SOUTHERN BRAZILIAN JOURNAL OF CHEMISTRY
SOUTH. BRAZ. J. CHEM., Vol. 9 , N° 10, 2001

CHROMIUM (III) COMPLEX ANIONS IN THE CHEMICAL ANALYSIS. THIORIDAZINE DETERMINATION

Ion Gănescu[a], George Brătulescu[a], Ion Papa[a], Anca Gănescu[a], Cristian Tigae[a] and Daniela Cârţâna[b]

[a] University of Craiova, Faculty of Chemistry, 13 A.I.Cuza, 1100 Craiova, România
[b] "C.Brâncuşi" Technical University, 1400 Târgu. Jiu, România

ABSTRACT

Complex anions of Cr(III) analogues of Reinecke's salt, $[Cr(NCS)_4(amine)_2]^-$ are good analytical reagents with high sensibility and selectivity for N-organic bases of pharmaceutical importance. We have observed that the phenothiazinic type drug, thioridazine, prescribed for the treatment of maniac-depressing psychosis precipitates with Cr(III) complex anions. Some new oxidative methods for the determination of thioridazine (10-[2-(1-methyl-2-piperidinyl)ethyl]-2-(methylthio)-10H-phenothiazine) are described. The results were evaluated statistically.

KEYWORDS: chromium (III), thioridazine, drugs, oxidimetric and spectrometric methods

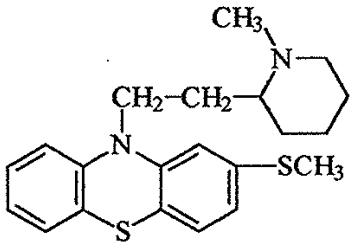
RESUMO

Complexox aniônicos de Cr(III), análogos do sal de Reinecke, são reagentes analíticos excelentes e possuem sensibilidade e seletividade alta para para bases orgânicas de N que tem importância farmacêutica. O presente estudo demonstrou que a tioridazina, um medicamento do tipo fenotiazínico, receitado para tratamento de psicóse maniaco-depressiva, forma precipitados com ânions complexos de Cr(III). Vários métodos oxidativos para a determinação de tioridazina (10- 2-(1-metil-2-piperdinil)etil -2-(metiltio)-10H-fenotiazina) sao descritos. Os resultados experimentais foram avaliados estatisticamente.

DOI: 10.48141/SBJCHEM.v9.n10.2001.34_2001.pdf

INTRODUCTION

Thioridazine is a piperidine phenothiazine with the structural formula:



that contains the methyl mercapto radical (-S-CH_3) at position 3 of the phenothiazine skeleton. Thioridazine, like the other three major groups of phenothiazine tranquilizers, is a drug that has principally a nonpsychotic sedative effect and is indicated for the treatment of acute or chronic schizophrenia, psychosis, maniac depressive psychosis, tension, anxiety, epileptic psychosis and old age psychosis.

Thioridazine is very useful drug in therapeutics and it less toxic than chlorpromazine. It is well absorbed by the alimentary tract and is eliminated both by the kidney and the intestine in 24 hours [1].

The common qualitative analysis methods used for the identification of thioridazine are, in general, those used for the phenothiazine derivatives. Because of the piperidine function (K_0=1.6x10^{-3}), thioridazine forms salts that are characterised by reduced solubility and high melting points with $HClO_4$, silicotungstic acid, sodium tetraphenyl borate etc. Oxidizing agents form compounds of different colours with thioridazine. Some common oxidizing agents are $FeCl_3$ [2,3], persulfates, HNO_3, MnO_2, PbO_2, etc.

EXPERIMENTAL PROCEDDURE

Combinations analogous to Reineck's salts have been obtained by Gănescu's method[8] using substitution reactions with $K_3[Cr(NCS)_6]$ without water and the respective amines in the absence of any solvent. Some combinations used involved aniline, morpholine, diethylphosphine, etc.

Complex salts of the type ThioridazineH$[Cr(NCS)_4(amine)_2]$ were studied with respect to their thermal stability in combustion process, having in view the gravimetric determination of this drug. The study showed a remarkable stability up to 150°C.

For the synthesis of these complexes, samples of 10 mmole of thioridazine·HCl in 100 mL of water were treated with a small excess of $K_3[Cr(NCS)_6]$ in 2% alcohol solution. The red – violet precipitates were filtered under vacuum and dried in air until the filtrate was colorless. Some of the new thioridazine salts prepared are summarized in Table 1.

