

Behaviour of 4-(p-tolyl)-5,6,7,8-tetrabromo 1(2H) phthalazinone towards some nucleophiles

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Summary: The reactivity of 4-(p-tolyl)-5,6,7,8-tetrabromo 1(2H) phthalazinone (I) which contains two reaction sites (C=O and C=N) was investigated for reaction with alkyl or aralkyl magnesium halide under Grignard reaction conditions. This work also deals with the synthesis of the chlorophthalazine (III) via the interaction of the titled phthalazinone with $\text{POCl}_3/\text{PCl}_5$ mixture, the chloro derivative having chlorine atom activated by heteryl moiety. Therefore nucleophilic substitution reaction took place readily with the chloro substrate. The structures assigned to the products are supported by IR and NMR spectra.

Discussion

It was reported [1] that 1,4-diphenyl phthalazine is readily obtained by the action of phenyl magnesium bromide on 1(2H)-phthalazinone, 4-phenyl, and 4-phenyl-2-acetyl-1(2H)-phthalazinones as well as 1(2H)-phthalazine thione.

The present work deals with the behaviour of 4-(p-tolyl)-5,6,7,8-tetrabromo-1(2H) phthalazinone [2] I towards carbon nucleophiles. Thus, when (I) submitted to react with methyl magnesium iodide, ethyl magnesium iodide and benzyl magnesium chloride in stirring dry benzene afforded 1-alkyl or aralkyl-4-(p-tolyl)-5,6,7,8-tetrabromo phthalazine II. The IR spectra revealed strong absorption bands at 1630 cm^{-1} attributable to ν (C=N) and lacked any absorption for ν C=O and ν NH. $^1\text{H-NMR}$ spectrum of IIc in DMSO showed the following signals: δ 2.4 (3H, s, Ar-CH₃); δ 3.2 (2H, s, CH₂ group); δ 7.2-7.8 (9H, m, aromatic protons). Further evidence for the phenomena of lactam-lactim equilibrium in phthalazinone I was demonstrated by the reaction

of I with phosphorous oxychloride [3]. Thus treatment of I with a mixture of $\text{POCl}_3/\text{PCl}_5$ on a steam bath gave 1-chloro-4-(p-tolyl)-5,6,7,8-tetrabromo phthalazine III. The IR spectrum showed band at 1630 cm^{-1} due to ν C=N, the $^1\text{H-NMR}$ spectrum in DMSO showed the following signals δ 2.4 (3H, s, Ar-CH₃), δ 7.4-7.8 (4H, two d, aromatic protons).

In the present investigation the authors synthesised the chlorophthalazine III which is the key starting material for heteryl moiety. In this study the authors planned to synthesis some triazolo (3,4-a)-phthalazine. Thus when chlorophthalazine III allowed to react with acyl hydrazine namely, acetyl hydrazine and benzoyl hydrazine in refluxing butanol afforded 3-methyl and/or phenyl-S-triazolo (3,4-a) phthalazine derivatives IV a and b. The IR spectrum exhibited absorption bands in the region 1630-1635 due to ν (C=N), the $^1\text{H-NMR}$ spectrum of IV-a in DMSO showed the following signals: δ 2.2 (3H, s, Ar-CH₃); δ 2.5(3H, s, CH₃), δ 7.2 (4H, d, aromatic protons).

Chlorophthalazine derivative III was allowed to react with anthranilic acid by fusion afforded the quinazolinone derivative V. The IR spectrum revealed strong absorption bands at 1675 cm^{-1} and 1630 cm^{-1} attributable to $\nu(\text{C}=\text{N})$ and $\nu(\text{C}=\text{N})$.

Similarly m-aminobenzoic and p-aminobenzoic reacted with chlorophthalazine derivative III and yielded the phthalazine derivatives VI a and b.

The IR spectrum exhibited strong absorption bands in the regions $1680\text{-}1690\text{ cm}^{-1}$ for $\nu\text{ C}=\text{O}$ and $1635\text{-}1630\text{ cm}^{-1}$ for $\nu\text{ C}=\text{N}$.

