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COLORIMETRIC DETERMINATION OF PHENOTHIAZINE DRUGS. 4-CORRELATION BETWEEN MOLAR ABSORPTIVITY AND $\mathcal{F},\mathcal{R}$ AND χ PARAMETERS OF RING SUBSTITUENTS.*

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ABSTRACT

Colorimetric determination of phenothiazines with NBS in strong sulfuric acid solution has been previously reported (6,7). Correlation of log ε_{max} with $\mathcal{R}$ and $2\chi v$ parameters of C-2 and N-10 substituents is highly significant only on absence of vulnerable groups at C-2 position. Log ε_{max} of four compounds with the same N-10 side chain was correlated with $\mathcal{F}$ parameters of C-2 substituents irrespective of their vulnerability to the reagents. Correlation equations were used to predict the electronic parameters $\mathcal{F}$, $\mathcal{R}$ and σ_p of $-SO_2N(CH_3)_2$ from the spectrophotometric reaction model.

INTRODUCTION

Phenothiazine drugs are essentially used as antipsychotics and antihistamines. Interest in the analysis of phenothiazines have been reviewed by Blazek[1,2] and Fairbrother[3]. Recently the reaction using I_3^- and N-bromosuccinimide[4-7] were applied for colorimetric determination of certain

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* Part 3-reference 8.

phenothiazines in diffetent dosage forms. El-Shabouri et al.[8] interpreted the contribution of nuclear substituents to the intensity of colour developed on treatment of twelve phenothiazines with I_3^- and morpholine. Such contribution was estimated through a set of simple regression and two variable second order regression equations e.g., the correlation between $\log \varepsilon_{max}$ and the Hammett electronic parameter σ_p and/or the molecular connectivity index $^1\chi^v$.

The present paper describes the correlation of $\log \varepsilon_{max}$ estimated for eleven phenothiazines, reacted with NBS in strong sulfuric acid solution, as functions of certain parameters of nuclear substituents. Swain and Lapton electronic parameters ($\mathcal{F}$, $\mathcal{R}$ of C-2 substituents (R_1) and the molecular connectivity index $^2\chi^v$ of the side chain at N-10 (R) were found to give the best correlation. From the derived equations it was possible to predict $\mathcal{F}$, $\mathcal{R}$ and σ_p values of R_1 = $SO_2N(CH_3)_2$ which were not previously reported.

EXPERIMENTAL

Log ε_{max} of the analysed phenothiazines, Table 1, have been taken from published data[6,7]. The parameters $\mathcal{F}$, $\mathcal{R}$ and σ_p of R_1 substituents, Table II, have been taken from literature[9a] and included as the electronic contribution variable. Calculation of molecular connectivity index of R followed the method described by Hall and Kier[10], Table III. The structural representation for the calculation of the second order connectivity index $^2\chi^v$ is illustrated by Scheme 1.

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RESULTS AND DISCUSSION

Correlation of log $\mathcal{E}_{max}$ with σ_p was previously reported for twelve phenothiazines treated with I_3 and morpholine[8]. Most of these phenothiazines were successfully quantitated colorimetrically using NBS in strong sulfuric acid solution[6,7]. However, the trial to correlate by simple regression the values of log $\mathcal{E}_{max}$ of the phenothiazines, obtained from the latter reaction, Table I, with σ_p values of R_1 substituents was unsuccessful. Taking into consideration the components of σ_p from equation (1) :

$$\sigma_p = \mathcal{R} + \alpha \mathcal{F} \ldots\ldots\ldots\ldots\ldots\ldots (1)$$

where α-is a predicted regression constant equals 0.921[9b]. Trial to work up the correlation between log $\mathcal{E}_{max}$ and the corresponding $\mathcal{R}$ and $\mathcal{F}$ values of R_1 as separate functions affecting the colour intensity was carried out.