Table I. New complex salts of the type ThioridazineH[$Cr(NCS)_4$(aniline)$_2$]

No	Formula	Molecular Weight calcd.	Yield [%]	Analysis [%]	
				Calcd.	Found
1	$A_3H_3[Cr(NCS)_6]$	1515.16	97	Cr** 3.43 S** 16.93 N** 11.12	3.40 16.86 11.12
2	$AH[Cr(NCS)_4(NH_3)_2]$	689.98	96	Cr 7.53 S 18.58 N 16.24	7.50 18.52 16.20
3	AH[Cr(NCS)$_4$(aniline)$_2$]	842.04	98	Cr 6.17 S 15.23 N 13.31	6.09 15.20 13.26
4	AH[Cr(NCS)$_4$(benzilamine)$_2$]	870.08	95	Cr 5.97 S 14.74 N 12.88	5.92 14.70 12.76
5	AH[Cr(NCS)$_4$(morfoline)$_2$]	830.16	93	Cr 6.26 S 15.45 N 13.50	6.15 15.41 13.44
6	AH[Cr(NCS)$_4$(imidazole)$_2$]	792.08	89	Cr 6.56 S 16.19 N 17.68	6.50 16.05 17.60
7	AH[Cr(NCS)$_4$(benzimidazole)$_2$]	892.16	92	Cr 5.82 S 14.37 N 15.70	5.76 14.24 15.61
8	AH[Cr(NCS)$_4$(benztriazole)$_2$]	894.12	94	Cr 5.81 S 14.34 N 18.80	5.76 14.24 18.72

* The obtained combinations have a microcrystalline aspect and have red-violet colour.
**Chromium was determined as Cr_2O_3, sulphur as $BaSO_4$ and nitrogen by volumetric method.
A= Thioridazine

Indirect Oxidative Determination of Thioridazine after Precipitation in the Form of ThioridazineH[Cr(NCS)$_4$(aniline)$_2$]

A sample of 1.82 – 14.56mg of thioridazine·HCl was precipitated from an aqueous alcohol solution (2%) in the form of Reinecke's salt. The precipitate was filtered under vacuum using a Büchner funnel with a 5 cm diameter and washed 3-4 times with 10 mL of water, until the filtrate was colorless. After washing, the precipitate was transferred to a Berzelius cup and the funnel was washed with 10 mL of 5% NaOH and 10 mL of water. This represent the initial volume ($V_{initial}$) in the relation below giving V_{HCl}. The cup was heated until the appearance of the green color of $Cr(OH)_3$. It was then cooled with tap water and concentrated HCl was added, the quantity being calculated according to the relation:

$$V_{HCl} = \frac{1.7(V_{initial} + V_{oxidizer})}{10.4}$$

In each test the normality of HCl was constant (1.7N). The normality of concentrated HCl with a density of 1.19 g/cm^3 was 12.1N. After the addition of the calculated quantity of HCl, 5 mL of CCl_4 and 10 drops of ICl [17] indicator were added to the solution and NCS^- was titrated with 0.1N $KMnO_4$ under continuos stirring until the nonaqueous violet layer became colorless. The reaction that took place was the following:

$$5NCS^- + 6MnO_4^- + 13H^+ \rightarrow 6Mn^{2+} + 5SO_4^{2-} + 5HCN + 4H_2O$$

respectively:

$$2NCS^- + 3BrO_3^- + 4H^+ \rightarrow 2SO_4^{2-} + 3Br^+ + 2HCN + H_2O$$
$$2NCS^- + 3IO_3^- + 4H^+ \rightarrow 2SO_4^{2-} + 3I^+ + H_2O$$

A volume of 1mL $KMnO_4$ (KIO_3, $KBrO_3$) is equivalent with 1.54 mg thioridazine.

The experimental results are given in the Tables 2 and 3.

Table 2. Permangante Oxidative Determination of Thioridazine after Precipitation in the form ThioridazineH[Cr(NCS)$_4$(aniline)$_2$] (A) and ThioridazineH[Cr(NCS)$_4$(Et$_2$PhP)$_2$] (B), respectively.

