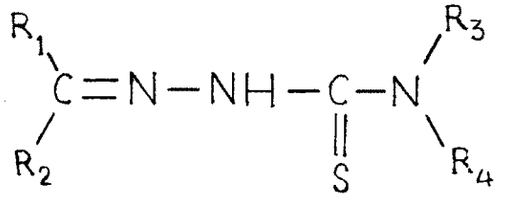
CHAPTER - I

INTRODUCTION

INTRODUCTION

Thiosemicarbazones (TSC) are a class of compounds obtained by condensing thiosemicarbazide with suitable aldehyde or ketones. These compounds have long been commonly used for identification of individual aldehydes or ketones. However, the first report on analytical use of this class of compounds was made by Scott et al.[1]. Since then the volumetric work on their analytical applications has appeared in the literature. The realisation of the importance of thiosemicarbazones as analytical reagents is reflected in gradual increase in the number of paper dealing with their applications in analytical problems. The review of the work on transition metal complexes of thiosemicarbazides and thiosemicarbazones was written by Campbell[2], Singh et al.[3] recently gave a critical review on analytical application of thiosemicarbazones and semicarbazones.

Thiosemicarbazones (TSC) contains active grouping for chelation as shown below in structure(I)



(I)

which involves bonding through sulphur atom with possible further coordination by the hydrazino nitrogen atom (marked with an asterisk in (I)) to give a five membered ring.

Depending upon the type of aldehyde or ketone used for condensation thiosemicarbazone's can act as unidentate, bidentate, or multidentate chelating agents for several metal ions producing highly coloured complexes. In case of unidentate ligands, bonding occurs only through the sulphur atom. The coloured complexes are used in selective and sensitive determination of metal ions.

Domagk et al.[4] pioneered pharmaceutical applications of metal thiosemicarbazone for the treatment of tuberculosis. Since then a number of papers have appeared on the pharmacology of these compounds. Moreover, metal-thiosemicarbazone complexes have been found to be active against influenza[5], protozoa[6], smallpox[7], tumours[8] and possess very good pesticidal[9] and fungicidal[10] activity. It is a well established fact that drugs increases the activity when administered in the form of metal complexes[11,12], and a number of metal chelates have been used as antitumour agents[13]. In the cancer treatment, it has been shown that the active species is not the thiosemicarbazone itself but a metal chelate of thiosemicarbazone[14,15]. The antituber activity of p-acetamido benzaldehyde thiosemicarbazone is found to be enhanced by the presence of a small amounts of copper ions[16].

Thiosemicarbazones, in general, are prepared by condensing thiosemicarbazide with an aldehyde or ketone in the presence of

a few drops of glacial acetic. Preparation of the mono-derivatives is simple but the di-derivatives of thiosemi-carbazones are a little difficult and required special treatment. Dipyridylglyoxal dithiosemicarbazone[17] was prepared by cyclizing the monoderivative with 6 M hydrochloric acid.

Chemical properties of reagent :

Just as hydrozones are weaker bases than hydrozides, thiosemicarbazones are weaker bases than thiosemicarbazides. Hydrolysis of these compounds yields first the hydrazones, hence these compounds resemble hydrazones in many of their reactions.

Mild reductions of thiosemicarbazones yield 1-substitute of thiosemicarbazide. Catalytic reduction of these compounds yield hydrazides which are further hydrolysed to hydrazines. Reaction with alkoxides such as sodium ethoxide converts semicarbazones into hydrazones and with a strong base, hydrocarbons are obtained. This reaction may be applied for replacement of the carboxyl group by CH_2 group.

The reagents can be readily hydrolysed to give the original carboxyl compound and hence are often useful for identification and isolation of carbonyl compounds. A method of obtaining the equivalent weight of the parent carbonyl compound is to hydrolyse the semicarbazone with aqueous hydrochloric acid and titrate with standard iodate solutions[39].

Analytical aspect of thiosemicarbazones :

The various thiosemicarbazones which have been used as analytical reagents are summarised in Table 1.1.

