An Najah National University

Faculty of Graduate Studies

Determination of a New Synthetic Pyrido-Pyrimidine By Adsorptive Cathodic Stripping Voltammetry

Master Thesis

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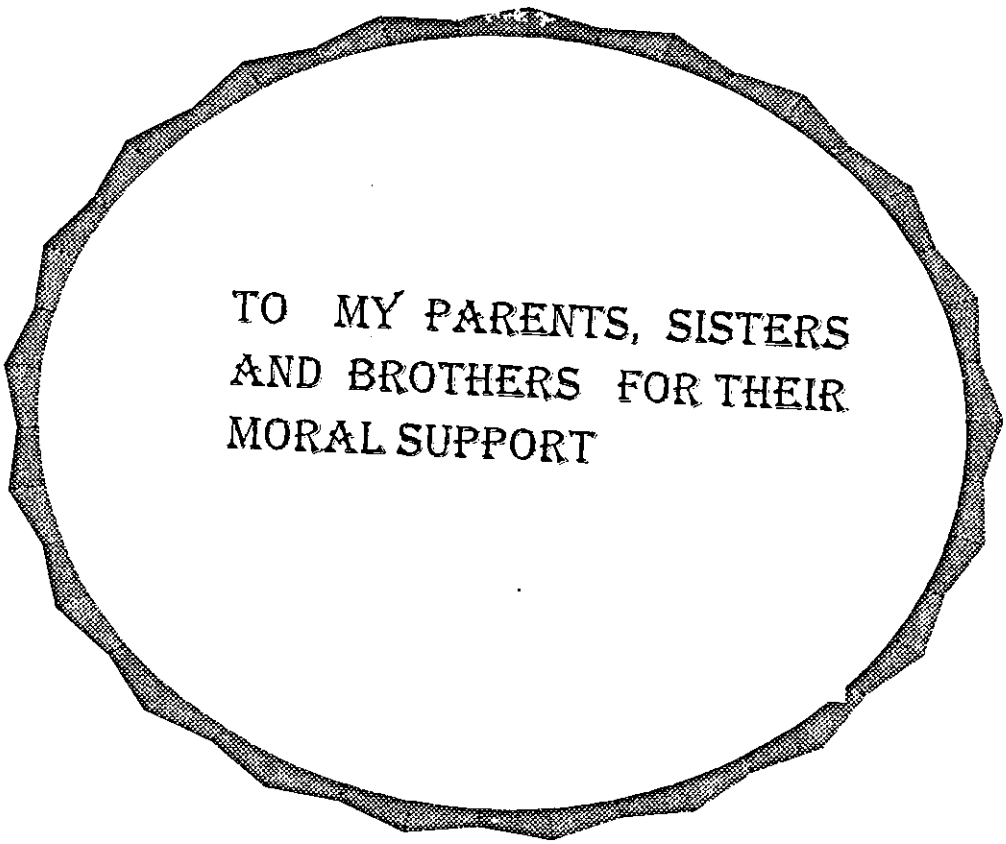
بسم الله الرحمن الرحيم

"إنما يخشى الله من عباده العلماء"

صدق الله العظيم



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ABSTRACT

Adsorptive cathodic stripping voltammetric (AdCSV) technique was used to determine trace amounts of (7-Bromo-2, 3-tetramethylene pyrido [1,2,a] pyrimidine -4-one), **BTP,** a new pyrimidine synthetic derivative. This compound is a potential drug which may be used to cure diseases such as cancer.

The determination was very sensitive and linearity between peak current and concentration was studied in the range $5x10^{-8}$ to $2x10^{-6}$ M with peak potential at about -0.8V. The detection limit is about $5x10^{-8}$M after 30 s accumulation time at -0.4V accumulation potential. The measurements have been taken in acetate buffer of pH 4.5 versus Ag/AgCl reference electrode. The RSD% at $2x10^{-7}$ M level didn't exceed 3.0% (six determinations). The optimum conditions for such determination was investigated and the addition of copper, nickel and some other metal ions did not affect the peak current. A calibration curve was built up at the optimum conditions and the method is useful to determine very low concentrations of this newly synthesized substance.

Chapter one

Chapter one

Introduction

This compound, (7-Bromo-2, 3-tetramethylene pyrido [1,2,a] pyrimidine -4-one), **BTP (1)**is expected to become a cure for some diseases such as cancer, because its structure resembles compounds used to cure such diseases [1,2]. Also it is expected to cure bacterial infections [3,4].

Some structurally related compounds are 2- Pyridones which had been found to be excellent practical DNA gyrase inhibitors. It exhibits a wide-range spectrum of antibacterial activity and is potent against organisms of chemically utilized fluroquinolones. Remarkably, it was active against resistant bacteria such as Methicillin - Resistant Staphylococcus Aureus (MRSA), vanomycin-resistant strains of enterococci, and ciprofloxacin-resistant organisms. It has a favorable physiochemical and pharmocokinetic properties [5] .

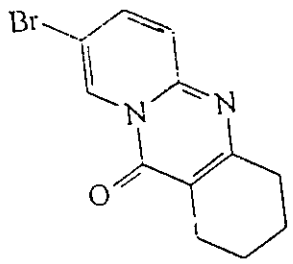
Agents related to quinolone antibacterial are to show an outstandingly important novel class of therapeutically useful compounds, such as piperazine, methyl piperazine and 3-aminopyrrolidine. Recently, a large number of such agents have been put for use successfully in the treatment process of many human bacterial infections [6] .

Of the most important subcellular targets of anticancer chemotherapeutics are microtubules. Some drugs are added to help mitotic arrest, because

these drugs attack microtubules through their major structural component, tubline [7,8]. These drugs which are used as antimitotic agents are natural products (e.g. taxol, podophyllotoxine and the vinca alkaloids [7]).

A tricyclic chemical structural pattern including a phenyl ring attached to the 2-position of a naphthalene nucleus such as **2**, or composed of various heterocyclic units with similar structural arrangements, was observed among a large number of antineoplastic compounds by Chang in 1986.

The flavonoids belonging to this common structural pattern "**2**" such as "**3**" have shown antimutagenic, anticarcinogenic and antileukemic activities. The antileukemic activity of flavonoids was seen in tricin.



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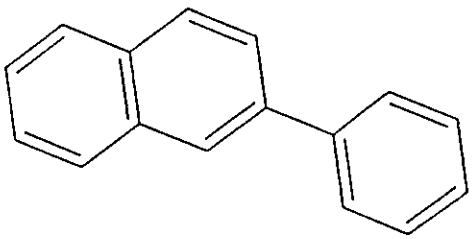

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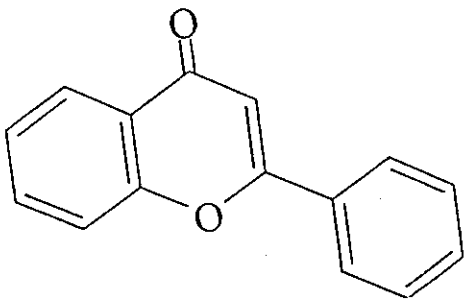


3

Voltammetry

Voltammetry has to do with concern to the voltage -current- time relationships study during the electolysis process. Voltammetry is one of the most sensitive analytical techniques in the determination of many pharmaceutical compounds) [9-12].