Glycine reacted with chlorophthalazine derivative III and yielded l-carboxy methyl amino-4-(p-tolyl)-5,6,7,8-tetrabromo phthalazine VII. The IR spectrum exhibited strong absorption bands at 1570 cm^{-1} $\nu\text{ C}=\text{O}$ (carboxylate anion) and 1640

$\text{cm}^{-1}\text{ C}=\text{N}$. The $^1\text{H-NMR}$ spectrum in DMSO showed the following signals: δ 1.2 (1 H, t, NH); δ 2.3 (3H, s, Ar-CH₃); δ 7.1 - 7.7 (4H, m, aromatic protons).

Recently [4], it was reported that N-alkyl/or aryl amino pyridazine derivatives having antidepressant activity. In this study the authors thought to synthesis the pyridazine allide structure (N-alkyl/or aryl amino phthalazinone in view of their pharmaceutical activity. Thus when the chlorophthalazine III was allowed to react with o-phenylene diamine, p-phenylene diamine, o-aminophenol, and p-aminophenol, it yielded N-substituted amino- phthalazine VIII. The IR spectrum revealed strong absorption bands in the regions $1640\text{-}1630\text{ cm}^{-1}$ due to $\nu\text{ C}=\text{N}$ and $3350\text{-}3300\text{ cm}^{-1}$ attributable to $\nu\text{ OH}$ or $\nu\text{ NH}$.

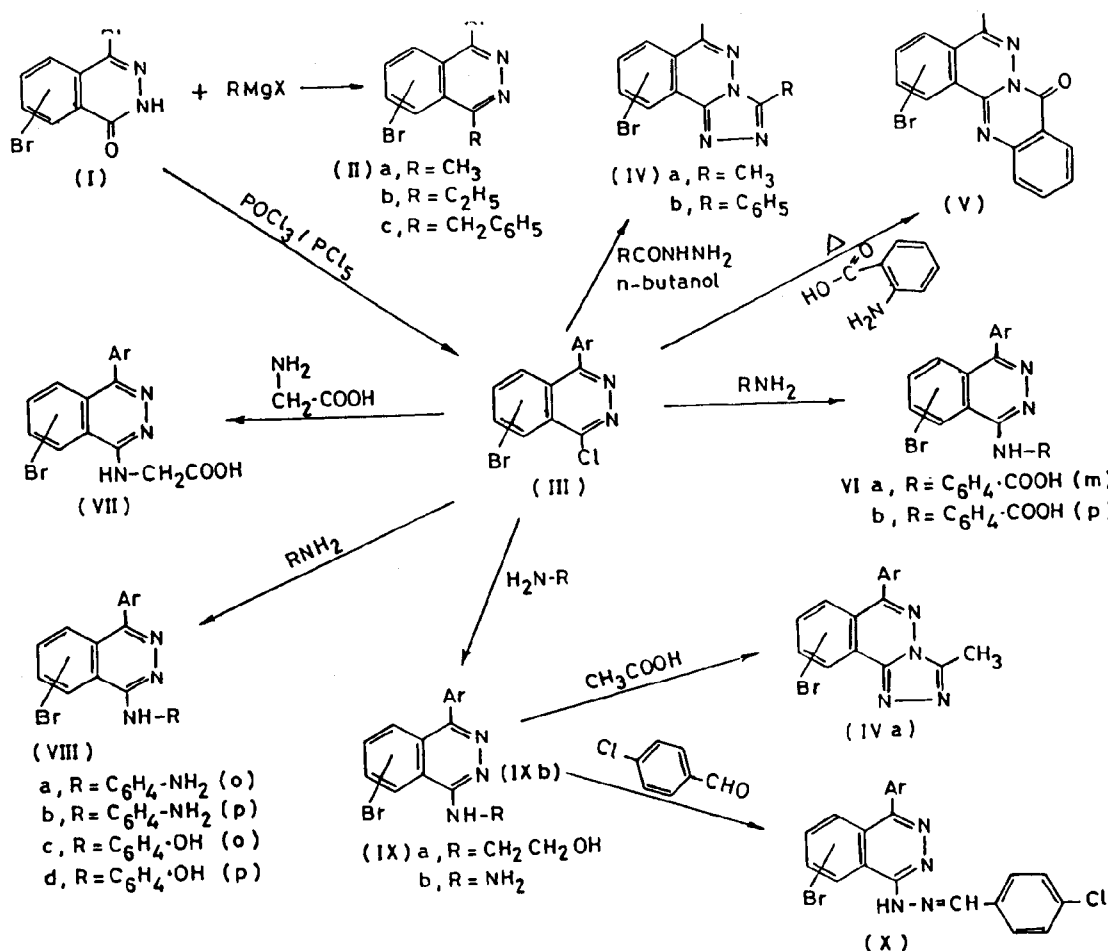


Table 1: Characterisation and physical data of new compounds.