No	The form of determination						
	A				B		
	Thioridazine mg taken	Thioridazine mg found	Error		Thioridazine mg found	Error	
			mg	%		mg	%
1	1.82	1.83	+0.01	0.54	1.81	-0.01	0.54
2	3.64	3.65	+0.01	0.27	3.62	-0.02	0.54
3	5.46	5.43	-0.03	0.54	5.48	+0.02	0.36
4	7.28	7.25	-0.03	0.41	7.30	+0.02	0.27
5	10.92	10.96	+0.04	0.36	10.93	+0.01	0.09
6	14.56	14.54	-0.02	0.14	14.60	+0.04	0.27

1 mL $KMnO_4$ 0.1N is equivalent to 1.544 mg thioridazine

A
$\bar{x}$=14.57
$s=2\cdot10^{-2}$
$s^2=4\cdot10^{-4}$
t=0.5
$t_{n-1,\alpha}$=2,26 ; α=95%
$\bar{x} - ts < A < \bar{x} + ts$
14.55 < 14.56 <14.57

B
$\bar{x}$=10.93
$s=2.58\cdot10^{-2}$
$s^2=6.65\cdot10^{-4}$
t=0.39
$t_{n-1,\alpha}$=2,26 ; α=95%
$\bar{x} - ts < A < \bar{x} + ts$
10.91 < 10.92 < 10.94

Table 3. Bromate Oxidative Determination of Thioridazine after Precipitation in the form ThioridazineH[$Cr(NCS)_4(NH_3)_2$] (A) and ThioridazineH[$Cr(NCS)_4$(morfoline)$_2$] (B), respectively.

No	The form of determination						
	A				B		
	Thioridazine mg taken	Thioridazine mg found	Error		Thioridazine mg found	Error	
			mg	%		mg	%
1	1.82	1.83	+0.01	0.54	1.84	+0.02	1.09
2	3.64	3.63	-0.01	0.27	3.66	+0.02	0.54
3	5.46	5.44	-0.02	0.37	5.44	-0.02	0.36
4	7.28	7.26	-0.02	0.27	7.25	-0.03	0.41
5	10.92	10.95	+0.03	0.27	10.94	+0.02	0.18
6	14.56	14.58	+0.02	0.13	14.60	+0.04	0.27

1 mL $KBrO_3$ 0.1N is equivalent to 1.544mg thioridazine

A
$\bar{x}$=14.57
$s=2.66\cdot10^{-2}$
$s^2=7.07\cdot10^{-4}$
t=0.38
$t_{n-1,\alpha}$=2,26 ; α=95%
$\bar{x} - ts < A < \bar{x} + ts$
14.55 < 14.56 < 14.58

B
$\bar{x}$=10.93
$s=1.82\cdot10^{-2}$
$s^2=3.33\cdot10^{-4}$
t=0.77
$t_{n-1,\alpha}$=2,26 ; α=95%
$\bar{x} - ts < A < \bar{x} + ts$
10.91 < 10.92 < 10.94

From statistic interpretation of the experimental data[15,16] we conclude that oxidative methods are reproducible, rapid, sufficiently accurate, in comparison with other dosing methods of phenothiazine found in the literature. Titration is made without extra consumption of reagent. For these reasons we believe that this method may be of use and interest for laboratories concerned with drug analysis and control.

Spectrometric Determination of Thioridazine after Precipitation in the Form of ThioridazineH[$Cr(NCS)_4$(aniline)$_2$]

A stock solution of a thioridazine hydrochloride of known titre was first prepared. Samples containing 2.2-30.8 mg of thioridazine were precipitated with a small

excess of the reagent in the form ThioridazineH[$Cr(NCS)_4(aniline)_2$]. After 10 – 15 minutes, the precipitate was filtered using a G_4 filter crucible and washed 2-3 times with 10 mL of water until the filtrate flowed colourless. The precipitate was then dissolved in acetone, the red-violet solution was transferred to a 50 mL volumetric flask and diluted with acetone to the mark. The absorbance of the respective solutions was then measured at 535-540 nm using a Spekol Zeiss Jena spectrophotometer.

The experimental absorbance values follow the Beer- Lambert law in the 0.088 to 1.232 mg of thioridazine/mL concentration range. The experimental results are illustrated in Figure 1 and Table 4. The molar absorptivity coefficient, ε, determined was at 218.44 L cm^{-1} mol^{-1}.