When the adsorbed layer is to be reduced, the *Hanging Mercury Drop Electrode* (HMDE) remains the best choice since the drop is renewed after each scan with high reproducibility when an automatic stand is used. Lower detection limits are obtained with the HMDE which also does not need conditioning prior to use (self-cleaning property) other advantages of mercury electrodes are their extended negative potential range (high hydrogen over potential). The disadvantages of these electrodes are their toxicity [13].

Voltammetry can be performed for many different purposes. To learn about the mechanism of electrode reaction is one of the major objectives. When mechanism is understood, the second goal arises which is to measure the kinetics of electron transfer process or of some associated homogeneous reactions. Furthermore, transport and themodynamic properties of solute species may be accessed by voltammetry [14] .

Adsorptive Cathodic Stripping Voltammetry (AdCSV).

The non-electrolytic nature of the accumulation process, where adsorption takes a major role, characterizes adsorptive stripping Voltammetry [15]. Because most neutral organic analytes are adsorbed as a result of hydrophobic force, adsorptive stripping procedure generally utilizes aqueous solutions [16]. This process, AdCSV, is less likely to affect the sample concentration as only a monolayer is usually measured at the surface of the electrode [17].

AdCSV is thus a stripping voltammetic technique, where the current produced is a result of reduction (cathodic scanning) of the species brought to the electrode surface by adsorption (a non-faradaic process) [18].

It is a sensitive method for the determination of several trace metal ions and organic substances, and achieves its low-level detection by combining an accumulation process with voltage scanning measurement [19]. This method has been demonstrated to be highly surface for calculating organic compounds with π-bonds (Aromatic rings), sulfur groups are more strongly adsorbed than those without [20]. Short times of adsorption (1-5 min) have led to be a very practical interfacial accumulation.

The stripping step is regarded very effective as all the deposits are reduced or oxidized. This combination results in highly low detection limit to cover the 10^{-6} to 10^{-10} M concentration range [18,21]. Nonelectroactive molecules may also be determined following their interfacial accumulation from tensammetric peaks resulting from their adsorption - desorption mechanism

[21]. AdSV is widely applied in determinations of traces of metal ions e.g Uranium [22], Indium [23] and Vanadium [24] after complexing with suitable ligands.

Cyclic voltammetric measurements

Cyclic voltammetry is capable of rapidly generating a new oxidation state during the forward scan and then probing its fate on the reverse scan. Peak heights are related to both concentration and reversibility of the reaction. [13]

Aim of Study

The aim of this work was to study:

1- Electrochemical behavior of this new Pyrido-pyrimidine and its reduction properties.

2- Suggested sensitive method for determination of trace levels of this compound.

Chapter Two

Chapter Two

Experimental

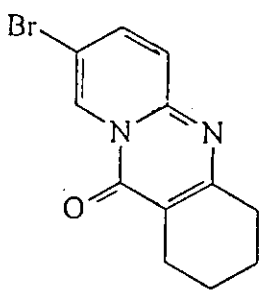
2.1 Chemicals and reagents

All chemicals used were of analytical grade (Aldrich, Sigma or Merk). Doubly distilled water was used through the work.

A) Preparation of 7-bromo-2, 3-tetramethylene pyrido [1,2-a] pyrimidine -4-one (**BTP**).

Amixture of ethyl 2-cyclohexanone carboxylate (1ml, 6.25 mmole), polyphosphoric acid (3gm) and 2-amino-5-bromopyridine (1.08gm, 6.25 mmole) was heated to 120°C for 2 hrs. The product was extracted using chloroform, and charcoal was added to remove color, then the solution was filtered and the solvent was evaporated under reduced pressure. The product was recrystalized from chloroform. The white precipitate was collected on a centered funnel.[25]

BTP:



Stock solution of (**BTP**) 10^{-3}M was prepared by dissolving 0.0279g in absolute ethanol up to 100 ml volumetric flask. The solution was stable in the refrigerator for not less than one month.

2.1.1 Preparation of Chemical reagents

B) Preparation of the buffers

Britton - Robinson (BR) buffer solution was prepared from acid mixture of acetic, phosphoric and boric acids, each being 0.04 M as a final concentration.

Sodium hydroxide (0.2 M) solution was added to set the desired pH in the range from (2-11).

Acetate buffer was prepared from 0.2 M sodium acetate solution, acetic acid (0.2 M) was added to get the desired pH of acetate buffers (pH 4.5) [26].

Phosphate buffer was prepared by mixing equal volumes of Na_2HPO_4 (0.1 M) and K_2HPO_4 (0.1 M) and adjusted to the required pH with NaOH solution [13].

Citrate buffer was prepared from 0.05 M citric acid and adjusted to the required pH4 with NaOH solution.

Instrumentation

All the voltammograms were carried out using Model 264B EG&G polarographic analyzer / stripping voltammeter, coupled with model 303 A stand and model 305 automatic stirrer and RE 0150 x-y recorder.
The three-electrode system completed using an auxiliary Platinum wire electrode and Ag/AgCl reference electrode. The pH measurements were carried out using HANNA pH meter, model HI 8424.

Methodology

A- Technique

Most of the adsorptive voltammetric measurements were carried out on a Hanging Mercury Drop Electrode (HMDE). The technique might be called differential - pulse adsorptive cathodic stripping voltammetry (DP-AdCSV).

B- Recommended Procedure

The general procedure for obtaining voltammetric results was as follows:

An accurate volume (usually 9-10 ml) of the buffer was pipetted into a clean and dry voltammetric cell, the stirrer was switched on at slow rate while purging with high purity nitrogen. After eight minutes, purging was stopped automatically.
A suitable accumulation potential usually (-0.40 V) and accumulation time (usually 30 s) were selected. A new drop (usually small size) was formed while the stirring was continued and after the completion of accumulation

and equilibration, a scan was initiated in the negative direction. The scan rate was 10 mVs^{-1} and the pulse amplitude was 50 mV.

De-oxygenation with purged nitrogen for 1-4 minutes was carried out between successive measurements depending on the length of the proceeding accumulation period. The same steps of accumulation and stripping were followed with the sample in the voltammetric cell. All experiments were carried out at room temperature (25 $\pm$ 0.5 °C). A calibration plot of concentration against current was constructed and used for subsequent determinations.