Compound	m.p. °C	Solvent	Formula (Mol.Wt)	Analysis %		
	colour			yield %	Found	Required
IIa	269	ethanol	$C_{16}H_{10}N_2Br_4$ (550)	C 35.0	34.90	
	pale			74	H 1.8	1.82
	yellow				N 6.9	5.09
IIb	256	ethanol	$C_{17}H_{12}N_2Br_4$ (564)	C 35.9	36.17	
	pale			68	H 2.3	2.13
	yellow				N 5.3	4.96
IIc	295	acetone	$C_{22}H_{14}N_2Br_4$ (626)	C 42.8	42.17	
	pale yellow			70	H 2.9 N 4.8	2.24 4.47
III	170	ethanol	$C_{15}H_7N_2Br_4Cl$ (570)	C 31.3	31.55	
	yellow			81	H 1.1	1.23
					N 5.2	4.91
IVa	225	toluene	$C_{17}H_{10}N_4Br_4$ (590)	C 34.4	34.58	
	pale			69	H 2.0	1.70
	yellow				N 9.8	9.49
IVb	232	benzene	$C_{22}H_{12}N_4Br_4$ (652)	C 40.9	40.49	
	pale			65	H 2.1	1.84
	yellow				N 8.8	8.59
V	220	ethanol	$C_{22}H_{11}N_3OBr_4$ (653)	C 39.9	40.42	
	brownish			63	H 1.4	1.68
					N 6.7	6.43
VIa	275	methanol	$C_{22}H_{13}N_3O_2Br_4$ (671)	C 40.0	39.31	
	pale			70	H 2.0	1.90
	yellow				N 6.4	6.21

Continued Table 1:

Compound	m.p.°C	Solvent	Formula (Mol.Wt)	Analysis %		
	colour			yield %	Found	Required
VIb	200	acetic	$C_{22}H_{13}N_3O_2Br_4$ (671)		39.34	
	pale			81	H 2.10	1.90
	yellow				N 6.31	6.21
VII	235	acetic	$C_{17}H_{11}N_3O_2Br_4$ (609)		33.50	
	pale			65	H 1.44	1.81
	yellow				N 8.00	6.90
VIIIa	232	ethanol	$C_{21}H_{14}N_4Br_4$ (642)		39.25	
	pale			70	H 2.03	2.18
	yellow				N 8.90	8.72
VIIIb	218	ethanol	$C_{21}H_{14}N_4Br_4$ (642)		39.10	
	pale			73	H 2.21	2.12
	yellow				N 9.00	8.70
VIIIc	283	methanol	$C_{21}H_{13}N_3OBr_4$ (643)		39.19	
	brownish			69	H 1.83	2.02
					N 6.71	6.53
VIIId	235	ethanol	$C_{21}H_{13}N_3OBr_4$ (643)		39.19	
	brownish			75	H 2.11	2.02
					N 6.84	6.53
IXa	260	acetic	$C_{17}H_{13}N_3OBr_4$ (595)		34.28	
	pale			65	H 2.01	2.11
	yellow				N 7.21	7.05
IXb	245	benzene	$C_{17}H_{14}N_4Br_4$ (594)		34.34	
	orange			68	H 2.04	2.35
					N 9.61	9.43

Continued Table 1:

Compound	m.p. °C	Solvent	Formula (Mol. Wt)	Analysis %	
	colour			yield %	Found
X	193	toluene	C ₂₂ H ₁₄ N ₄ Br ₄	C 38.72	38.37
	yellow	65	(688)	H 2.11	1.88
				N 8.30	8.13

The chlorophthalazine III reacted with ethanol amine and/or hydrazine hydrate and yielded B-hydroxyethylamino phthalazine and hydrazinophthalazine IX a and b.