Thiosemicarbazones form coloured metal complexes in conditions ranging from moderately acidic to moderately alkaline. However only a few are reported for the spectrophotometric determination of metal ions in highly acidic medium[18-20]. 3-Hydroxypicolinaldehyde thiosemicarbazone is used to determine Co(II) in highly acidic medium[18]. Similarly glyoxal dithiosemicarbazone reacts with Ag(I) and Hg(II) at pH 1.1 [19]. Salicylaldehyde thiosemicarbazone has been used to determine Mo(VI) in presence of iron in highly acidic medium[20].

Metal complexes are also extractable in various organic solvents resulting in an enhanced sensitivity thereby enabling extraction and simultaneous determination of metal ions. Dipyridylglyoxal dithiosemicarbazone[21] reacts with Ni(II) and Co(II) at pH 5.2, but only the Ni(II) complex is extractable into the chloroform and hence allows the determination of both metals when present together. Biacetyl monoxime thiosemicarbazone[22] has been used to determine Bi(III) in presence of Cu(II), by extraction of the complex into isobutyl metyl ketone.

The reagent 2-Acetylpyridine-4-phenyl-3-thiosemicarbazone (APPT)[23] react with Fe(II) to form a green colour complex (λ max = 610 nm) at certain pH values (4.9 - 11.0) with a high absorptivity. However, this complex can be extracted into

benzene, in which the absorptivity remains constant for at least 3 hours while Fe(III) - APPT complex is not extractable. The complexes of APPT with Fe(II) and Fe(III) contained the metal and ligand in 1:2 ratio.

3-Hydroxypicalinaldehyde thiasemicarbazone[18] (HAPT) forms a yellow orange colour complex with trace amounts of Cobalt(II). The spectrophotometric determination may be done in weakly alkaline medium or in very acid medium. In the first case, the sensitivity is high but the selectivity low; while in other, although the sensitivity is smaller, interferences are rare. The reagent form octahedral complex with Co(II) and act as terdentate chelating agents.

The ligand 1,3-cyctohexanedione bisthiosemicarbazone monohydrochloride[25] has been used for the photometric determination of copper(II) and zinc(II), Cu(II) forms a yellow coloured 1:2 complex in slighily acidic medium while Zn(II) forms orange red coloured 1:1 complex in fairly alkaline medium. The ligand has been used for the determination of trace amount of metal ions in milk, vegetable oils and sheep liver samples.

A new reagent 5,5-dimethyl-1,2,3-cyclohexanetrione 1,2-dioxime-3-thiosemicarbazone[26] was synthesised and a simple, rapid, selective and sensitive method for spectrophotometric determination of iron in wines, minerals and fools was developed based upon the formation of reagent - Fe(II) complexes. A violet colour is formed in strongly acid medium and the molar absorptivity of the complex is 8.9×10^3 at 550 nm.

Recently the spectrophotometric determination of palladium in standard Pd-C powder (Pd catalyst) has been reported by using 3,5-dichlorosalcylaldehyde-4-phenyl-3-thiosemicarbazone[27]. The complex between Pd(II) and this reagent is extractable into chloroform from an aqueous solution at pH 0.

Bhatt et al.[28] studied the complexes of 2-hydroxy 1-naphthaldehyde-4-phenyl-3-thiosemicarbazone with Cu^{2+}, Ni^{2+}, Co^{2+} and VO^{2+} by pH-titration. The stability constants of these metal complexes with same reagent were determined by potentiometrically in 70 % dioxan medium and follow the order $VO^{2+} > Cu^{2+} \simeq Co^{2+} > Ni^{2+}$. Complexation by salicylaldehyde-4-phenyl-3-thiosemicarbazone[29] with these same metal ions has also been studied potentiometrically at 25° in 50 % aqueous dioxan.

Cyclohexane-1,2-dione dithiosemicarbazone has been used to determine Cu(II) in alkaline medium, alkaline tartrate medium and EDTA[30]. It was generally observed that thiosemicarbazones containing hydroxy groups ortho to aldehyde group gave good colour reactions. Besides the application in spectrophotometry, thiosemicarbazones have been reported as gravimetric reagents for many metal ions[31-34], as indicators in direct titrations of metal with EDTA[35,36] in titration in non-aqueous solvents[37]. Recently reports have appeared on separation of metal ion using thiosemicarbazones by thin layer chromatography an alumina with ethyl acetate as a solvent[38].