Chapter Three

Chapter Three

Results and Discussion

Different experimental parameters that affect the differential-pulse adsorptive cathodic stripping voltammetric response were studied in order to optimize the experimental conditions for the determination of **BTP**. These parameters include the effect of pH, buffer constituents, scan rate, pulse amplitude, accumulation time [t_{acc}], accumulation potential (E_{acc}) and the effect of Cu^{2+}.

Effect of pH

The differential - pulse adsorptive cathodic stripping voltammograms (DP-AdCSV) of $1x10^{-6}$M **BTP** was carried out over a wide pH range (3-9) using Britton-Robinson (BR) buffer as shown in Figure 3.1. The compound exhibits one reduction peak in the whole pH range.

The height of the peak initially increases in the pH range 2-4.5, then the peak height decreases markedly at pH greater than 4.5 and disappears completely above pH 10. The peak potential, E_p of the reduction was shifted towards more negative potentials by increasing the pH, indicating that the H^+ is consumed in the reduction process. The optimum pH with respect to peak height was found to be 4.5.

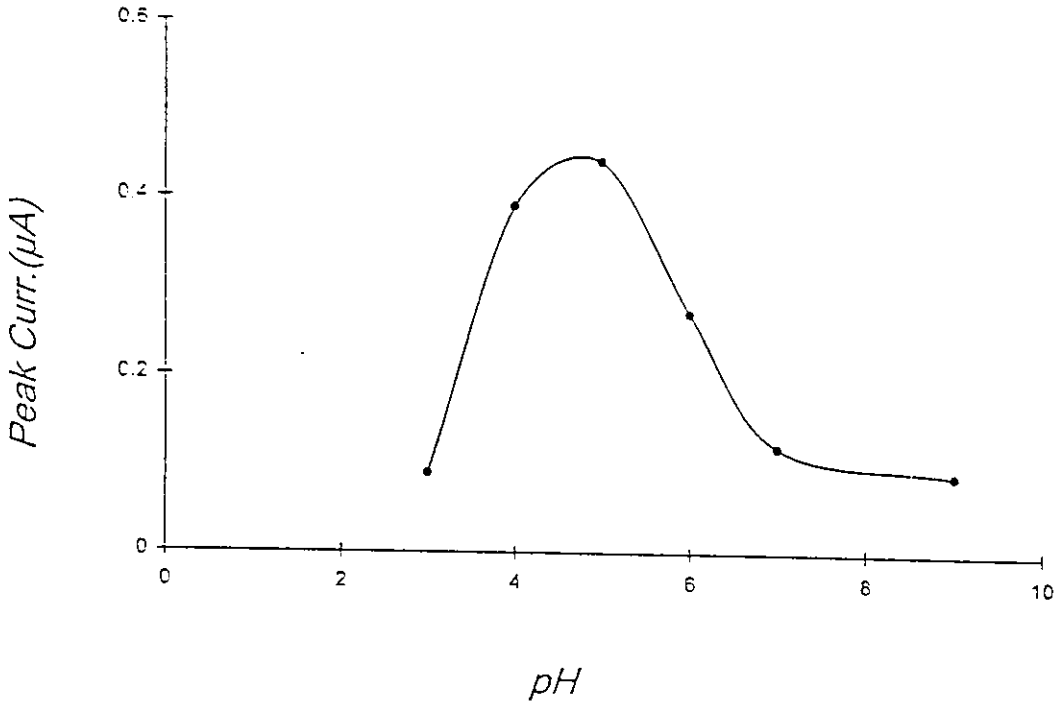


Fig 3.1 Effect of pH of Britton-Robinson buffer on the DP-AdCSV of $1x10^{-6}$ M **BTP**. Other conditions as in Table 3.1

Table 3.1 :Effect of pH of Britton-Robinson buffer on the DP-AdCSV of $1x10^{-6}$M **BTP** accumulated at 0V for 30s, scanned form 0 to -1.2V, small drop size, pulse amplitude 50mV at 0.5s intervals and scan rate $10mVs^{-1}$.

pH	peak current (μA)	peak potential (V)
3	0.09	-0.86
4.5	0.46	-0.88
5	0.44	-0.88
6	0.27	-1.0
7	0.12	-1.05
9	0.09	-1.08

Effect of Buffer Constituents

The choice of buffer constituents is important for the adsorptive stripping behavior of this analyte. The AdCSV peak has been examined in the presence of many subsidiary buffer electrolytes, having the same pH i.e. (pH 4): e.g. Britton Robinson (BR), acetate, citrate and phosphate buffers. The best results regarding the peak shape, enhancement, signal to background ratio and reproducibility, were obtained in the acetate buffer solution (Table 3.2). Therefore, acetate buffer (pH 4.5) has been recommended for all DP-AdCSV measurements.

Table 3.2 : Effect of buffer constituents on the peak current and potential at pH 4, t_{acc} 30 s. $1x10^{-6}$ M **BTP** accumulated at 0 V. Small drop size, pulse amplitude= 50 mV at 0.5 s intervals and scan rate 10 mV s^{-1}.

Buffer	Peak Current(μA)	Peak Potential(V)
Acetate	0.42	-0.88
Citrate	0.33	-0.88
Phosphate	0.26	-0.88
BR	0.40	-0.87

Effect of Accumulation Potential

The impact of the changeable accumulation potential on the peak current of $5x10^{-7}$ and $1x10^{-6}$ M **BTP** has been examined over a wide potential range 0.0 to -1.1 V). The highest peak was observed for the accumulation potential at -0.4 V. In order to avoid high baseline which appeared at about 0.0 V (partially due to capacitive current); the scan has been started from the accumulation potential of -0.4V, as selected.

Effect of Accumulation Time

The effect of accumulation time was studied at various times. : 30, 60, 90, 120, 180, 240 sec. Accordingly, it was observed that there was no significant improvement in peak height with increasing accumulation time. The studied solutions were of $5x10^{-7}$ and $1x10^{-6}$ M **BTP**. Long accumulation times as 180, 240 s are not preferred (due to bad resolution of peaks), while zero accumulation time or 30 s is preferred. Further work has been conducted using 30 s accumulation time.

Effect of Pulse Amplitude

The effect of pulse amplitude on the peak current, peak potential and peak width of $3x10^{-6}$ M **BTP** has been investigated. It was found that the peak current increases as the pulse amplitude increases. On the other hand, the peak potential is positively shifted as pulse amplitude increases in the cathodic scan. However, the peak width (it is the width of the peak at its half height) is not affected with increasing peak current.

Table 3.3 : Effect of pulse amplitude on the DP-AdCSV peak current and peak potential of $3x10^{-6}$M **BTP**. Other conditions as in Fig 3.2.