A poor correlation was obtained between log $\mathcal{E}_{max}$ and $\mathcal{R}$ values, equation (2) :

$$\log \mathcal{E}_{max} = 4.006 - 0.4148\,\mathcal{R} \ldots\ldots\ldots (2)$$

$$r = -0.558 \qquad s = 0.146; \quad n=10;$$

$$F = 3.61\,, \qquad p < 0.10$$

In eq. 2 and the following equations, n is the number of compounds included in the analysis, r is the correlation coefficient, and s is the standard deviation while F is F-ratio between the variances of the observed and calculated values at the given p value.

Compound V was excluded as the $\mathcal{R}$ value is not available for the group-$SO_2N(CH_3)_2$. This correlation although significantly was improved, yet it is still unsatisfactory, after excluding from the regression treatment the compounds III, IV and VI to give eauation (3):

$$\log \varepsilon_{max} = 3.972-0.6277\mathcal{R} \quad \ldots\ldots\ldots\ldots (3)$$

$r = -0.790$ $\quad s = 0.128$; $\quad n = 7$

$F = 8.43$, $\quad p< 0.05$

Exclusion of the compounds III,IV and VI was based on the most probable reaction that can take place between R_1 substituents of these compounds and NBS reagent used in the colour development procedure. Thus compound III where $R_1 = COC_3H_7$ can easily participate in bromination reaction under acidic conditions[11a,12a] to give the brominated R_1 derivative, most probably having different electronic $\mathcal{R}$ value than that considered for the COC_3H_7 group (Table II). Similarly, deviation of $\mathcal{R}$ values from reported ones can be assigned for $R_1 = SC_2H_5$ and $-SCH_3$ in the compounds IV and VI respectively with the formation of the oxidation products of aralkylsulfides[11b,12b].

Further improvement of the correlation coefficient was obtained on using the second order connectivity index $^2\chi^v$ as a second variable representing the bulkiness and branching of R group, equation (4):

$$\log \varepsilon_{max} = 3.521 - 0.8869\,\mathcal{R} + 0.1623\ {}^2\chi^v \quad \ldots\ (4)$$

$r = 0.958$; $\quad s = 0.060$; $\quad n=7$

$F = 56.17$, $\quad p<0.005$

Meanwhile correlation by simple regression of $\log \varepsilon_{max}$ of the compounds I-XI versus $^n\chi^v$ Table III was unsuccessful. Equation (4) displays the counterbalanced contribution of R and R_1 groups to $\log \varepsilon_{max}$. Also the regression parameters of $^2\chi^v$ and $\mathcal{R}$ illustrates the higher weight of the latter relative to the former one in the mechanism of the chromogen formation.

Colorimetric Determination of Phenothiazine Drugs. 4-Correlation Between Molar Absorptivity and $\mathcal{F}$, $\mathcal{R}$ and χ Parameters of Ring Substituents.

Trials to investigate the relation between log ε_{max} and the field electronic parameters $\mathcal{F}$ of all compounds except V ($\mathcal{F}$-value is not available in literature) were unsuccessful. However, for compounds I-IV, where R is the same, an excellent correlation coefficient was obtained as shown in equation (5):

$$\log \varepsilon_{max} = 3.947 + 0.6717\mathcal{F} \quad \ldots\ldots\ldots\ldots\ldots\ldots (5)$$