The literature survey has revealed that 2 chloroquinoline-3-carbaldehyde thiosemicarbazone has not been used for spectrophotometric determination of copper, iron and nickel. Hence, the present work centers around the synthesis and application of this reagent in spectrophotometric determination of Cu(II), Fe(II) and Ni(II).

Table 1.1 : Summary of thiosemicarbazones

Abbreviation	Structure	Systematic name	Reference
1	2	3	4
PAT	II	Picolinaldehyde thiosemicarbazone	40-42
DPGT	III	Dipyridyl glyoxal dithiosemicarbazone	17,21,43
DPKT	IV	Di-2-pyridyl ketone thiosemicarbazone	44
PAPT	V	Picolianaldehyde-4-phenyl-3-thiosemicarbazone	45,46
APPT	VI	2-Acetylpyridine-4-phenyl thiosemicarbazone	23
MPAT	VII	6-Methyl picolinaldehyde thiosemicarbazone	47,48
HPAT	VIII	3-Hydroxypicolinaldehyde thiosemicarbazone	18
GDT	IX	Glyoxal thiosemicarbazone	19
APT	X	Acetophenone thiosemicarbazone	24
HMAPT	XI	2-Hydroxy-5-methyl acetophenome thiosemicarbazone	49-50
DAPT	XII	2,4-Dihydroxy acetophenone thiosemicarbazone.	51
BAMOT	XIII	Biacetyl monoxime dithiosemicarbazone.	22
BAMOPT	XIV	Biacetyl monoxime-4-phenyl-3-thiosemicarbazone	52
DBAT	XV	2,4-Dihydroxybenzaldehyde thiosemicarbazone	53
NBAT	XVI	4-Nitrobenzaldehyde thiosemicarbazone	54

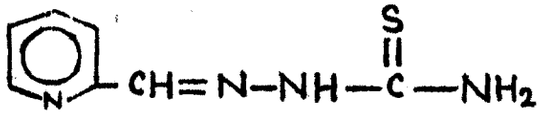
...

Table 1.1 (contd..)

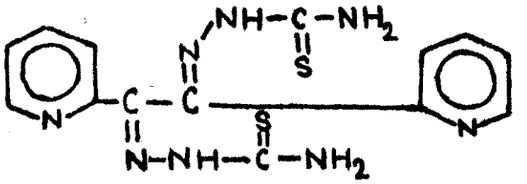
1	2	3	4
AMBAT	XVI	4-Acetamido benzaldehyde thiosemicarbazone	54
ESBAT	XVI	p-Ethylsulphonyl benzaldehyde thiosemicarbazone	31,32
SAT	XVII	Salicylaldehyde thiosemicarbazone	20,55
HANT	XVIII	2-Hydroxy-1-naphthaldehyde thiosemicarbazone	28,56
TAT	XIX	Thiophene-2-aldehyde thiosemicarbazone	57
PADT	XX	O-Phthalaldehyde dithiosemicarbazone.	58
PIDT	XXI	Phthalimide dithiosemicarbazone	59,60
FAT	XXII	2-Furaldehyde thiosemicarbazone	61
PTFA	XXIII	4-phenyl-3-thiosemicarbazone of 2-funaldehyde	34
NQT-4S	XXIV	1,2-Naphthoquinone-2-thiosemicarbazone-4-sulphonic acid	35-37,62
PQMT	XXV	Phenanthrequinone monothiosemicarbazone	63
SAPT	XXVI	salcylaldehyde-4-phenyl-3-thiosemicarbazone.	29
1,3CDDT	XXVII	1,3-cyclohexanedione dithiosemicarbazone	64
IT	XXVIII	β-Ionone thiosemicarbazone	65
FPDT	XXIX	Furylpentadinal thiosemicarbazone	66
BTDD	XXX	Bisthiosemicarbazone of diethyl-3, 4-dioxadioate	67

Structures in Table 1·1.

