

SYNTHESIS OF ASYMMETRICAL 2(3)-OXASOLINO- (PYRAZOLINO)- 2(4)-METHINE CYANINE DYES

Ragab Abu el-Hamd, Ahmed Koraiem, Reda Abdel-All
and Adel A. El-Bahnasawy*

Chemistry Department, Aswan-Faculty of Science, Aswan;

** Chemistry Department, Faculty of Science, Zagazig University, Egypt.*

ABSTRACT

Synthesis of new types of asymmetrical-2(3)-oxazolino - (pyrazolino)-[4,3-b]-quinoline-2(4)-methine cyanine dyes including mono-, di-, trimethine cyanines (IVa-d, V, VII a,b and IXa-d) was achieved by interaction of 4-hydroxy-2(3)-methyl oxazololino (pyrazolino)-[4,3-b]-quinoline (Ia,b) with active components. The new cyanines were identified through IR and ¹H NMR spectra. The electronic absorption spectra of the dyes in the visible region is reported. Bacteriocidal activity of selected cyanine dyes (IVa, IVd, V, VIIb, IXc) were tested against some bacterial strains.

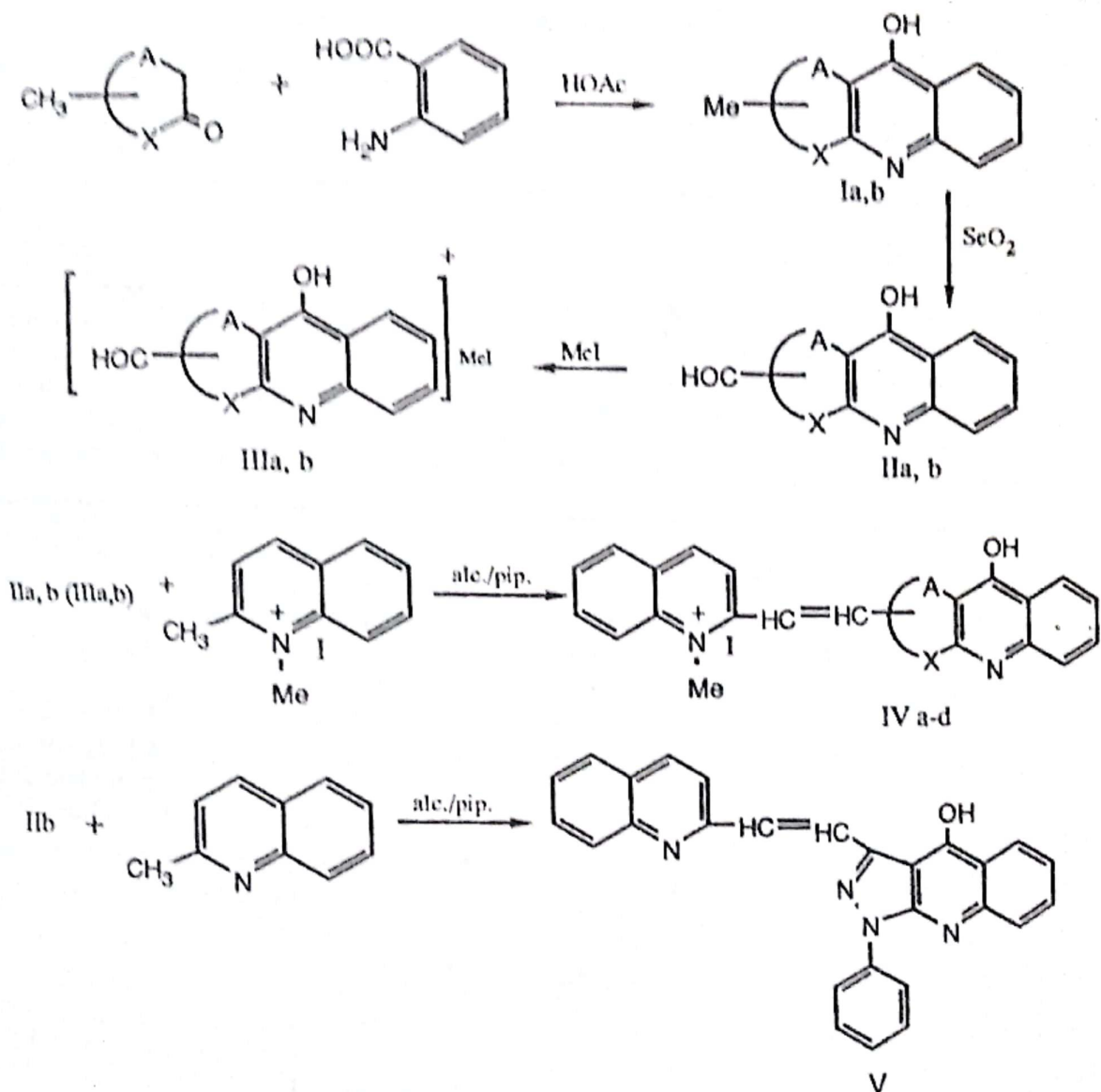
INTRODUCTION

In continuation of our earlier work on the synthesis of five-membered heterocyclic rings in conjunction with other six-membered rings involving cyanine dye molecules⁽¹⁻⁵⁾. These dyes are useful as photosensitizers⁽⁶⁾, textile dyes⁽⁷⁾ and bactericidal agents^(8,9). Some new oxazolino/pyrazolino-[4,3-b]-quinoline cyanine dyes were prepared. The spectral data of the prepared cyanines (Table 1) is given in order to ensure the optimal photosensitizing effect and to study the effect of the oxazolino/pyrazolino-[4,3-b]-quinoline moieties on the type of cyanine molecules.