$$r = 0.998 \; ; \quad s = 0.032 \; ; \quad n = 4$$

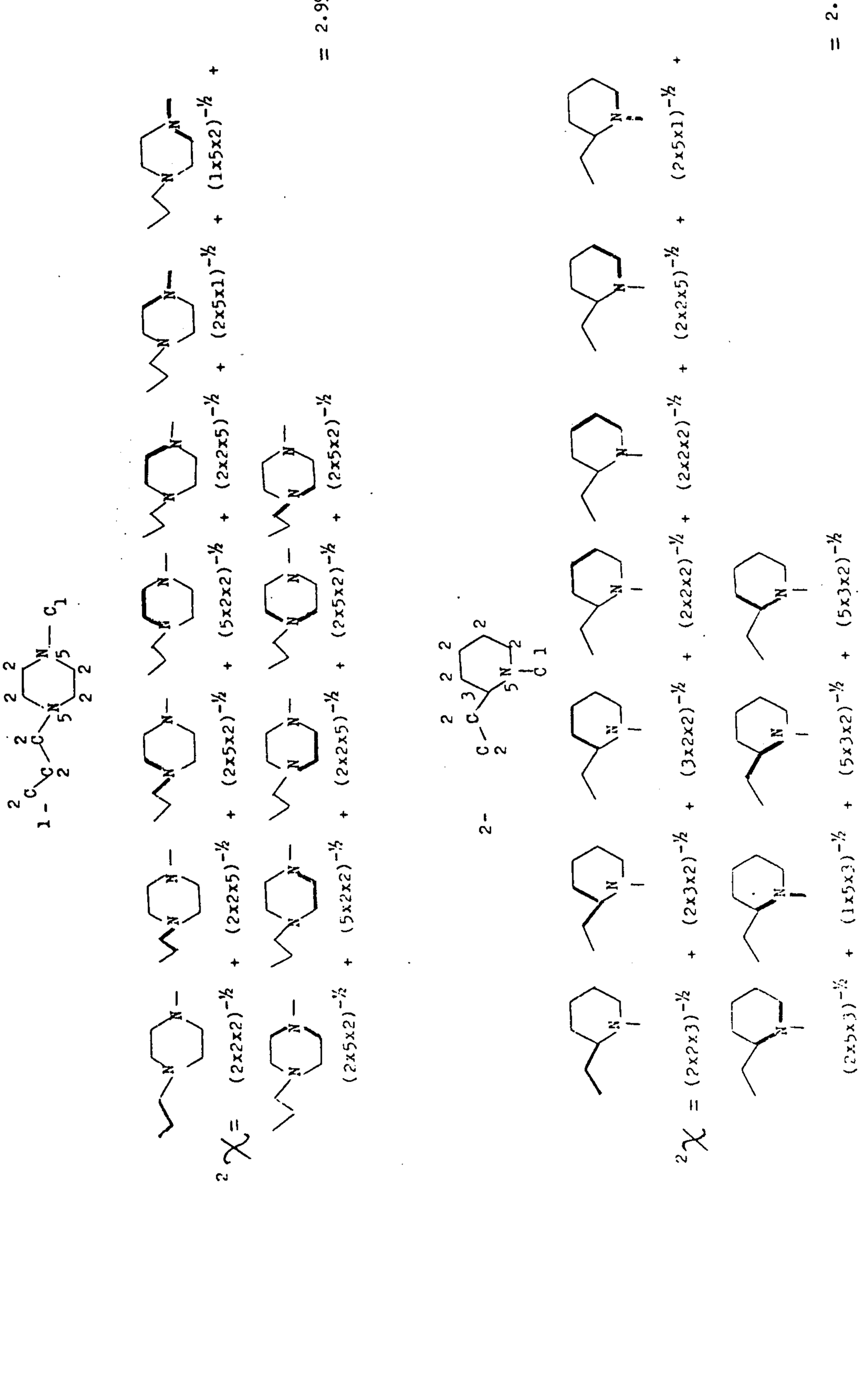
$$F = 411.18 \; ; \quad p < 0.005$$

It can be noticed that compounds III and IV are not excluded from the compounds treated by equation (5) as is the case with equation (3). Since the present interpretation about the possible derivatization of R_1 groups of compounds III and IV is based on a well known theoretical background, then it can be deduced that $\mathcal{F}$ values of the derivatized functions are not affected or insignificantly changed under the given reaction conditions. Hence the excellent correlation and the highly significant level of equation (5) and also the improved correlation obtained from equation (3) after the exclusion of the compounds carrying vulnerable R_1 groups. It is clear that under these reaction conditions, the variance of log ε_{max} for all compounds analysed cannot be explained by a single equation. Application of equation (4) is limited to those phenothiazines with stable R_1 substituents, while equation (5) is applicable for the prediction of log ε_{max} of the given compounds only. Further study is needed in order to examine the validity of equation (5) to predict log ε_{max} of compounds carrying R groups different from R =1 in the compounds I-IV.