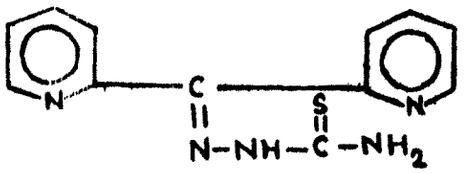
II



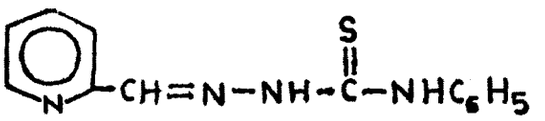
III



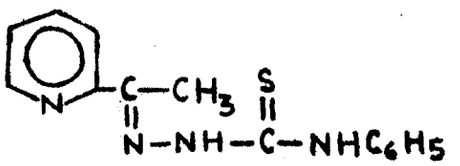
IV



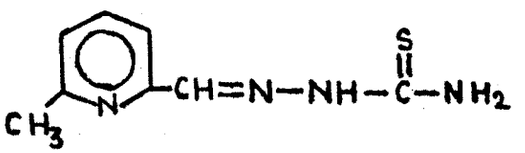
V



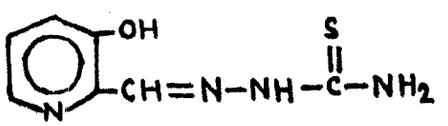
VI



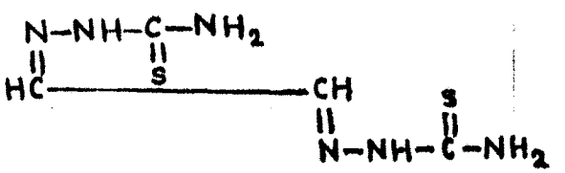
VII



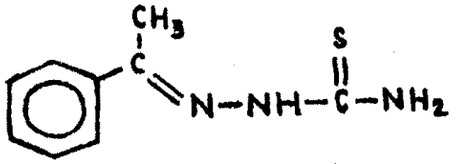
VIII



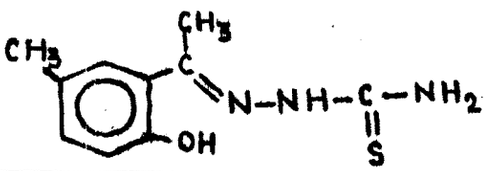
IX



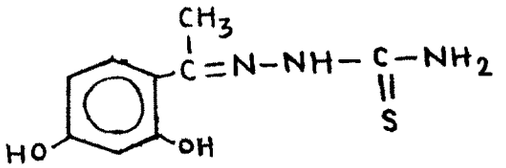
X



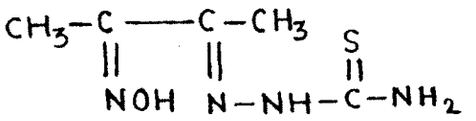
XI



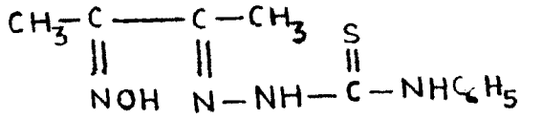
XII



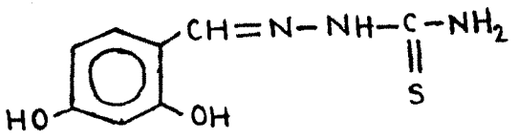
XIII



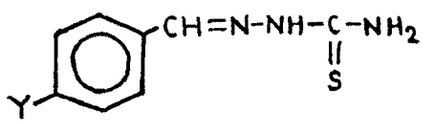
XIV



XV



XVI

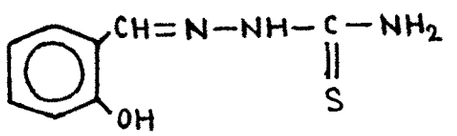


WHEN Y = NO_2, NBAT.