It was reported that some heterocyclic compounds react with anthranilic acid to give the corresponding hydroxyquinoline derivative⁽¹⁰⁾. The main goal of the present work is to synthesize some 4-hydroxyquinolines in conjunction with oxazolino/pyrazolino derivatives be used for the synthesis of some cyanine dyes. The interaction of 2(3)-methyloxazole/pyrazol-5-one with anthranilic acid in the

presence of acetic acid afforded the corresponding 2(3)-methyloxazolino/pyrazolino-[4,3-b]-quinoline (Ia,b), scheme (1).

Oxidation⁽¹²⁾ of (Ia,b) using SeO₂ gave the corresponding 4-hydroxy oxazolino/pyrazolino-[4,3-b]-quinoline-2(3)-carboxaldehyde (IIa,b). Quaternization⁽¹³⁾ of IIa,b afforded the corresponding 4-hydroxy oxazolino/pyrazolino-[4,3-b]-quinoline-3(2)-2(3)-carboxaldehyde methiodide (IIIa,b) which were used for the synthesis of the desired asymmetrical monocationic dimethine cyanines and their styryl bases. The reaction of (IIa,b) and/or their 3(2)-methiodide (IIIa,b) with methyl quinolinium salt in the presence of piperidine gave the corresponding asymmetrical 4-hydroxy oxazolino/pyrazolino-[4,3-b]-quinoline 2(3) [2(4)]-mono-, dicationic dimethine cyanines (IVa-d). On the other hand, interaction of IIb with quinaldine in the presence of NaOH gave the asymmetrical 4-hydroxy oxazolino/pyrazolino-[4,3-b]-quinoline 2(3)-styryl base (v), scheme (1).