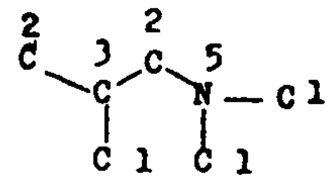
The regression analysis discussed can be further utilised to predict the unreported electronic parameters $\mathcal{R}$, $\mathcal{F}$ and σ_p of $SO_2N(CH_3)_2$ group. Thus for compound V, $\log \varepsilon_{max}$ Table I, and the calculated $^2\chi^v$ Table III were substituted in equation (4) and (5) to give the $\mathcal{R}$ and $\mathcal{F}$ constants of this group. Then the deduced $\mathcal{R}$ and $\mathcal{F}$ values were substituted in equation (1) to give the σ_p value Table II

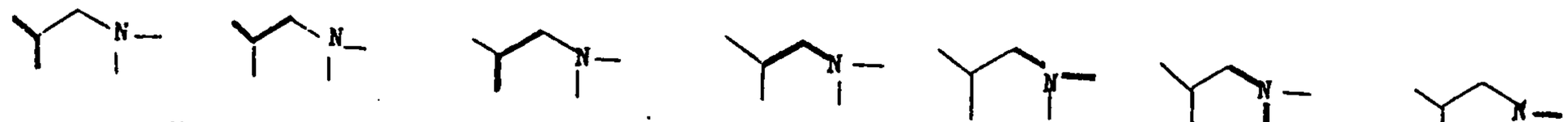
The electronic parameters of $-SO_2N(CH_3)_2$ group like those already reported for other functional groups are of special value in chemical and biochemical correlations.

Colorimetric Determination of Phenothiazine Drugs. 4-Correlation Between Molar Absorptivity and $\mathcal{F}$, $\mathcal{R}$ and χ Parameters of Ring Substituents.