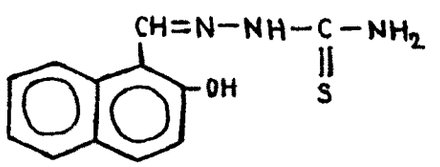
Y = $-CH_2CONH$, AMBAT.

Y = SO_2Et, ESBAT.

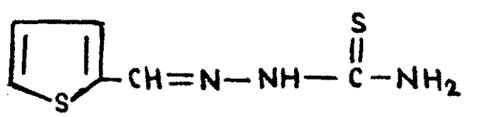
XVII



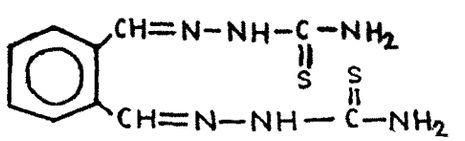
XVIII



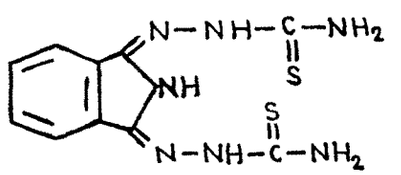
XIX



XX

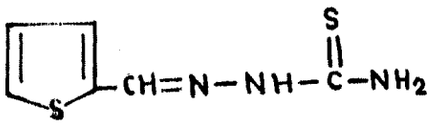


XXI

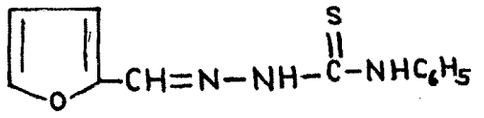


Structures in Table 1.1. (contd.)