Pulse amplitude, mV	**Peak current , μA**	**Peak potential,V**
25	0.20	-0.62
50	0.74	-0.60
100	1.35	-0.53

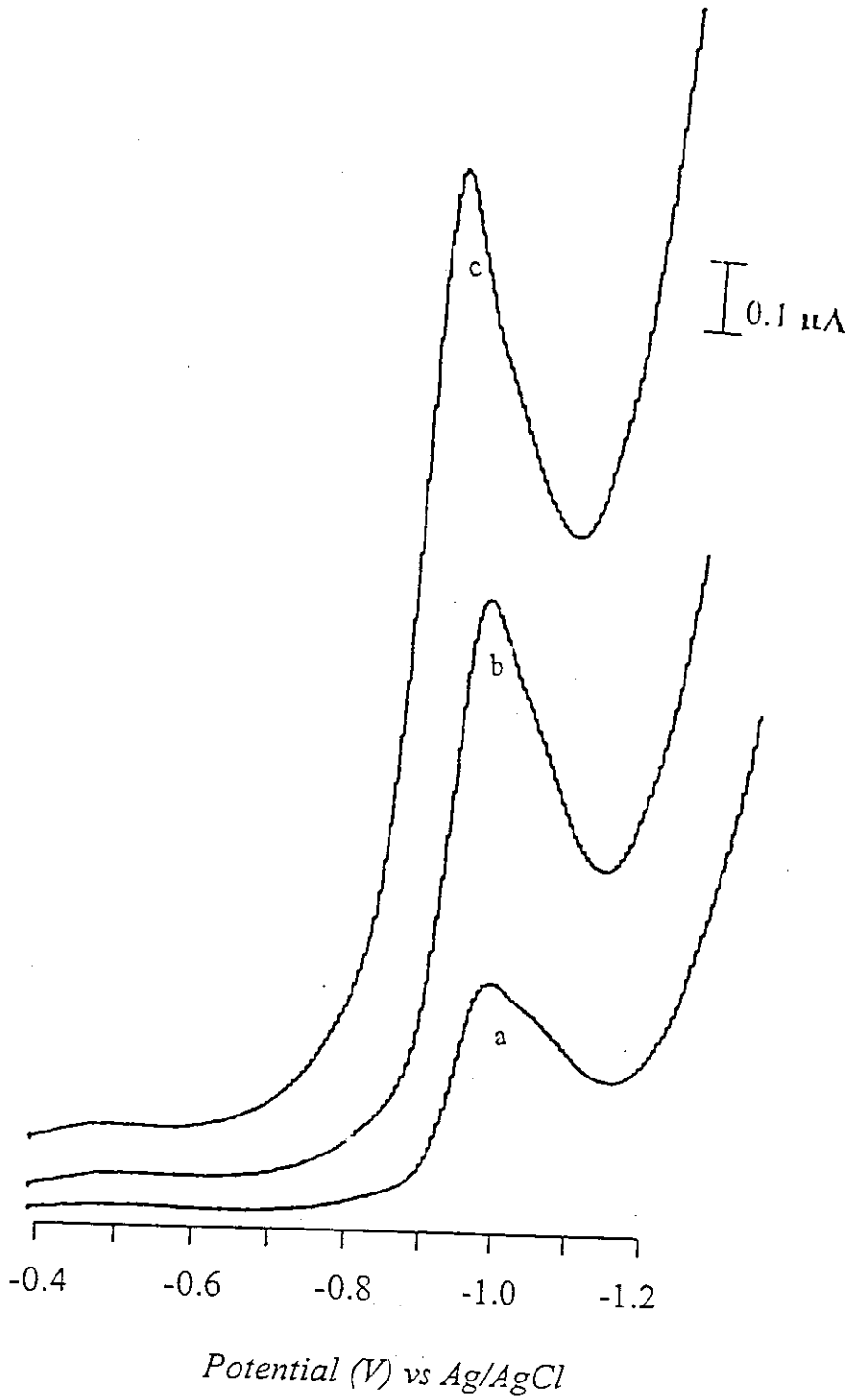


Fig 3.2 Effect of pulse amplitude on the DP-AdCSV peak current and peak potential of $3x10^{-6}$ M **BTP**, pH 4.5 acetate buffer, E_{acc} -0.4 V, t_{acc} 30 s and scan rate 10 mVs^{-1}. (a): 25, (b): 50, (c): 100 mV

Cyclic Voltammetric Measurement

The cyclic voltammetric measurement of the drug showed a single reduction peak at the HMDE in acetate buffer pH 4.5. No anodic peak was observed which indicates an irreversible reduction process (Nernstian behavior is not expected). The shift in peak potential is attributed to the adsorption phenomenon.

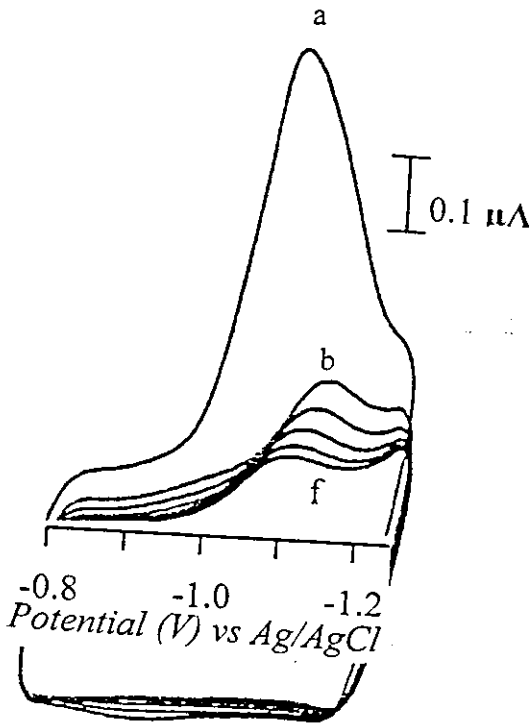


Fig 3.3 Repetitive cyclic voltammograms for $5x10^{-6}$ M **BTP** at $100mVs^{-1}$ scan rate, scan from –0.8 to -1.2V. Other conditions acetate buffer pH 4.5, t_{acc} 30s, small drop size and scan rate 10 mVs^{-1}. (a) the first cycle (b) the second cycle. (c) the third cycle. (d) the fourth cycle (e) the fifth cycle (f) the sixth cycle.

Effect of Scan Rate

For an adsorbed compound, the peak height of the reduction current is expected to increase linearly with scan rate. The reduction current will not be affected by the diffusion of reducible material to the electrode during the scan. For the diffusional behavior, the height of the cathodic peak increases linearly with the square root of the scan rate [13].

The negative shift of cathodic peak potential with increasing scan rate indicates a degree of irreversibility of the electrode process.