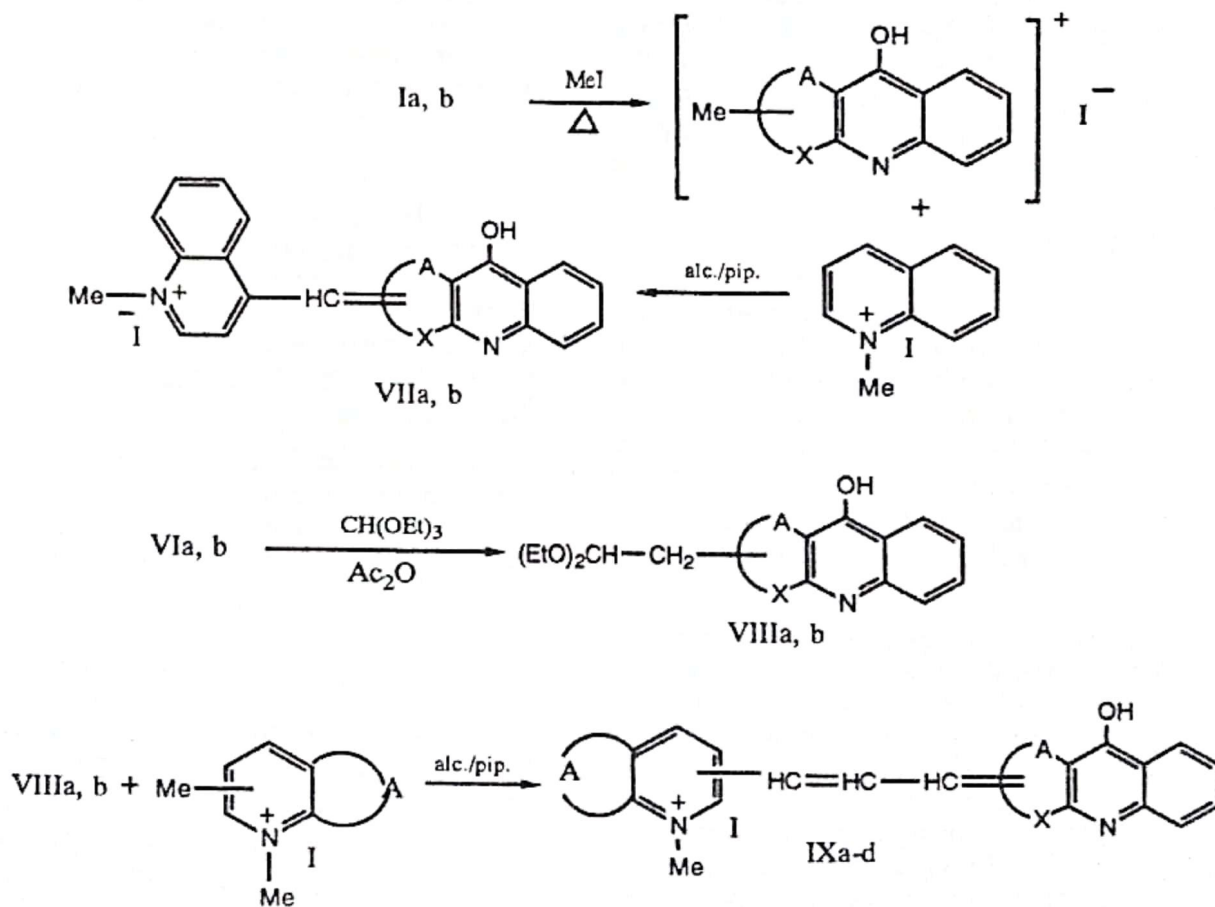


Scheme (1)

The dimethine cyanines (IVa,d) are distinctively coloured compounds (reddish-brown to violet), fairly soluble in polar organic solvents and in conc. H_2SO_4 liberating iodine vapour on heating. They possess colours in alkaline medium, and disappears upon acidification.

The visible spectra of asymmetrical mono-(di)-cationic dimethine cyanines (IV a-d) in 95% ethanol exhibited absorption bands which became bathochromically or hypsochromically shifted

according to the nature of oxazolino/pyrazolino-[4,3-b]-quinoline moieties or the mono- and di-cationic types. Thus, the absorption spectra of (IVa, X (A) = oxazole) are more red shifted than the analogous pyrazolino cyanine (IVb, X (A) = pyrazole) by 60 nm (Table 2). On the other hand, the dicationic dimethine cyanine (IVc) is more blue shifted than those analogous monocationic cyanine (IVa) by 25-90 nm (Table 2). Quaternization at the quinoline residue (as in IVb) causes



Scheme (2)

a strong red shift with intensification of the absorption bands (Table 2).

Quaternization of (Ia,b) using methyl iodide gave the corresponding oxazolinium/pyrazolinium-3(2)-methiodide salts (VIa,b). This compound (VIa,b) could be converted to VIIa,b and VIIIa,b. The latter could provide IXa-d. Quaternization is oriented on a five membered ring due to the presence of two asymmetrical arsymmetrical hetero atoms. Thus, the reaction of (VIa,b) with quinolinium methiodide salt in the presence of piperidine catalyst affords the corresponding asymmetrical 4-hydroxy oxazolino/pyrazolino-[4,3-b]-quinoline 2(3) [4(1)]-monomethine cyanines (VII a,b). Interaction of (VIa,b) with an equimolar amount of ethyl orthoformate in the presence of Ac_2O gave intermediates (VIIIa,b). Further reaction of (VIIIa,b) with 1-methyl-2(4)-methyl quaternary salts in the presence of piperidine gave the asymmetrical oxazolino (pyrazolino)-[4,3-b]-2(3) [2 (4)]-trimethine cyanine dyes (IX a-d), scheme (2).