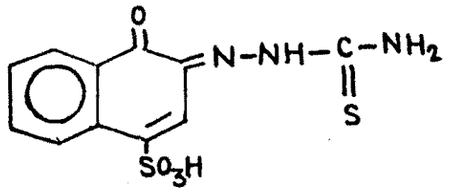
XXII



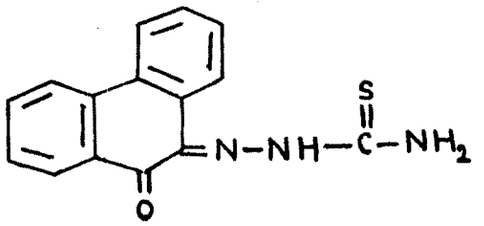
XXIII



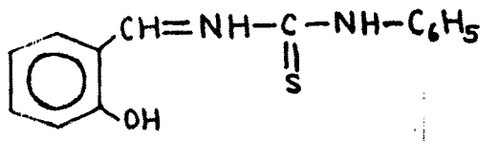
XXIV



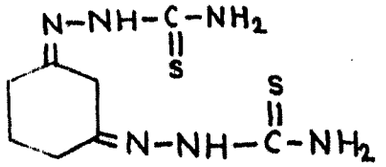
XXV



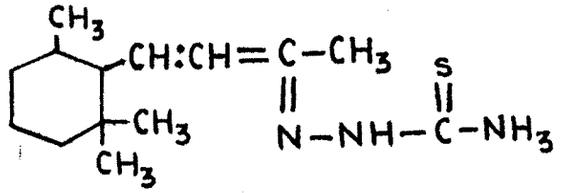
XXVI



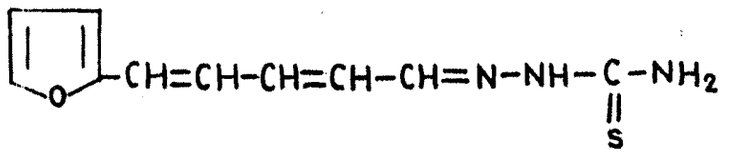
XXVII



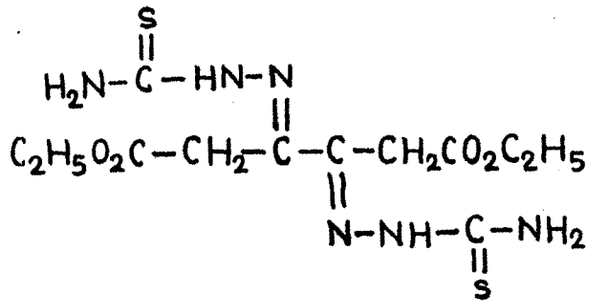
XXVIII



XXIX



XXX



REFERENCES

1. A.W.Scott and M.P.McCall, J.Am.Chem.Soc., 67, 1767 (1945).
2. M.J.M.Campbell, Coordination Chem.Review, 15, 276 (1975).
3. R.B.Sing, B.S.Garg and R.P.Singh, Talenta, 25, 619 (1978).
4. G.Domagk,R.Behnisch, F.Mietzsch and H.Schmidt., Naturwissenschaften, 33, 315 (1946).
5. N.N.Orlova, V.A.Aksenova, D.A.Selidovkin, N.S.Bogdanova and G.N.Pershin, Russ.Pharm.Toxic, 348 (1968).
6. K.Butler, U.S.Patent No.3, 382 (1968).
7. D.J.Bauer,L.St.Vincent, C.H.Kempe and A.W.Docone,Lancet, 20, 494 (1963).
8. H.G.Petering,H.H.Buskirk and G.E.Underwood, Cancer Res., 64, 367 (1964).
9. C.W.Johson, J.W.Joyner and R.P.Perry, Antibiotics and Chemotherapy, 2, 636 (1952).
10. a) H.W.Gansman, C.L.Rhykerd, H.R.Hinderliter, E.S.Scott and L.F.Audrieth, Batan.Gaz., 114, 292 (1953).
    b) B.G.Benns, B.A.Gingras and C.H.Bayley, Appl.Microbiol., 8, 353 (1961).
11. D.R.Williams, Chem.Rev., 72, 203 (1972).
12. A.Furst and R.T.Haro, Prog.Exp.Tumour Res.,12, 102 (1969).
13. F.P.Dwyer, E.Mayhew, E.M.F.Roe and A.Shulman, Br.J.Cancer, 19, 1278 (1965).
14. J.Acrim and H.G.Petering, 27, 1278 (1967).
15. H.G.Petering and G.I.Van Geissen, "The Biochemistry Copper", Academic press, New York, 166.
16. K.Libermeister, Z.Naturforsch B., 5, 79 (1950).