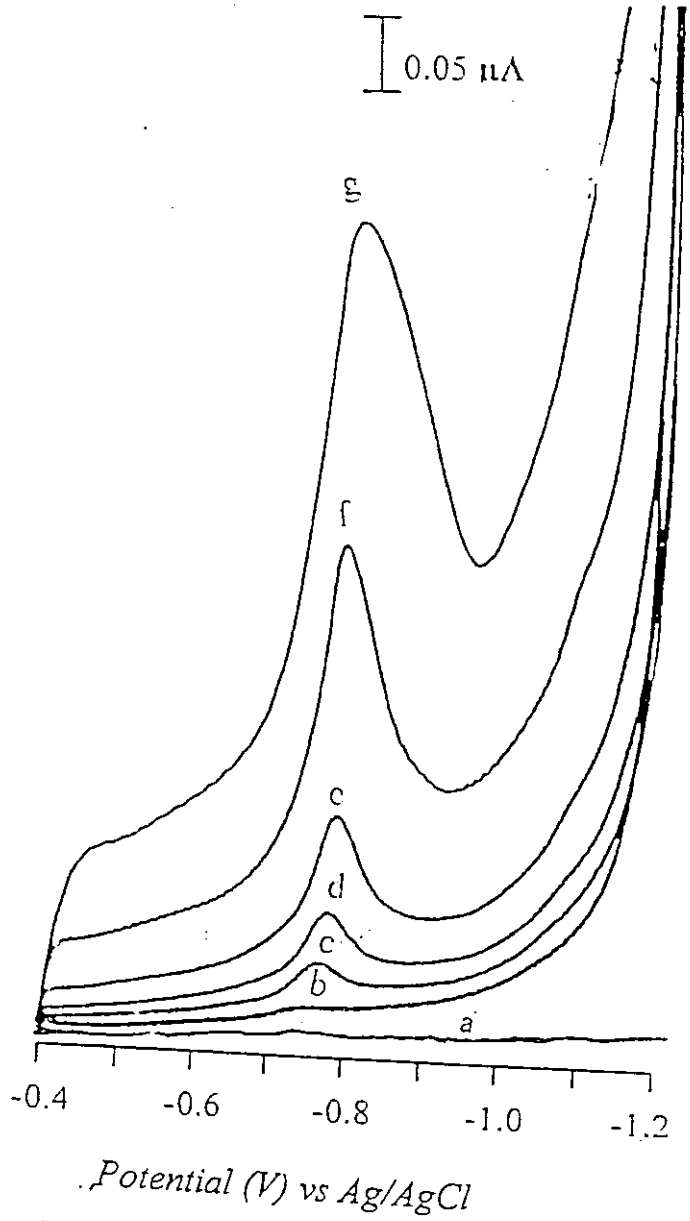


Fig. 3.4 DC-AdCSV peak heights of 1.2×10^{-6} M **BTP** at different scan rates (a) blank (b) 10 (c) 50 (d) 100 (e) 200 (f) 500 (g) 1000 mVs^{-1}.Scanning from -0.4 to -1.2V in acetate buffer pH 4.5, E_{acc} -0.4 V and t_{acc} 30s.

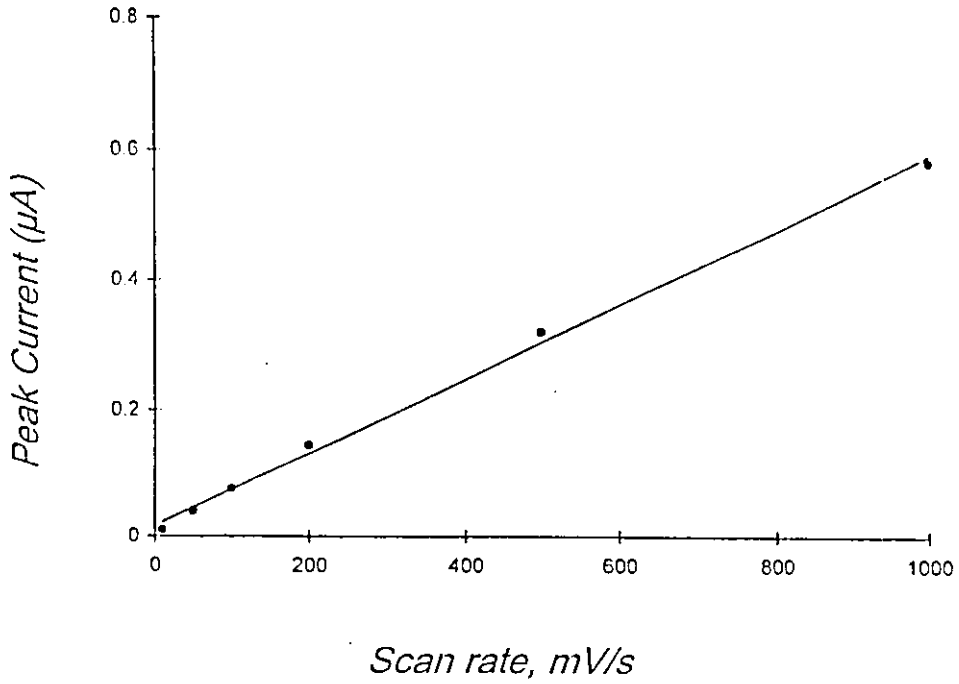


Fig 3.5 Effect of scan rate on the DC-AdCSV peak height of 1.2×10^{-6} M **BTP**. Other conditions as in Figure 3.4.

Calibration Curve :

According to the obtained results, the optimum conditions for the analytical determination of **BTP** by DP-CSV at HMDE are the following: pH=4.5, t_{acc}=30 s, E_{acc}= -0.4V, pulse amplitude 50mV and scan rate 10mVs^{-1}. Under the above conditions, the dependence of the peak height on the concentration of **BTP** is linear. Typical voltammograms showing successive enhancement of peak current with increasing **BTP** concentration are shown in Figure 3.7 and Table 3.4. Calibration curve was obtained with arectilinear concentration range $5x10^{-8}$ - $2x10^{-6}$ M, and the detection limit was found to be about $5x10^{-8}$M. Table 3.5 summarizes the optimum conditions for determination of **BTP** as well as the characteristics of the calibration curve. The effect of **BTP** concentration on its DPP peak current is summarizes in table 3.6.

Table 3.4 : Effect of **BTP** concentration on its peak current in acetate buffer pH=4.5 pulse amplitude 50mV, scan rate 10 mVs^{-1}, t_{acc} =30 s, E_{acc} = -0.4V.