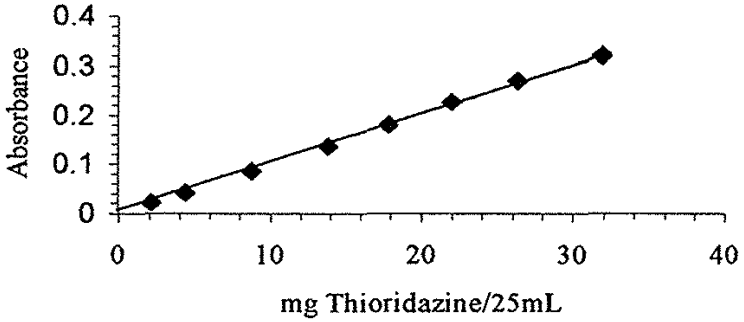


Figure 1. Calibration curve for the Spectrometric Determination of Thioridazine as ThioridazineH[$Cr(NCS)_4(aniline)_2$]

Table 4. Spectrometric Determination of Thioridazin after Precipitation in the Form of ThioridazineH[$Cr(NCS)_4(aniline)_2$]

No	x mg	x^2	y	y^2	xy	x+y	$(x+y)^2$
1	2.20	4.84	0.022	0.000484	0.0484	2.222	4.9373
2	4.40	19.36	0.045	0.002025	0.1980	4.445	19.7580
3	8.80	77.44	0.091	0.008281	0.8008	8.891	79.0499
4	13.20	174.24	0.136	0.018496	1.7952	13.366	177.8489
5	17.60	309.76	0.181	0.032761	3.1852	17.781	316.1639
6	22.00	484.00	0.227	0.051529	4.9940	22.227	494.0395
7	26.40	696.96	0.272	0.073984	7.1808	26.672	711.3956
8	30.80	948.64	0.320	0.102400	9.8560	31.120	968.4544
Total	125.40	2715.24	1.294	0.28996	28.0588	126.694	2771.6475

The statistical analysis presented in Table 4 was done using the following equations:

$$\Sigma (x+y)^2 = \Sigma (x^2 + 2xy + y^2) = \Sigma x^2 + \Sigma y^2 + 2\Sigma xy$$

So $\Sigma (x+y)^2 = 2771.647$

$$\Sigma x^2 + \Sigma y^2 + 2\Sigma xy = 2715.24 + 0.28996 + 2x28.0588 = 2771.647$$

The comparison of the experimental results from Table 2 and Table 4 shows that the spectrometric method proposed in the present study for dosing thioridazine is reproducible and exact and can be applied in the laboratory for the analysis and control of this drug.

The equation that gave the best agreement between the absorbance and the concentration of the active product (Thioridazine) in the test samples expressed in mg or μg obtained by linear regression analysis [15-16] was the following:

$y-\bar{y}=r\frac{\sigma_y}{\sigma_x}(x-\bar{x})$ where $\bar{y}=0.16175$; σ_x and σ_y are standard calculated with the help of the relations:

$\sigma_x=\sqrt{\frac{\sum x^2}{n}-\bar{x}^2}$ in our case:

σ_x being equal with 9.6798 and $\bar{x}=15.675$

$\sigma_y=\sqrt{\frac{\Sigma y^2}{n}-\bar{y}^2}$ in our case:

$\sigma_y=0.10004$

$y=0.01037x-0.00083$ respectively
$x=96.4123y+0.08030$ $\qquad x-\bar{x}=r\frac{\sigma_x}{\sigma_y}(y-\bar{y})$

The calculation of the correlation (regression) coefficient is done according to the relation:

$$r=\frac{[\frac{1}{n}\Sigma xy]-xy}{\sigma_x\sigma_y}$$

The angle between the two straight lines was very small, the dependence between the absorbance and the concentration of thioridazine was linear and the correlation coefficient r was 1.000.

Using the same method we determined the thioridazine concentrations shown in Tables 2 and 3. (One tablet contains 0.05g thioridazide hydrochloride). Twenty samples were weighed on an analytical balance and pulverized in a mortar. A sample of this powder, about one gram in weight (representing the average weight of a tablet) was placed in a porcelain capsule, 10 mL of water were added, followed, by stirring for 15-20 minutes. The contents of the capsule was filtered, and the capsule was washed several times with water. The filtrate and all the washings were collected in a 100 mL volume flask and diluted to the mark.

A 10 mL aliquot was transferred to a Berzelius cup and the active principle was precipitated according to the reaction mentioned above. The precipitate was filtered, washed with water and dissolved in acetone or absolute methanol. The red-violet solution was transferred to 50 mL volumetric flask and diluted to the mark with acetone. The absorbance was measured at λ=540nm and the amount of thioridazine was determined using the calibration curve shown in Figure 1. The tablets contained between 0.048 g and 0.050 g of thioridazine.