The asymmetrical monomethine cyanines (VIIa,b) possess red colour while trimethine cyanines (IXa-d) possess violet colour in solutions. They are fairly soluble in polar organic solvents and in conc. H_2SO_4 liberating iodine vapour on heating. Their colours are unaffected in alkaline medium but disappear on acidification.

The visible absorption spectra of asymmetrical mono and trimethine cyanines (VIIa,b, IXa-d) in 95% ethanol exhibit absorption bands which become bathochromically or hypsochromically shifted according to the nature of oxazolino/pyrazolino moieties or the type of quaternary heterocyclic residue (A). Thus, the absorption spectra of monomethine cyanine incorporating oxazolino nucleus (VIIa) is more red shifted by 10 nm than the analogous pyrazolino nucleus (VIIb) (Table 2). The same behaviour is observed in trimethine cyanines. Thus, trimethine cyanine which contains

oxazolino nucleus (IXa) is more red shifted by 15-20 nm than the pyrazolino-trimethine cyanine analogous (IXc). On the other hand, (IXb, A = pyridinium-2yl-salt) is more blue shifted than the trimethine analogous (IXd; A = pyridinium-4yl-salt) and (IXc; A = quinolinium-2yl-salt). It is quite obvious that increasing the number of methine groups in trimethine cyanine causes a strong bathochromic shift in the absorption bands (Table 2).

The antibacterial activity of some synthesised cyanine dyes (IVb, IVd, V, VIIb, IXc) was tested against Bacillus stearothermophilus, Bacillus cereus, Bacillus subtilis, Nitrobacter sp., Hytrosomollas s.p. and Micrococcus s.p. The cyanine base (V) possesses antibacterial activity. Inserting a quaternary salt in the quinoline nucleus (IVb) is active against some bacterial species e.g., Bacillus stearothermophilus, Bacillus cereus and Micrococcus sp. while inactive against Bacillus subtilis, Nitrobacter sp., and Nitrosomollas sp. On the other hand, inserting an extra quaternary group in the pyrazoloquinoline nucleus (IVd) showed only antibacterial activity against Bacillus stearothermophilus and Nitrobacter sp.

It seems that the antibacterial activity depends upon the nature of the cyanine dye molecules. Thus, mono- and trimethine cyanines (VIIb, IXc) are inactive against the bacterial species under investigation (Table 4).

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded in KBr on a PYE-Unicam SP 1100 Infrared spectrophotometer. 1H NMR spectra were determined on JEOL 60 MH_2 NMR spectrometer. Elemental analysis were carried out at the Microanalytical Center Cairo-University. Absorption spectra in the visible region (300-800) were recorded on a SHIMADZU UV-Vis 240 recording spectrophotometer.

4-Hydroxy-2(3)-methyl-oxazolino pyrazolino-[4,3-b]-quinoline (Ia,b):

These compounds were synthesised in accordance to a previously described method⁽¹⁰⁾, using equimolar amounts of 2 (3)-methyl oxazol/pyrazol-5-one and anthranilic acid in the presence of acetic acid, the results are summarized in (Table 1).

4-Hydroxy oxazolino/pyrazolino-[4,3-b]-quinoline 2(3) carboxaldehyde (IIa,b):

A mixture of Ia,b and selenium dioxide (0.01 mol) was dissolved in dioxane (20 ml) and heated at reflux for 6-8 hr. The deposited selenium metal was filtered and the filtrate was concentrated. On adding cooled water, the precipitated product was filtered and crystallized from ethanol to give IIa,b (Table 1).

4-hydroxyl oxazolino/pyrazolino-[4,3-b]-quinoline 3(2)-2(3)-carbox-aldehyde methiodide (IIIa,b):

A pure sample of IIa,b (0.5 g) was suspended in excess of methyl iodide (5 ml) and heated at 120°C for 4-5 hr, in a sealed tube. The tube was cooled, opened and the products (IIIa,b) were collected, washed with ether and recrystallized from ethanol. The results are listed in (Table 1).

Asymmetrical 4-hydroxy oxazolino/pyrazoline-[4,3-b]-quinoline 2(3) [2(4)]-dimethine cyanines (IVa-d):

Equimolar amounts of IIa,b or (IIIa,b) and the appropriate N-methylquinolinium iodide (0.01 mol) were dissolved in ethanol (30 ml) containing 2 ml piperidine (2 ml). The reaction mixture was refluxed for 5-7 hr, filtered while hot, concentrated, cooled and acidified with acetic acid. The precipitated product after dilution with water were filtered and recrystallized from aqueous ethanol to give (IVa-d) (Table 2).