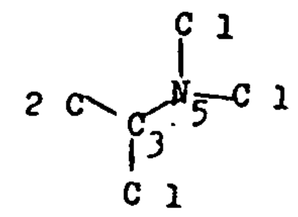


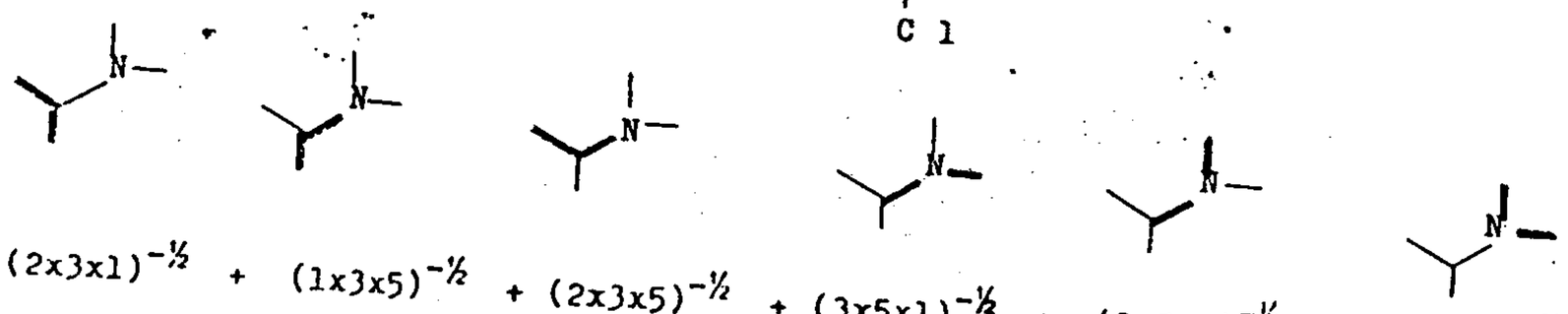
Scheme I

3- 

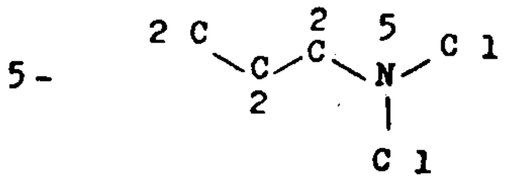


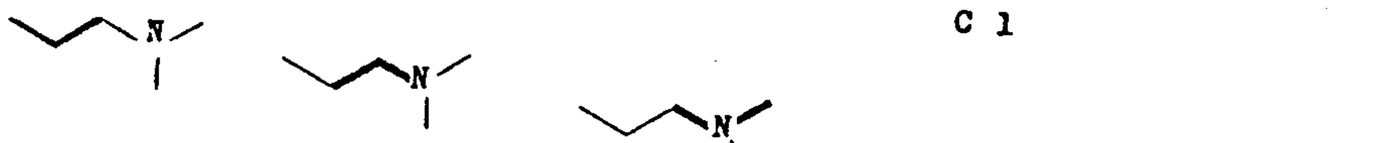
$^{2}\chi = (2x3x1)^{-1/2} + (2x3x2)^{-1/2} + (1x3x2)^{-1/2} + (3x2x5)^{-1/2} + (2x5x1)^{-1/2} + (2x5x1)^{-1/2} + (1x5x1)^{-1/2} = 2.367$

4- 



$^{2}\chi = (2x3x1)^{-1/2} + (1x3x5)^{-1/2} + (2x3x5)^{-1/2} + (3x5x1)^{-1/2} + (3x5x1)^{-1/2} + (1x5x1)^{-1/2} = 1.812$

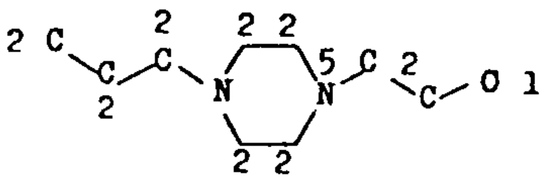
5- 

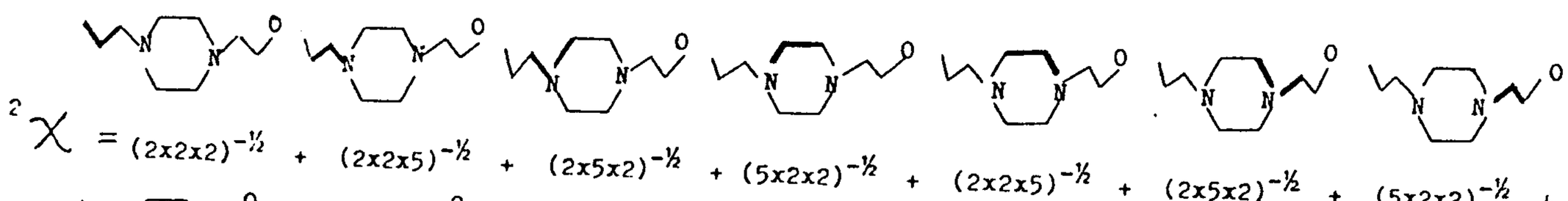


$^{2}\chi = (2x2x2)^{-1/2} + (2x2x5)^{-1/2} + (2x5x1)^{-1/2} + (2x5x1)^{-1/2} + (1x5x1)^{-1/2} = 1.657$

Scheme I (Continued)

6-

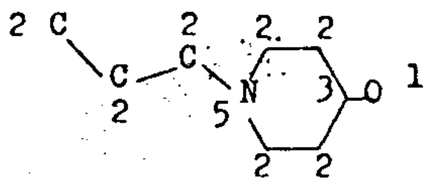


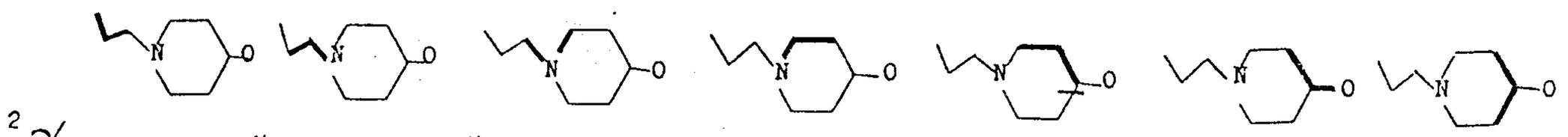


$^2\chi = (2x2x2)^{-½} + (2x2x5)^{-½} + (2x5x2)^{-½} + (5x2x2)^{-½} + (2x2x5)^{-½} + (2x5x2)^{-½} + (5x2x2)^{-½} +$