The ¹H-NMR spectrum in DMSO showed the following signals: δ 2.1 (3H, s, Ar-CH₃); δ 2.4 (2H, t, NH₂); δ 3.2 (1H, g, NH); δ 7.3 (4H, δ, aromatic protons). Triplet for NH₂ and quartet for NH are wide due to quadrupole of nitrogen atom. Boiling of IXb with ACOH afforded IV a. The compound IX b reacted with p-chlorobenzaldehyde in boiling butanol and yielded N-heteryl p-chlorobenzaldehyde hydrazone (X).

The ¹H-NMR spectrum in DMSO showed the following signals: δ 2.5 (3H, s, Ar-CH₃), δ 3 (1 H, s, NH); δ 7.4 (4H, d, aromatic protons); δ 7.9 (4H, d, aromatic protons) δ 8.5 (1 H, s, olefinic protons).

Experimental

All melting points are not corrected, IR spectra were measured on a Unicam sp 1200 Spectrophotometer, the ¹H-NMR spectra were recorded on Varian instrument division EM-360, 60MHz NMR Spectrometer, in DMSO using TMS as internal standard.

Characterisation and physical data are listed in Table 1.

Reaction of phthalazinone I with Grignard reagent:

Formation of II

To Mg metal (0.7g) in dry ether (30 ml) an alkyl/or aralkyl halide (0.03 mole) in dry ether (15 ml) was added dropwise. The reaction mixture was stirred and phthalazinone (I) (0.01 mole) in dry

ether (50 ml) added in portions wise during 2 hrs. The mixture was further refluxed for 3 hrs, left overnight and decomposed with dil. HCl. The ethereal layer was washed with water, dried over anhydrous Na₂SO₄ and evaporated to give a solid which was crystallized from a suitable solvent to give (II).

Action of phosphorous oxychloride on the phthalazinone I:

Formation of 1-chloro-4-(p-tolyl)-5,6,7,8-tetrabromo phthalazine III

A mixture of (I) (0.01 mole) phosphorous oxychloride (0.02 mole) and PCl₅ (1 gm) was refluxed on a steam bath for 3 hrs, then poured slowly into ice-cold water. The solid that separated was washed several times with water, dried and crystallized from suitable solvent.

Action of acylhydrazines on chlorophthalazine III:

Formation of IV

A mixture of III (0.01 mole) and acylhydrazine namely acetyl hydrazine and benzoyl hydrazine in n-butanol (50 ml) was heated under reflux for 48 hours. The solid separated after concentrating and cooling was filtered off, and crystallized from proper solvent to give IV.

Action of aromatic aminoacids on chlorophthalazine III:

Formation of V and VI

A mixture of chlorophthalazine III (0.01 mole) and aminoacids namely, anthranilic acid, m-aminobenzoic acid, and p- aminobenzoic acid was

heated into oil bath at 170°C for 3 hrs, after cooling water was added and the solid obtained filtered off and recrystallized from proper solvent to give V and VI a and b respectively.

Reaction of chlorophthalazine III with glycine:

Formation of VII

A mixture of III (0.01 mole) and glycine (0.02 mole) in pyridine (4 ml) was heated under reflux for 3 hrs. The reaction mixture poured into ice-HCl. The solid that separated filtered off and crystallized from proper solvent to give VII.

Action of phenylenediamine and amino phenols on chloro phthalazine III:

Formation of N-substituted aminophthalazine VIII

A mixture of III (0.01 mole), and *o*-phenylene diamine, *o*-aminophenol and *p*-aminophenol (0.015 mole) in benzene (40 ml) was heated under reflux for 15 hrs; then the reaction mixture was concentrated by evaporation. The solid products obtained were crystallized from the proper solvent to give VIII.

Action of ethanol amine and hydrazine hydrate on chlorophthalazine (III):

Formation of IX

A mixture of III (0.01 mole), and ethanol amine and/or hydrazine (0.015 mole) in *n*-butanol

(40 ml) was heated under reflux for 4 hrs. The solid that separated after concentrating was crystallized from the proper solvent giving IX.