RESULTS AND DISCUSSIONS

Researching the analytical characteristics of thioridazine, the specialized literature mentions some methods of determination of this drug, a lot of them being the same as for the other phenothiazine derivatives. R. Semionovici and his collaborators[4] as well as Karkhuff and his collaborators [5], dose Melleril (Thioridazine·HCl) by means of the surfactant, sodium laurylsulfonate and Morait and his collaborators dose this pharmaceutical product using sodium tetraphenylborate [6].

Because of its basic function, thioridazine is also determined in nonaqueous solvents such as acetonitrile, chloroform, dioxane, acetone, etc., using $HClO_4$ in dioxane as a reagent and methyl and blue methylene, as an indicator (1:1). Since the drug under consideration is a hydrochloride, mercury acetate is added to the titration medium in order to bind the halogen ion [7] in the form of undissociated $HgCl_2$.

Gănescu and his collaborators noticed that all the drugs with phenothiazine skeleton precipitate in acid medium with Cr(III) anions complex like $[Cr(NCS)_6]^{3-}$, Reinecke salt and its analogous of the type $[Cr(NCS)_4(amine)_2]^-$, where amine = Py, aniline, toluidine, imidazole and even urotropine, resulting in heavy soluble violet crystalline complexes [8-14]. This led to the possibility of establishing new gravimetric, volumetric and spectroscopic methods for the determination of these drugs [8-14].

Like other phenothiazine drugs studied by us thioridazine forms stable crystalline salts soluble in water with $K_3[Cr(NCS)_6]$, $NH_4[Cr(NCS)_4(NH_3)_2]$, and respectively $NH_4[Cr(NCS)_4(amine)_2]$. These salts can be easily filtered washed with water and dried at 110°C and directly weighed. The great SCN^- content of the reagents used has allowed the elaboration of new oxidative methods (permanganometric, bromatometric and iodometric) that are very sensible and have a clear and point in CCl_4, using ICl as an indicator [10]. Thioridazine complex salts with the reagents already mentioned are slightly soluble in acetone forming red–violet solution. This allowed the elaboration of spectrophotometric methods for the dosing of this drug.

CONCLUSIONS

Eight new complexes, salts of the ionic type association have been obtained. New oxidative and spectrophotometric methods, for the determination of thioridazine were developed.

Statistical analysis of our results showed that the new methods are very reliable compared to others described in the Romanian Farmacopea and specialized literature.

REFERENCES

1.***''Produse Farmaceutice Româneşti'' (in Romanian), Ed. Medicală, Bucharest, Romania, 1985.
2.***''Farmac.Uffic.della Republica Italiana'', vol.II (nouvo edizione), Roma, Italy, 1993.
3.***''Farmac. Française'' , Ed. X, Paris, France, 1986.
4. R. Simionovici, H.Aftalon and F. Albert, *Rev. Chim. (Bucharest)*, *3*, 181 (1969).
5. D.E.Carkhuff and F.W.Brody, *J.Amer.Pharm.Ass.Sci.*, *43*, 240 (1954).
6. Gh.Morait, V.Turculet and Gh.Ciogoles, *Farmacia (Bucharest)*, *18*, 276 (1970).
7.***''Farmacopeea Română''(in Romanian), Ed. Medicală, Bucharest, Romania, Ed.X, 1981.
8. I.Gănescu, *Studia Univ. Babes - Bolyai, Chem.*, *12*, 103 (1967).
9. C.Liteanu and V.Rusu, *Stud.Univ.Babes - Bolyai, Chem.*,*10*, 99, (1965).
10. I.Gănescu, Cs.Várhely and D.Oprescu, *J.Inorg.Nucl.Chem.*,*37*, 324 (1973).
11. I.Gănescu, Cs.Várhely, G.Brânzan and M.Proteasa, *Z.Anorg.Allg.Chem.*, *428*, 259 (1976).
12. I.Gănescu, M.Preda and I.Papa, *Arch.Pharm.*, *324*, 321(1991).
13. J.Zsako, Cs.Varhely, I.Gănescu and M.Mate, *Rev.Roum.Chim.*, *37*, 187 (1992)
14. I.Gănescu, L.Chirigiu and M.Mureseanu, *Rev.Chim. (Bucharest)*, *45*, 323 (1994)
15. M. Steinbach, ''Prelucrarea statistică în medicină şi biologie''(in Romanian), Ed. Acad., Bucharest, Romania, 1961, p.233.
16. L.Butner and M.Pozin, ''Metode matematice în tehnicã'', (in Romanian), Ed. Acad., Bucharest, Romania, 1956, p.486.
17. G.Desmuch and M.Josif, *Z.Anorg.Chem.*, *142*, 275 (1969).