4-hydroxy oxazolino/pyrazolino-[4,3-b]-2 (3) [2(4)]-dimethine base (V):

An ethanolic solution (30 ml) containing IIa, quinaldine (0.01 mol) and

2% NaOH solution (10 ml) was refluxed for 5-7 hr. The reaction mixture was filtered while hot, the filtrate was concentrated, diluted with water and the precipitated product was filtered and recrystallized from aqueous ethanol to give (V) (Table 2).

4-Hydroxy 2(3) methyl oxazolino/pyrazolino-[4,3-b]-quinoline 3(2)-yl salt (VIa,b):

A pure sample of Ia,b (0.5 g) reacted with methyl iodide (5 ml) and heated at 170° for 4.5 hr, in a sealed tube. The tube was cooled, opened and the products (VIa,b) were collected, washed with ether and recrystallized from ethanol (Table 1).

Asymmetrical 4-hydroxy oxazolino/pyrazoline-[4,3-c]-quinoline 2(3) [4(1)]-monomethine cyanines (VIIa,b):

These were prepared by the reaction of VIa,b (0.01 mole) with N-methylquinolinium iodide (0.01 mole) in the presence of ethanol (20 ml) containing few drops of piperidine. The reaction mixture was refluxed for 5-8 hr. The products (VIIa,b) were collected, washed with ethanol and then recrystallized from aq. ethanol to give crystalline products (VIIa,b). The results are summarized in (Table 2).

Asymmetrical 4-hydroxy oxazolino/pyrazolino-[4,3-b]-quinoline 2 (3)-[2(4)]-trimethine cyanines (IXa-d):

These were synthesised through the preparation of compounds VIIIa,b as intermediate for the synthesis of the trimethine cyanines (IXa-d) by refluxing VIa,b (0.05 mole) with ethyl orthoformate (0.05 mole) in the presence of acetic anhydride for 5-10 hr. The products (VIIIa,b) were washed with ethanol and recrystallized from acetic acid to give brown crystals (Table 1).

The intermediates VIIIa,b (0.01 mol) and 2(4)-methylquaternary salts (0.01 mole) were dissolved in ethanol (30 ml) and a few drops (2 ml) of piperidine was added. The reaction mixture was

Table (1): Characterization of starting materials for oxazolino/pyrazolone [4,3b] quinoline cyanine dyes (Ia,b: IIa,b: III a,b: VIa,b & VIIa,b).

Comp. No	m.p. °C	Yield (%)	Mol. formula	Colour of products	(Found) (%) Calcd.		
					C	H	N
Ia	170-2	65	C ₁₁ H ₃ N ₂ O ₂ (200)	Brown	66.00 (65.83)	4.00 (4.21)	14.00 (13.75)
Ib	119-21	32	C ₁₇ H ₁₃ N ₃ O (275)	Reddish-brown	74.18 (74.51)	4.73 (4.18)	15.27 (15.43)
IIa	125-7	74	C ₁₁ H ₆ N ₂ O ₃ (214)	Red	61.68 (62.01)	2.80 (2.44)	13.08 (12.94)
IIb	132-5	39	C ₁₇ H ₁₁ N ₃ O ₂ (289)	Brown	70.59 (70.32)	3.81 (3.99)	14.53 (14.14)
IIIa	110-2	66	C ₁₂ H ₉ N ₂ O ₃ I (456)	Brown	40.45 (39.92)	2.53 (2.23)	7.87 (8.10)
IIIb	144-6	49	C ₁₃ H ₁₄ N ₃ O ₂ I (431)	Brown	50.12 (49.73)	3.25 (3.81)	9.74 (9.70)
VIa	220-3	67	C ₁₂ H ₁₁ N ₂ O ₂ I (342)	Brown	42.11 (41.88)	3.22 (2.81)	8.19 (8.33)
VIb	128-31	44	C ₁₃ H ₁₆ N ₃ O I (417)	Deep brown	51.80 (51.52)	3.84 (3.13)	10.07 (9.91)
VIIa	106-9	45	C ₁₇ H ₂₁ N ₂ O ₃ I (428)	Brown	47.66 (47.46)	4.91 (5.15)	6.53 (6.63)
VIIb	111-13	38	C ₂₃ H ₂₆ N ₃ O ₂ I (503)	Brown	54.87 (54.50)	5.17 (4.92)	8.35 (8.53)

refluxed for 5-8 hr. The products (IXa-d) were collected, washed with ethanol to give crystalline product (IXa-d) as coloured needles. The results listed in Table 2.