Conversion of IXb to IVa:

The hydrazinophthalazine IXb (0.01 mole) in ACOH (30 ml) was heated under reflux for 8 hrs. The solid separated after concentration and cooling was identified as IVa via melting point determination.

Condensation of p-chlorobenzaldehyde with hydrazinophthalazine IXb:

Formation of X

A mixture of IXb (0.01 mole) and *p*-chlorobenzaldehyde (0.015 mole) in *n*-butanol (40 ml) was heated under reflux for 4 hrs. The solid separated after concentrating and cooling was crystallized from proper solvent to give X.

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Experimental

Equipment

A Pyc-Unicam SP-8400 double beam UV/VIS Spectrophotometer was used. The absorbance was measured in 10 mm glass cells.

Reagents

Iron(III)-Phenanthroline Solution:

Iron(III) solution, was prepared by dissolving 0.482 g of ferric ammonium sulphate, $\text{NH}_4\text{Fe}(\text{SO}_4)_2 \cdot 12 \text{H}_2\text{O}$, in distilled water and diluting to one litre. To prepare phenanthroline solution 2.00 g of 1,10-phenanthroline monohydrate was dissolved in 450 ml water and heated to 70-80°C. After dissolution the solution was diluted to 500 ml.

Iron (III)-phenanthroline solution was prepared by mixing the equal volumes of both the solutions at the time of use.

Standard Sulphide Solution

4.006g hydrated sodium sulphide (containing 60% Na_2S determined iodimetrically) was dissolved in 1000 ml water to get 1000 $\mu\text{g}/\text{ml}$ solution. Working solutions were prepared by further dilution of this work solution.

Calibration

Transfer 5 ml of iron(III) - phenanthroline reagent in five 25 ml calibrated flasks. Add the standard sulphide solution aliquots, containing 2-10 μg of sulphide, and mix the contents thoroughly. Place the set of flasks in a water bath at 60°C for ten minutes and then make up the volume with water after cooling to room temperature. Measure the absorbance of each solution at 510 nm against a compensatory blank. Plot absorbance values against sulphide concentrations.

Discussion

Calibration

A linear calibration graph, shown in Fig.1, was obtained for 2-10 μg of sulphide per 25 ml. Absorbance was measured against a compensatory blank but the calibration showed a little intercept along y-axis. When the absorbance was measured against water the intercept increased significantly. The calibration could be further lowered by using smaller flasks and long-path sample cells. The Beer's Law was obeyed upto 3.2 μg of sulphide per ml. The precision of the method has been checked by measuring the sulphide in ten equivolume samples. The value obtained for relative standard deviation was 0.25%.

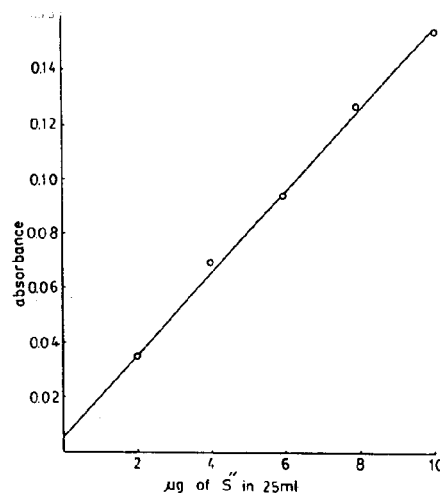


Fig. 1. Calibration for sulphide determination.

The Blank.

When colourless, 1,10-phenanthroline solution was mixed with slightly yellow iron (III) solution a greenish-yellow blank was obtained. The intensity of the colour was dependent upon the amount of iron (III) and 1,10-phenanthroline. In previous work ammonium bifluoride and phosphoric acid have been recommended to decolorize the blank [10]. In this

work however both of the reagents did not prove themselves completely unavoidable. Fluoride (used as sodium fluoride) did not reduce the colour of the blank but changed it from greenish-yellow to brownish-yellow probably due to the formation of dimeric iron(III)-phenanthroline species. Phosphoric acid caused a significant variation in pH and hence affected the final absorbance adversely. It has been noticed that if adequate quantities of iron(III) and phenanthroline were mixed the light greenish-yellow colour of the blank did not produce any problem. However decolorization of the blank with some suitable reagent may enhance the sensitivity of the method.

pH Effect.