$(2x2x1)^{-½} + (2x5x2)^{-½} + (2x5x2)^{-½} + (5x2x2)^{-½} + (2x2x5)^{-½} + (2x5x2)^{-½} + (2x5x2)^{-½} = 3.537$

7-



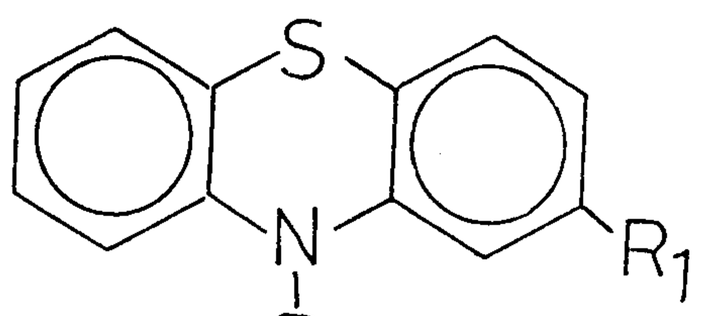


$^2\chi = (2x2x2)^{-½} + (2x2x5)^{-½} + (2x5x2)^{-½} + (5x2x2)^{-½} + (2x2x3)^{-½} + (2x3x1)^{-½} + (2x3x2)^{-½} +$

$(1x3x2)^{-½} + (3x2x2)^{-½} + (2x2x5)^{-½} + (2x5x2)^{-½} + (2x5x2)^{-½} = 3.379$

Scheme I (Continued)

Table 1: Observed and calculated log ε_{max} of the investigated phenothiazines.



R

No.	Name	Nuclear substituents		Log ε_{max}		
		R^a	R_1	obs.	Eq. 4	Eq. 5
I	Perazine	1	H	3.9518[b]	4.0080	3.9469
II	Prochlorperazine maleate	1	Cl	4.2276[b]	4.1411	4.2223
III	Butaperazine dimaleate	1	COC_3H_7	4.1638[b]	------	4.1618
IV	Thiethylperazine maleate	1	SC_2H_5	4.0892[b]	------	4.1014
V	Thioproperazine mesylate	1	$SO_2N(CH_3)_2$	4.0358[b]	------	------
VI	Thioridazine hydrochloride	2	SCH_3	3.9731[c]	------	------
VII	Methotrimeprazine hydrochloride	3	OCH_3	4.3143[b]	4.3579	------
VIII	Promethazine hydrochloride	4	H	3.7731[b]	3.8155	------
IX	Chlorpromazine "	5	Cl	3.9818[b]	3.9234	------
X	Fluphenazine "	6	CF_3	3.9370[b]	3.9270	------
XI	Pericyazine	7	CN	3.8887[b]	3.9014	------

a) The numeral refers to the side chain as given in Scheme I.

b) Ref. 7 ; c) Ref. 6

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Table II- Electronic parameters of substituents R_1 [a]

R_1	$\mathcal{F}$	$\mathcal{R}$	σ_p
Cl	0.41	-0.15	0.23
H	0.00	0.00	0.00
CF_3	0.38	0.19	0.54
CN^3	0.51	0.19	0.66
OCH_3	0.26	-0.51	-0.27
SCH_3^3	0.20	-0.18	0.00
SC_2H_5	0.23	-0.18	0.03
COC_3H_7	0.32	0.20	0.50
$SO_2N(CH_3)_2$	0.13[b]	-0.03[c]	0.09[d]

a) Ref. 9b
b) Predicted value eq. (5)
c) Predicted value eq. (4)
d) " " " (1)

Table III- Connectivity index $^n\chi^v$ of the side chain R

R*	$^1\chi^v$	$^2\chi^v$	$^3\chi^v$
1	4.028	2.998	2.070
2	3.838	2.919	2.255
3	2.603	2.367	0.677
4	2.137	1.812	0.881
5	2.210	1.657	0.605
6	5.103	3.537	2.479
7	4.341	3.379	2.350

* The numeral refers to the side chain as given in Scheme I.