Concentration of BTP (M)	**Average peak current** (μA)
$5.0x10^{-8}$	0.033
$1.5x10^{-7}$	0.096
$2.5x10^{-7}$	0.15
$4.0x10^{-7}$	0.21
$5.5 x10^{-7}$	0.25
$7.0x10^{-7}$	0.30
$1.0x10^{-6}$	0.39
$1.5x10^{-6}$	0.52
$2.0x10^{-6}$	0.60

Table 3.5: Characteristics of optimum conditions and calibration curve for pure **BTP**

Optimum pH	**Acetate buffer, pH=4.5**
Accumulation time	30 s
Accumulation potential	-0.4 V
Pulse Amplitude	50 mV
Scan rate	10 mVs^{-1}
Drop size	small
Concentration range	$5x10^{-8}$ - $2x10^{-6}$ M
Detection limit	$5x10^{-8}$ M

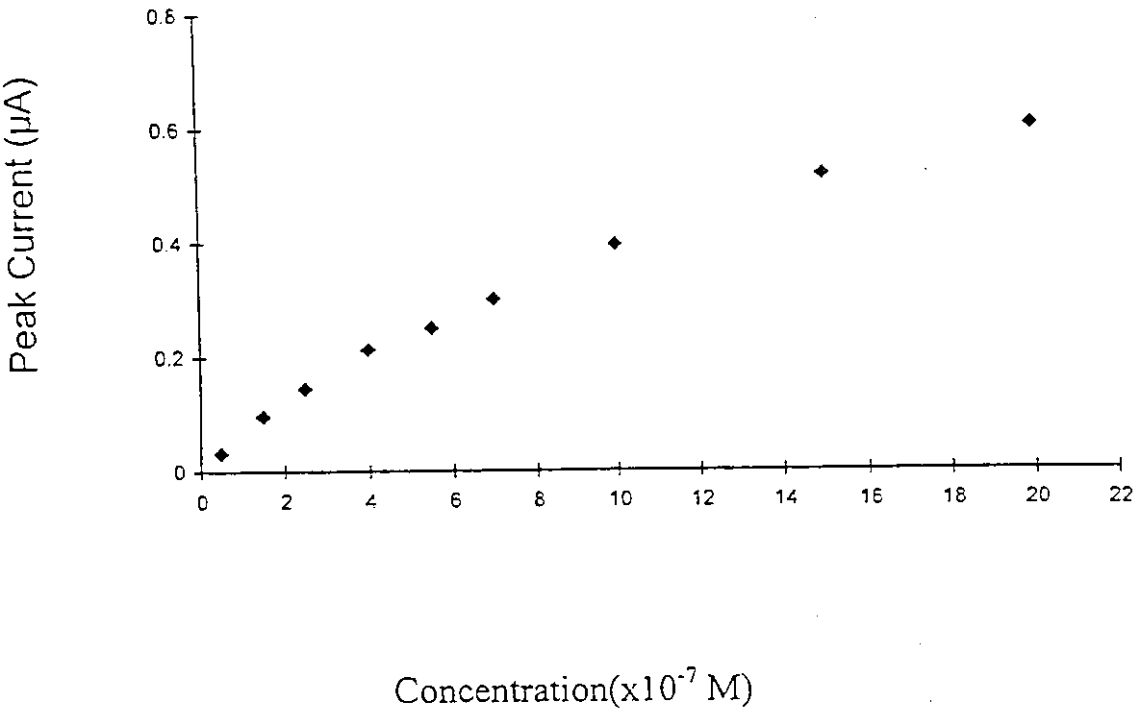


Fig 3.6 Calibration graph of the compound (BTP) in pH 4.5 acetate buffer. Other conditions as in Table 3.5

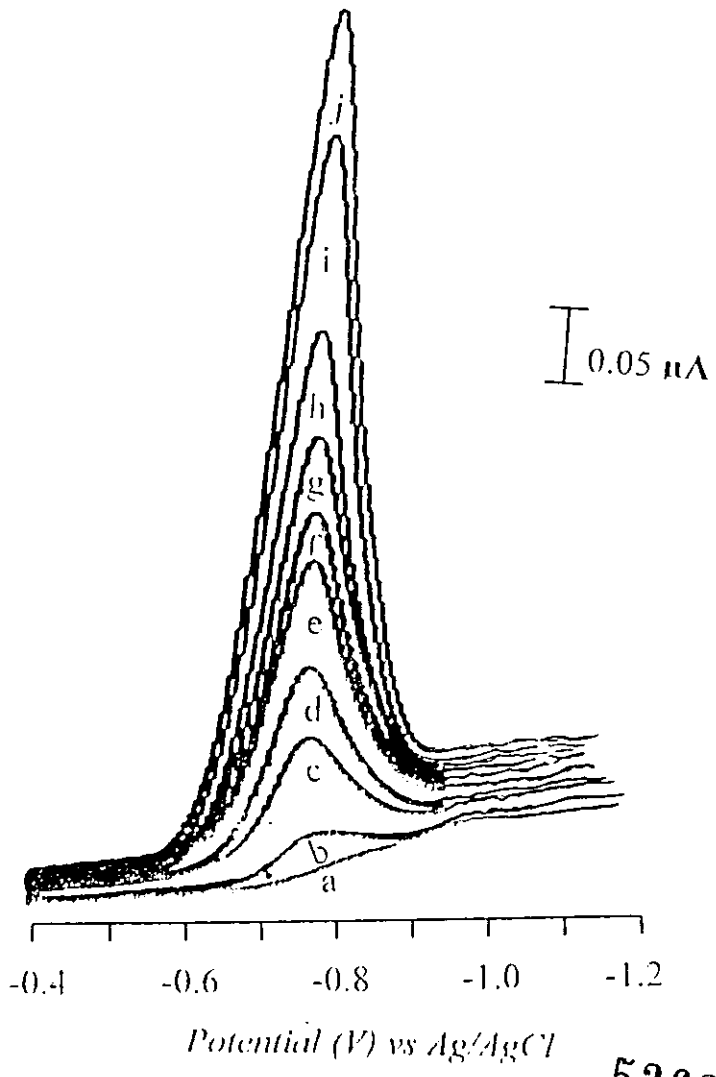


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Fig 3.7 DP-AdCS voltammograms at different concentrations of **BTP**. (a) blank (b) $5x10^{-8}$ M. (c) $1.5x10^{-7}$M. (d) $2.5x10^{-7}$M (e) $4x10^{-7}$M (f) $5.5x10^{-7}$M. (g) $7x10^{-7}$M. (h) $1x10^{-6}$M. (I) $1.5x10^{-6}$M. (j) $2x10^{-6}$M. Other conditions as in Table 3.4

Table 3.6 : Effect of **BTP** concentration on its DPP peak current in acetate buffer pH= 4.5, pulse amplitude 50mV (0.5 s intervals) ; scan rate 10 mVs^{-1}, t_{acc} =30 s, scanning from (-0.4 to -1.2V)

Concentration of BTP (M)	**Average peak current** (μA)
$5.0x10^{-7}$	0.18
$1.0x10^{-6}$	0.35
$1.5x10^{-6}$	0.63
$2.5\ x10^{-6}$	0.95
$4.0x10^{-6}$	1.58
$6.0x10^{-6}$	2.57
$8.0x10^{-6}$	3.45
$1.0x10^{-5}$	4.25