When equal volumes of the aqueous solutions of iron(III) and phenanthroline were mixed the final solution was slightly acidic with a pH 5.5. As reported in the literature [10,11] and confirmed by the present work the optimum pH range for the formation of tris-1,10-phenanthroline-iron(II) is 5-6, hence no additional reagent for pH adjustment has been added. However if some extra amount of acid is added to suppress the hydrolysis of iron(III) then addition of some base or a buffer is required to bring the pH in the desired range.

Order of adding the reagents.

To get the maximum absorbance of iron-phenanthroline complex more than one orders of combining the iron(III), phenanthroline and sulphide have been tried. More or less the same values of absorbance have been obtained when the three reagents were mixed in different orders except when 1,10-phenanthroline was added at the last to a mixture of iron(III) and sulphide. The most precise results were achieved when a stock reagent was prepared by combining the equal values of 0.001M iron(III) solution and 0.02M 1,10-phenanthroline solution. Calibration shown in Fig.1, was obtained by adding the different amounts of sulphide in 5 ml of the stock reagent and diluting to 25 ml.

Effect of Time and Temperature

Effect of time has been checked by measuring the absorbance of the same solution after different intervals of time. As it is shown in Fig. 2, absorbance was increased rapidly in first ten minutes and then the increase become mild. However reproducible results could be achieved after fifteen minutes of combining the reagents. After one hour the absorbance became steady.

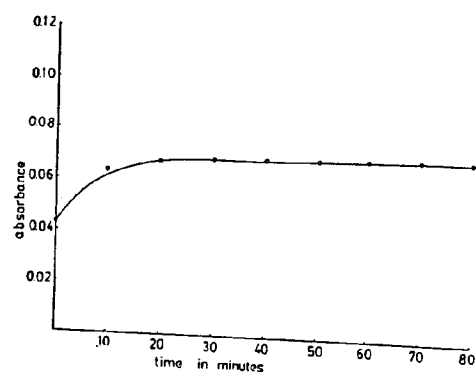


Fig. 2. Effect of time on the absorbance of iron (II) -1,10-phenanthroline complex.

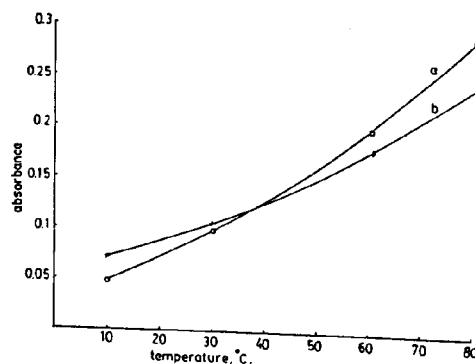


Fig. 3. Effect of temperature on the absorbance of iron (II) -1,10-phenanthroline complex.

- Reagents were heated/cooled after mixing.
- Reagents were heated/cooled before mixing.

Two approaches were adopted to check the temperature effect. In the first the reagents were cooled or heated at certain temperatures and then mixed to measure the absorbance. In the second the reagents were mixed at room temperature and the final solution was cooled or heated before measuring its absorbance. As shown in Fig.3, in both cases the absorbance was enhanced significantly at elevated temperatures. In the latter case the absorbance has been found slightly better than the former. Moreover it is convenient to heat the final solution rather heating the reagents individually. Keeping in view the results of these experiments heating of the final solution at 60-70°C for fifteen minutes is recommended in the calibration procedures.

Effect of iron(III) and phenanthroline concentration

Effect of iron(III) and phenanthroline concentration was checked by using iron(III)-phenanthroline reagent of different concentrations

for the same amount of sulphide. It has been found that the phenanthroline to iron ratio was not critical but the best results were obtained by using the reagent which was prepared by mixing the equal volumes of .001M iron(III) solution and 0.02M phenanthroline solutions.

When the molar ratio of phenanthroline to iron was less than 10 the absorbance was somewhat dependent upon the concentration of phenanthroline but when this ratio exceeded than 20:1 the absorbance become independent. The further increase in phenanthroline concentration enhanced the absorbance of the blank hence it was undesirable to exceed the molar ratio than used for calibration.