Tests for biological activity using the filter paper disc method⁽¹⁴⁾ :

The cyanine dyes (IVb, IVd, V, VIIb, IXc) were dissolved in ethylene glycol (2

ml 10 cm⁻³). The bacteria used in these experiments were among several soil micro-organisms previously found to be susceptible in such tests.

Bacterial suspension:

This was prepared by adding 10 cm⁻³ of sterile distilled water to a 10-day-old culture of the test bacteria grown on Nutrient Agar (NA)⁽¹⁵⁾ (beef extract 10 g

Table (2): Characterization of cyanine dyes incorporating mono-, di- and trimethine cyanines dyes (IVa,-d; V, VIIa, b; IXa-d).

Comp. No	m.p. °C	Yield (%)	Molecular formula (M.Wt.)	Nature of prod.	Elemental analysis %			Absorption spectra	
					Calcd. (Found)			λ_{\max}	ϵ_{\max} m ⁻¹ cm ²
					C	H	N		
IVa	220	41	C ₂₂ H ₁₆ N ₃ O ₂ I (481)	Violet crystal	54.89 (55.10)	3.33 (3.45)	8.73 (9.02)	560,585, 690 sh.	1000,11800, 6400
IVb	155	66	C ₂₈ H ₂₁ N ₄ OI (556)	Violet crystal	60.43 (60.39)	3.78 (3.55)	10.07 (9.75)	500,540, 582,690 sh.	11400,4600, 11200,7100
IVc	115	34	C ₂₃ H ₁₉ N ₃ O ₂ I ₂ (623)	Violet crystal	44.30 (44.62)	3.05 (3.22)	6.74 (6.65)	518,557, 605 sh.	8400,12400 8700
IVd	137	79	C ₂₉ H ₂₄ N ₄ OI ₂ (698)	Violet crystal	49.86 (49.35)	3.44 (3.34)	8.02 (7.89)	520,560, 600 sh.	2800,12500 8400
V	118	28	C ₂₇ H ₁₈ N ₄ O (414)	Red-br.* crystal	78.26 (78.52)	4.35 (4.14)	13.53 (13.85)	490	5800
VIIa	181	39	C ₂₂ H ₁₈ N ₃ O ₂ I (483)	Red crystal	54.66 (54.43)	3.73 (3.67)	8.70 (8.92)	460	9200
VIIb	97	51	C ₂₈ H ₂₃ N ₃ O ₂ I (558)	Red crystal	60.22 (60.53)	4.12 (3.59)	10.04 (10.21)	450	5800
IXa	235	55	C ₂₄ H ₂₀ N ₃ O ₂ I (509)	Violet crystal	56.58 (56.84)	3.93 (4.14)	8.25 (8.11)	515,555, 600	12400,13400, 5800
IXb	137	58	C ₂₆ H ₂₃ N ₄ OI (534)	Blue crystal	58.43 (58.58)	4.31 (4.06)	10.49 (10.22)	370	11200
IXc	197	75	C ₃₀ H ₂₅ N ₄ OI (584)	Violet crystal	61.64 (61.52)	4.28 (4.01)	9.59 (9.39)	500,532, 580	10600,13200, 8700
IXd	165	71	C ₂₆ H ₂₃ N ₄ OI (534)	Red-br.* crystal	58.43 (58.82)	4.31 (4.14)	10.49 (9.99)	490	4200

* Red. br. = Reddish brown

Table (3): IR and H^1 n.m.r spectral data of started materials and asymmetrical 2(3)-oxazolino/pyrazoline methine cyanine dyes.

