROGRAPHIC CHARACTERISTICS OF 2-MERCAPTO-4-METHYL-6-HYDROXY-5-BENZOTHIAZOLYLAZOPYRIMIDINE

Concentration mM	$E_{1/2}$ V	i_d μA	$\frac{i_d}{c}$, uA/mol x 10^2
pH 4.5			
0.05	0.78	0.21	4.20
0.1	0.82	0.36	3.60
0.15	0.90	0.54	3.60
0.2	0.98	0.69	3.45
pH 6.5			
0.05	0.77	0.18	3.60
0.1	0.81	0.36	3.60
0.15	0.85	0.45	3.00
0.2	0.90	0.60	3.00



The polarized molecule formed in the first step readily accepts a proton from the medium and results in the fast protonation. The last step is the rate determining step representing the reduction by taking two electrons and another proton from the medium. The reduction of -N=N- group at the expense of H^+ ions is supported by the shift of $E_{1/2}$ towards negative values with pH. At higher pH values the values of half-wave potential was found to become constant. Fig.2 shows that above pH 8.0 the shift in $E_{1/2}$ is not so marked as in the lower pH range.

The benzothiozolyl pyrimidine may be assumed to dissociate as

$$HA \overset{pK_1}{\rightleftharpoons} A^- + H^+$$

and both HA and A^- are electroactive and reducible.

$$HA + n_1 e \longrightarrow P_1$$

$$A^- + n_2 e \longrightarrow P_2$$

Though both HA and A are electroactive, in the range where protonation decreases $(pK_1 + 1) > pH > (pK_1 - 1)$ the $E_{1/2}$ of the two forms are close by and only one wave results [14]. The plots of $E_{1/2}$ against pH in the region is linear and corresponds to equation,

$$E_{1/2} = C - (RT/\alpha nF) \ln K_1 + (RT/\alpha nF) \ln [H^+]$$

At $pH > (pK_1 + 1)$ the half-wave potential of the acidic form is pH independent and practically equal to the half-wave potential of the basic form :

$$(E_{1/2})_{HA} = C - \frac{RT}{\alpha nF} \ln K$$

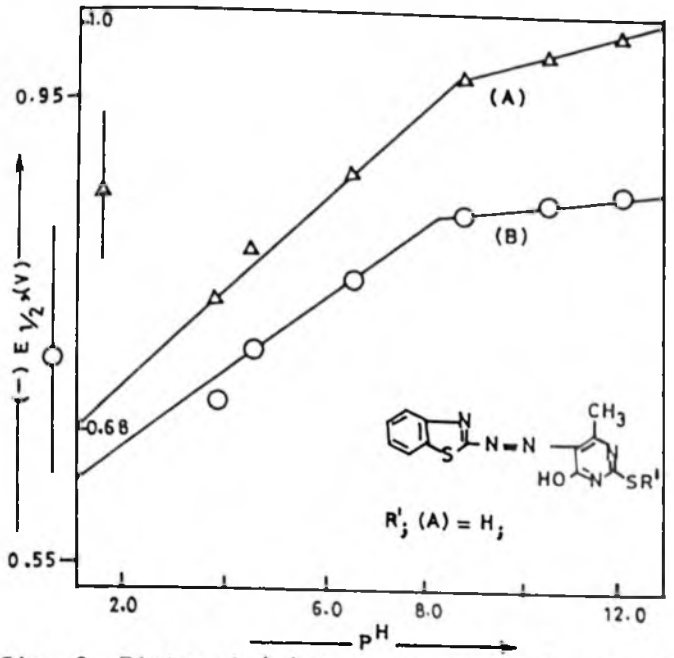


Fig. 2 Plots of (-) $E_{1/2}$ vs pH for 2-mercapto -4-methyl-6-hydroxy-5-benzothiazolylazopyrimidines at pH 4.5, C = 1.0x10 M

$$-\frac{RT}{\alpha nF}\ln 0.806\sqrt{K_1 t} - \frac{RT}{\alpha nF}\ln K_1 \approx (E_{1/2})_A$$

The plot of $E_{1/2}$ vs pH is composed of two linear curves intersecting each other (Fig. 2) and the pH at the point of intersection of its two linear parts is approximately equal to pK_1.

When the electrolysed solution of depolarizer was tested, it was found that it did not give the dye test thereby showing that -N=N- group is reduced to -HN-NH- and further reduction of -HN-NH- grouping is not taking place. Similar results for the reduction of azo compounds has also been reported by other workers [15].

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