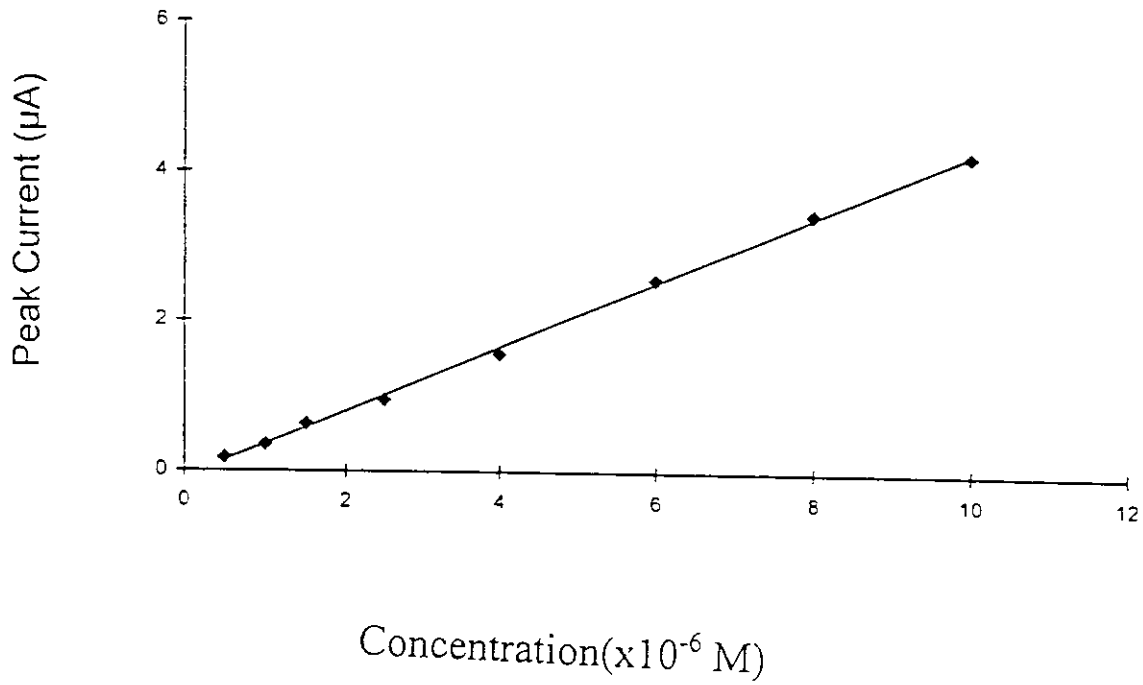


Fig. 3.8 Dependence of peak current (DPP) of **BTP** on its concentration. Conditions as in Table 3.6

Table 3.7 : Comparison between DPP & DP-CSV measurements of **BTP**

	DPP	**CSV**
RSD	5%	3% (6 measurement)
DL	$5.0x10^{-7}$ M	$5.0x10^{-8}$M
Linearity	Good linearity in concentration range $5.0x10^{-7}$M - $1.0x10^{-5}$ M DC - polarography is also linear for $1.0x10^{-5}$ M - $1.0x10^{-4}$M level	Bad linearity in its range of determination $5.0x10^{-8}$M - $2.0x10^{-6}$ M.

Electrochemical reduction of BTP

The following method was used to calculate the number of electrons involved in the reduction of BTP. The method depends on measuring the peak current for two known concentrationC_1,C_2 moles/L(preferably in the linear range). The HMDE is formed and the potential is scanned until it is in region of peak potential(-0.8 V). The potential is stopped at that value(pause button on instrument is pushed) and the stirrer is kept on while the reduction current is recorded at 3-minutes intervals. The current decreases gradually due to decrease in concentration of BTP by time. After about 90 minutes, the current values were summed up and the average current was calculated.

The quantity of electricity passed = average currentx90x60 coulombs

This quantity will be compared with one Faraday(=96500 Coulombs/equivalent). The decrease in no. of equivalents is thus known from Faraday's law. To calculate no. of moles decreased in this reduction process, the final cell solution is completed to its initial volume(10 ml) with the buffer to compensate for evaporation of buffer with purging nitrogen. The peak current is then measured which usually corresponds to a concentration intermediate (C_f) between C_1 and C_2. Thus, no. of moles decreased due to continuous reduction for 90 minutes=(C_2-C_f) x10/1000

no. of millimoles = no. of milliequivalents / n

where n= no. of electrons involved in the reduction per molecule. So, n can be calculated experimentally. The following data was obtained in this method:

$C_1=2x10^{-7}$ M, $C_2=6x10^{-7}$ M, $C_f=3.6x10^{-7}$ M

Decrease in concentration=$(6-3.6)x10^{-7}=2.4x10^{-7}$ M

The no. of millimoles=$2.4x10^{-7}x10=$**$2.4x10^{-6}$ mmoles**

Total time=92 minutes

Average current=0.0417 uA

Coulombs passed=$0.0417x10^{-6}x92x60$

and no. of meq=$0.0417x10^{-6}x92x60x10^{3}/96500=$**$2.39x10^{-6}$ meq**

n=2.39/2.40 =1

Another method for supporting the postulation of number of electrons involved in the reduction was dealing with the polarograms themselves.

DC Polarography was carried on for $1x10^{-4}$ M **BTP** in acetate buffer, pH 4.5. The rising part of the polarogram gave the following data for a selected point after $E_{1/2}$:

$E_{1/2}$ = -0.82V (half - wave potential).

E = -0.87V (potential of the selected point).

i_d = 4.5 μA (maximum diffusion current).

i = 4.0μA (current of the selected point).

Now applying the following equation [13]:

$$E = E_{1/2} + (0.059/n) \log \frac{id - i}{i}$$

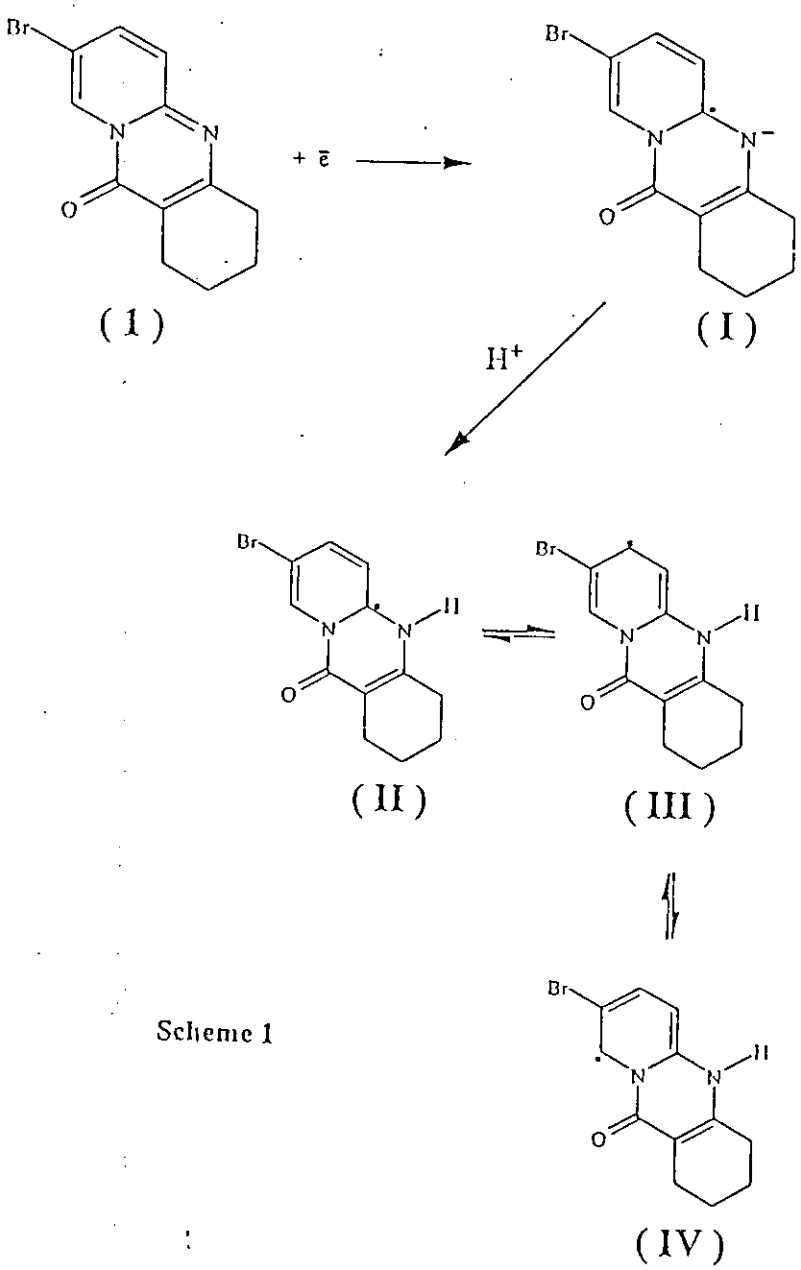
and substituting the above data in this equation:

$$-0.87 = -0.82 + \frac{0.059}{n}(-0.90)$$

n = 1.06 =1

This confirms from another side the conclusion of 1 electron reduction in the voltammetric determination.

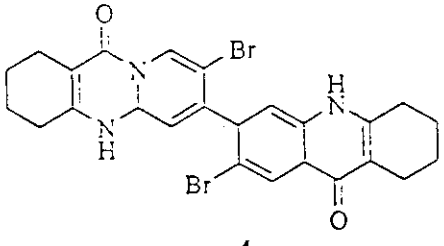
The following proposed mechanism accounts for the observed experimental data:



Scheme 1

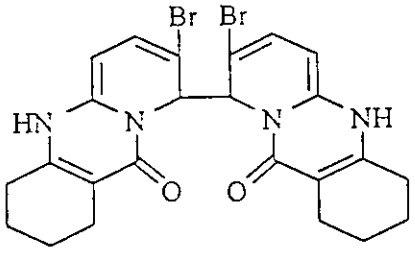
Scheme 1

2 (III) ⟶



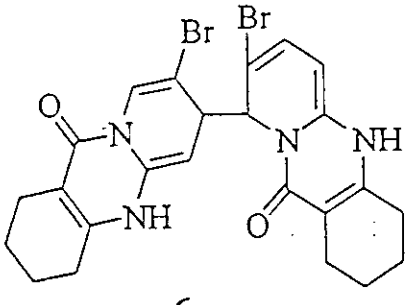
4

2 (IV) ⟶



5

(III) + (IV) ⟶



6

Scheme 2

From the above data, it was shown that compound **BTP** is reduced by one electron to give intermediate I, which then abstracts one proton to give II. Intermediate II exists in three resonance structures II, III and IV, as in scheme 1.

The resonance structures may dimerize as follows: two molecules of III dimerize to give compound **4** or two molecules of IV dimerize to dilver compound **5**, or intermediate III and IV terminates to compound **6**, as in scheme. 2.

Conclusion

The adsorptive cathodic stripping voltammetric method (AdCSV) is useful to determine this new pyrimidine derivative at low concentration in aqueous solutions. The interference is limited, and metal cations probably found in water doesn't alter the peak current. This method is suggested as a cheap instrumentation method, in addition to saving organic reagents usually used in usual extraction procedures. High sensitivity is a great advantage of this method.

The addition of Cu^{2+} did not improve peak height of **BTP** and no complexation of it with Cu^{2+} is suggested. The same was true with Ni^{2+}, Cd^{2+}, Hg^{2+} and pb^{2+}. DPP is better to depend on, as less dilution is required (minimized errors) and actual concentrations used.

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بسم الله الرحمن الرحيم

الملخص

تم استخدام طريقة الانتزاع المهبطي الفولتمتري التجميعي لتعيين مركب حديث التحضير من مركبات البيرميدين Pyrimidines بتراكيز منخفضة. وهذا المركب المحضر يحمل خصائص يحتمل ان تكون مفيدة في استخدامه كعلاج لبعض انواع السرطان كما هو الحال مع مركبات مشابهة له في التركيب.

ان هذه الطريقة حساسة جدا وتعطي نتائج خطية جيدة محصورة بين 5×10^{-8} حتى 2×10^{-6} مول/لتر عند جهد مقداره -0.8 فولت. ان الحد الادنى للتركيز الذي يمكن تقديره من هذا المركب يقل عن 5×10^{-8} مول/لتر بعد تجميع لمدة 30 ثانية على جهد قدره -0.4 فولت مقابل قطب الفضة القياسي Ag/AgCl، في محلول منظم من الخلات على درجة حموضة (pH) 4.5 . ان الانحراف المعياري النسبي RSD% بلغ 3% تقريبا عند مستوى 2×10^{-7} مول/لتر من المركب بعد ست قراءات متجددة.

لقد تم اختيار الظروف المثلى لدراسة هذا المركب، كما تم التأكد ان اضافة ايونات معدنية كأيون النحاس Cu^{2+} والنيكل Ni^{2+} وغيرهما لا تزيد من قيمة التيار المقروء.

لقد تم رسم منحنى قياسي لتعين هذا المركب من ناحية كمية دقيقة عند الظروف المختارة، وهذا المنحنى القياسي يشكل اساسا يعتمد عليه في تعيين هذا المركب عند تراكيز منخفضة (في المدى المحصور اعلاه).