Comp. No	IR	(KBr max. cm^{-1})	H^1 nmr ($CDCl_3$) ppm
Ia	760-738 1250 1665 3400	(disub. benz.) (COC cyclic) (C=N) (OH)	8.9 (s, 1H, OH) 7.5-7 (m, 4H, arom -H) 2.2 (s, 3H, CH_3 -)
IIa	760-735 1240 1660 1700 3440	(disub. benz.) (COC cyclic) (C=N) (CHO) (OH)	9.7 (s, 1H, CHO) 8.8 (s, 1H, OH) 7.6-7 (m, 4H, arom-H)
IVa	760-735 1600 1240 2980 3440	(disub. benz.) (C=C) (COC cyclic) (methiodide) (OH)	7.5-6 (m, 12H, arom + hetero+ CH= CH system) 8.8 (s, 1H, OH) 3.8 (s, 3H, CH_3 I)
V	770-710 1600 1660 3400	(mono.& di-sub.benz.) (C=C) (C=N) (OH)	7.5-6.1 (m, 17H, arom + hetero+ CH= CH system) 8.4 (1H, OH)
VIb	770-710 1660 2980 3445	(mono.& di-sub.benz.) (C=N) (methiodide) (OH)	8.7 (s, 1H, OH) 7.5-7 (m, 9H, arom -H) 3.7 (s, 3H, CH_3 I) 2.1 (s, 3H, CH_3 -)
VIIb	760-700 1380 2980 3400	(mono.& di-sub. benz.) (=CH -) (methiodide) (OH)	8.8 (s, 1H, OH) 7.5-6 (m, 16H, arom + hetero+ CH= CH system) 3.8 (s, 3H, CH_3 I) 2.7 (s, 3H, CH_3 - N)
IXb	765-710 1380 1600 3050 2980 3400	(mono.& di-sub. benz.) (=CH) (C=C) (-CH=CH-) (methiodide) (OH)	8.8 (s, 1H, OH) 7.5-5.9 (m, 16H, arom+hetero+=CH-CH=CH system) 3.9 (s, 3H, CH_3 I) 2.6 (s, 3H, CH_3 -N)

dm⁻³, peptone 5 g dm⁻³, sodium chloride 5 g cm⁻³, agar 17 g dm⁻³, pH 7.4). Samples (1 cm⁻³) of the bacterial suspensions were added to NA Petri dishes (two plates for each test compound). The excess liquid was removed and two filter paper discs (15 mm) containing the test compounds were placed on each plate. Plates were then incubated at 37° and the diameters of the inhibition zones were measured after 24 hr. The experiments were repeated three times and the results are listed in Table (4).

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Table (4): Antibacterial screening of selected cyanine dyes.

Organism used	Compound tested (mg)				
	IVb	IVd	V	VIIb	IXc
<i>Bacillus stearothermophilus</i>	+	+	+	-	-
<i>Bacillus cereus</i>	+	-	+	-	-
<i>Bacillus subtilis</i>	-	-	+	-	-
<i>Nitrobactes</i> sp.	-	+	+	-	-
<i>Nitrosomollas</i> sp.	-	-	+	-	-
<i>Micrococcus</i> sp.	+	-	+	-	-

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تخليق ٢(٣)-أوكسازولو(بيرازولينو)-٢(٤)- ميثين أصباغ السيانين الغير متماثلة

رجب أبو الحمد - أحمد كريم - رضا عبدالعال وعادل البهنساوي*

قسم الكيمياء - بكلية العلوم بأسوان

* قسم الكيمياء بكلية العلوم جامعة الزقازيق - مصر

يشتمل البحث على تحضير أنواع جديدة من أصباغ السيانين وتسمى ٢(٣)-أوكسازولينو (بيرازولينو)-٢(٤)-ميثين أصباغ السيانين الغير متماثلة.

وقد تم تحضير أنواع جديدة من ٢(٣)-أوكسازولينو (بيرازولينو)-٣(٤)-ب-٤-٣-كينولين-٢(٤)-أصباغ الميثين السيانين الغير متجانسة شاملة جميع الأنواع واحادي وثنائي وثلاثي ميثين السيانين والتي يمكن الحصول عليها عن طريق تفاعل ٤-هيدروكسي-٢(٣)-ميثيل أوكسازولينو (بيرازولينو)-٣(٤)-ب-٤-٣-كينولين مع مكونات نشطة أخرى.

أثبتت نتائج التحليل ومنها طيف الأشعة تحت الحمراء، كذلك الرنين النووي المغناطيسي وطيف الامتصاص في المنطقة المرئية صحة التركيب الكيميائي لهذه الأنواع الجديدة من أصباغ السيانين.

تم فحص بعض هذه الأنواع الجديدة من أصباغ السيانين المحضرة للنشاط البيولوجي فأثبتت نشاطاً مهبطاً ملحوظاً على بعض أنواع البكتريا.