REFERENCES

1) J. Blazek, Pharmazie, 22, 129 (1967).

2) J. Blazek, A. Dymes and Z. Stejskal, Pharmazie, 31, 681 (1976).

3) J.E. Fairbrother, Pharm. J., 32, 271 (1979).

4) A.F. Youssef, S.R. El-Shabouri, F.A. Mohamed and A.M.I. Rageh, J. Assoc. Off. Anal. Chem., 69,513 (1986).

5) S.R. El-Shabouri, A.F.Youssef, F.A. Mohamed and A.M.I. Rageh, ibid, 69, 821 (1986).

6) A.M. Taha, N.A.El-Rabbat, M.E. El-Kommos and I.H. Refaat, Egypt. J. Pharm. Sci., 22, 163 (1981).

7) A.M. Taha, N.A. El-Rabbat, M.E. El-Kommos and I.H. Refaat, Analyst, 108, 1500 (1983).

8) S.R. El-Shabouri, A.F. Youssef, F.A. Mohamed and A.M.I. Rageh, Bull. Pharm. Sci., Assiut University, 9 (1), 137 (1986).

9) C. Hansch, A. Leo; "Substituent Constants for Correlation Analysis in Chemistry and Biology" John Wiley & Sons, New York (1979).
   a) p. 49-52 ; b) p. 6

10) H.L. Hall and L.B. Kier, Eur. J. Med. Chem, 16, 399 (1981).

11) G. Hilgetag and A. Martini, Ed., "Preparative Organic Chemistry", 4th ed., John Wiley & Sons, New York (1972).
   a) p. 189 ; b) p. 667

12) Jerry March " Advanced Organic Chemistry-Reaction, Mechanisms, and Structure" 2nd ed., MeGraw-Hill Kogakusha Ltd., (1977).
   a) p. 538 ; b) p.1112.

التحليل الطيفى لمركبات الفينوثيازين

٤ـ مدى العلاقة بين لوغاريتم شدة الامتصاص الجزيئى وبعض المعايير الالكترونية وعامل الترابط الجزيئى للمجموعات المستبدلة فى حلقة الفينوثيازين

ميشيل ايليا القمص ـ عادل فوزى يوسف

قسم الكيمياء الصيدلية ـ كلية الصيدلة ـ جامعة أسيوط

فى هذا البحث تم ربط شدة اللون من تفاعل احدى عشر عقارا من عقارات الفينوثيازين مع ن ـ بروموسكسينيمايد فى محلول مركز من حامض الكبريتيك ببعض المعايير الفيزيوكيميائية للمجموعات المستبدلة فى حلقة الفينوثيازين وهى المعايير الالكترونية للمجال وللرنين وعامل الترابط الجزيئى . وقد أوضحت النتائج أن العلاقة بين لوغاريتم شدة الامتصاص الجزيئى من ناحية والمعيار الالكترونى للرنين وعامل الترابط الجزيئى من ناحية أخرى ذات دلاله احصائية عالية فى حالة عدم وجود مجموعات قابلة للتأكسد بالكاشف المستعمل فى الموضع رقم ٢ من حلقة الفينوثيازين . كما تبين أن العلاقه بين لوغاريتم شدة الامتصاص الجزيئى والمعيار الالكترونى للمجال ذات دلاله احصائية عالية فى المركبات التى تحتوى على نفس المجموعه المستبدلة فى الموضع رقم ١٠ من حلقة الفينوثيازين بغض النظر عن قابلية المجموعة المستبدلة فى الموضع رقم ٢ من حلقة الفينوثيازين للتأكسد بواسطة الكاشف .

ولقد تم استخدام المعادلات المستنبطة فى حساب المعايير الالكترونية سيجما واف وآر للمجموعة ـ كب $أ_{٢}$ ن (ك يد ٣)$_{٢}$ من النموذج الطيفى .

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