Interferences

Possible interferences have been checked by measuring a known amount of sulphide in presence of different anions and cations. The results obtained

Table-1: Effect of diverse ions on sulphide determination

Anion	Added As of anion	Concentration µg/25 ml.	S ²⁻ found	Cation	Added as of cation	Concentration s ²⁻ found ug/25 ml
CH ₃ COO ⁻	Sodium	100 ppm	8.10	Ca ⁺⁺	Chloride	1000 ppm 8.05
NO ₂ ⁻	Potassium	10 ""	10.0	NH ₄ ⁺	Chloride	1000 ppm. 7.90
NO ₃ ⁻	Potassium	1000 ""	7.95	Pb ⁺⁺	Acetate	100 ppm 6.15
S ₂ O ₃ ²⁻	Sodium	5 ""	12.25	Zn ⁺⁺	Acetate	1000 ppm 6.80
SO ₄ ²⁻	Sodium	1000 ""	8.00	Ag ⁺	Nitrate	100 ppm 6.80
Cl ⁻	Sodium	1000 ""	8.20	Cu ⁺⁺	Sulphate	1000 ppm. 8.10
CO ₃ ²⁻	Sodium	1000 ""	8.15	Ni ⁺⁺	Sulphate	1000 ppm. 8.10
PO ₄ ³⁻	Sodium	1000 ""	7.90	Ba ⁺⁺	Chloride	1000 ppm 7.95
Br ⁻	Potassium	1000 ""	8.10	Al ⁺⁺⁺	chloride	1000 ppm. 8.20
SO ₃ ²⁻	Sodium	5 ""	17.5	Cr ⁺⁺⁺	Chloride	1000 ppm. 7.85

Sulphide taken: 8µg/25 as sodium sulphide

are summarized in Table 1. As it can be seen from the table that sulphite had severely also significantly affected the results. Interference by these ions was expected because they have an ability to reduce iron(III) to iron(II) hence ions would interfere the sulphide determination.

Among the cations lead and silver depressed the absorbance of iron(II)-phenanthroline complex probably due to the formation of insoluble sulphides of these ions. Tin(II) caused a considerable positive error in the results due to its reducing nature.

Samples

Two types of samples were analysed by the described procedure as well as by a reference ethylene blue method [6].

For synthetic samples hydrogen sulphide was entrapped in 0.001M zinc acetate solution. Different volumes of the resulted colloidal suspension of zinc sulphide after diluting with water and stabilizing with amyl alcohol were used as samples. Second were sewage water samples collected from different sewages in the City. To remove the suspended particles the samples were filtered before analyses. Sulphide was determined by both methods in a measured volume of these samples.

As it can be seen from Table 2, that the results of synthetic samples obtained by both methods are not very different from each other. In certain cases a non-significant error exists which is probably due to the heterogeneity of the samples. The results obtained for sewage water samples are firstly very different in sulphide content, as found by both methods,

Table-II Results for analysis of some sulphic samples by described procedure and reference method.

Samples	Sulphide found ug/mg		
	by described procedure	by Ethylene Blue method	
Synthetic Samples			
H ₂ S passed through	1	5.50	5.30
Zinc acetate solution	2	18.05	17.50
	3	28.20	29.5
	4	45.50	45.00
	5	80.00	78.20
	Sewage Water Samples		
(Collected from various sewages at Lahore)	A	95.40	92.5
	B	43.05	42.0
	C	10.00	9.5
	D	45.9	43.5
	E	67.30	65.20

which is obviously due to the fact that samples were obtained from different origins and secondly the results of some of the samples obtained by the described procedure are relatively higher than that obtained by reference method. This is probably due to the presence of some positively interfering ions.

Conclusion

The described method proved itself a simple, precise and adequately sensitive method for sulphide determination. Though a few anions and cations interfered but these can be eliminated chemically before sulphide determination. The method can also be used for environmental samples as hydrogen sulphide can be entrapped by zinc acetate solution resulting zinc sulphide turbidity which can be analysed by the described method.

The method is free from critical concentrations of the reagents and strict control of physical conditions.

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