17. J.L.Bahamode, D.P.Bendito and F.Pino, Inform.Quim. Anal., 26, 7 (1972).

18. J.M.Cano Pavon, A.Levado and F.Pino, Micknchim. Acta, 11, 233 (1976).

19. B.W.Budesinsky and J.S.Vec., Anal.Chim.Acta.,55, 115 (1971).

20. D.P.Bendito and F.Pino, Mickrochim.Acta., 1, 613 (1976).

21. J.L.Bahamande, D.P.Bendito and F.Pino, Analyst, 99,355(1974).

22. M.Vakarcel and D.P.Bendito, Inform.Quim.Anal., 24, 49 (1970).

23. M.T.Martinez Aguilar, J.M. Cano Pavon and F.Pino, Anal. Chim.Acta, 90, 335 (1977).

24. L.C.Calzolari, L.L.Coassini, P.Benci and L.Favretto, Ann.Chim., 63, 363 (1973).

25. K.Hussain Reddy and D.V.Reddy, Acta Ciencia Indica. X(4), 204 (1984).

26. Salimas Francisco, Jimenez Sanchez, Juan Carlas, Galeano Dioz, Anal. Chem. (Eng.) 58(4), 824 (1986).

27. Yamaguchi,Shigeraku, Uesugi, Katsuya, Analyst.(London), 110(10), 1241 (1985).

28. Y.N.Bhatt, K.K.Patel, K.J.Shah and R.S.Patel, J.Indian Chem. Soc., 52, 1035 (1975).

29. Idem, ibid, 52, 1214 (1975).

30. J.A.Munoz Leyva, J.M.CanoPavon and F.Pino, An.Quim., 72, 392 (1976).

31. S.Komatsu and Z.Hiroaki, Nippon Kagaku Zasshi, 79,895 (1958).

32. S.Komatsu, T.Kida and Z.Hiroaki, ibid., 77, 1437 (1956).

33. V.Hovarka and Z.Holzbeeker, Bull.Intern.Acad.Tech'que, Sci.Cl.Math.Natur.Med., 51, 125 (1953).

34. J.M.Cano Pavon and F.Pino, Anal.Lett., 7, 159 (1974).

35. S.Kesavan, B.S.Garg and R.P.Singh, Talenta, 24, 51 (1977).

36. Idem., J.Chinese Chem.Soc., 24, 32 (1977).

37. S.Kesavan, Thesis University of Delhi, 1977.

38. U.Niederschulte and K.Ballschmiter, Z.Anal.Chem., 261, 191 (1972).

39. S.Patai, The Chemistry of Carbonyl Groups, Interscience, New York, 1966.

40. J.M.Cana Pavon, D.P.Bendito and F.Pino, An.Quim, 65,667 (1969).

41. D.J.Leggett and B.W.Budesinsky, Microchem.J., 16,87 (1971).

42. J.M.Cano Pavon and D.P.Bendito, Inform.Quim.Anal., 27, 20 (1973).

43. J.M.Bahamonde, D.P.Bendito and F.Pino, Talenta, 20,694 (1973).

44. M.P.Martinez, M.Valcarcel and F.Pino, Anal.Chim.Acta, 81, 157 (1976).

45. J.L.Gomez Ariza and J.M.Cano Pavon, Anal.Lett., 9, 677(1976).

46. J.L.Gomez Ariza, J.M.Cano Pavon, and F.Pino, Talenta, 23, 640 (1976).

47. J.M.Lopez Fernandez, M.Valcarcel & F.Pino, An.Quim, 71, 789 (1975).

48. Idem, Quim.Anal. 30, 8 (1976).

49. G.S.Manku, Curr.Sci. (India), 45, 294 (1976).

50. B.H.Patel, J.R.Shah and R.P.Patel, J.Indian Chem.Soc. 53, 9 (1976).

51. A.Aydin and F.Baykul, Chim.Acta.Turc, 3, 51 (1975).

52. J.M.Cano Pavon, J.C.J.Sanchez and F.Pino, Anal.Chim.Acta, 75, 355 (1975).

53. S.Stankoviansky, A.Beno, J.Carsky and E.Kominakova, Chem.Zvesti, 25, 123 (1971).

54. G.Baiulescu, C.Lazar and C.Cristescu, Zh.Analit.Khim., 15, 505 (1960).

55. V.Hovorko and Z.Holzbecker, Bull.Intern.Acad., Tech'que, Sci.Cl.Math.Natur.Med., 51, 43 (1953).

56. K.Harumi, B.Norikagu,K.Satoshi and O.Takeo, Bunseki Kagaku, 20, 1315 (1971).

57. J.A.Munoz Leyva, J.M.Cano Pavon and F.Pino, An.Quim, 69, 251 (1973).

58. M.R.Rueda, J.A.Munoz Leyva and J.Antonio, Quim.Anal., 29, 122 (1975).

59. M.Guzman, D.P.Bendito and F.Pino, Anal.Chim.Acta., 83, 259 (1976).

60. Idem, An.Quim, 72, 651 (1976).

61. J.M.Cano Pavon and F.Pino, Talenta, 20, 339 (1973).

62. V.Vajgand and M.Jaredic, Chem.Anal.(Warsaw), 20, 1125(1975).

63. A.K.Singh, K.C.Trikha, R.P.Singh and M.Katyal, Talenta, 22, 551 (1975).

64. J.J.B.Nevado, J.A.Munoz Leyva and M.R.Ceba, Talenta, 23, 257 (1976).

65. M.Guzman, D.P.Bendito and F.Pino, Inform.Quim.Anal., 27, 209 (1973).

66. J.A.Munoz Leyva, J.M.Cano Pavon and F.Pino, An.Quim.72, 392 (1976).

67. W.Gorski and S.Podlasin-Paradowska, Acta.Pol.Pharm., 29, 31 (1972).