A Thesis entitled

SOME NOVEL CYANINE DYES

submitted by

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ABSTRACT

The reactions of 1,3-di-iminoisoindoline with various active-methyl-substituted-quaternary-ammonium-salts in boiling butanol, pyridine, and nitroethane have been studied extensively. The products comprise a wide range of new cyanine dyes with absorption maxima from 405 to 735 mμ which have an isoindolenine ring as part of the chromophoric path. These compounds are mostly obtained in high yields. Among pyridine, benzothiazole, quinoline and pyrimidine derivatives, the quinoline compounds gave the longest wave-length absorption maxima and best tinctorial values.

The reaction of 3-imino-1-oxoisoindoline with 2,6-lutidine ethiodide gave a dinuclear cyanine with a terminal amide group. When this product was treated with potassium hydroxide, a merocyanine was obtained.

2-Aminopyridine ethiodide did not react with 1,3-di-iminoisoindoline or with 3-imino-1-oxoisoindoline in either boiling butanol or pyridine, but 2-amino-6-methylbenzothiazole ethiodide and 2,6-diaminopyridine ethiodide reacted readily with these heterocyclic imines. A possible explanation of this phenomenon is discussed.

The light absorptions of compounds resulting by formal substitution of one, two, and three methin groups with one, two, and three aza groups have been assessed for the pentamethincyanines with terminal benzothiazole nuclei. Asymmetrical pentamethindiazacyanines have also been made.

The effect of a polar solvent has been studied on the ease of quaternization of a three-unit condensation product prepared from one mol. of imidine and 2 mols. of aminopyridine. Bisquaternary salts were successfully prepared in nitroethane with an excess of ethyl iodide. A penta-ethiodide has been prepared for one of the three-unit condensation products.

Some evidence for the existence of macrocyclic cyanines has been collected and finally the light absorption data of the pentamethincyanines having an isoindolenine ring has been discussed in the light of the current theory of colour.

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The cyanines, which belong to a class of the polymethine dyes, have been actively studied for the past forty years because of their usefulness in sensitizing photographic plates and because they have bacteriostatic and chemotherapeutic activities. (1)(2)(3). Recently cyanine dyes with indolenine nuclei, the Astraphloxines and Astrazones have been successfully used as colouring matters for textiles particularly for printing on acetate rayon.(4)

A cyanine is a mesomeric monoacid salt, the essential structural features being two basic groups (frequently the nitrogens in heterocyclic nuclei) linked by an odd-numbered methine chain as shown below:

$$\overbrace{NR(-(CH=CH)_n}C=CH(CH=CH)_m\overbrace{C(=CH-CH)_n=NR'}^{+}\ X^-$$

$$X^- \quad \overbrace{NR(=CH-CH)_n}=C-CH(=CH-CH)_m=\overbrace{C(CH=CH)_nNR'}^{+}$$

General Preparative methods for cyanines

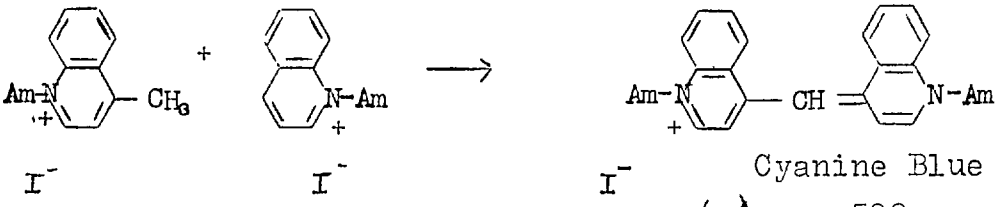
The dinuclear cyanines have been the most widely studied. Up to the first world war, the production of cyanines was a German monopoly but from that time work was begun elsewhere. Pioneers in this country were William Pope of Cambridge and W. H. Mills. Later, Hamer, and particularly Brooker in the United States, and many others have contributed tremendously to cyanine chemistry.

Though the discovery of the first cyanine by C. G. William was made as early as 1856, by heating a quaternary quinolium salt with caustic alkali, the correct structure was not ascertained until 1920 by Mills and Wishart [5] who used the oxidative degradation method and later [6] disproved the earlier suggested open chain structure.

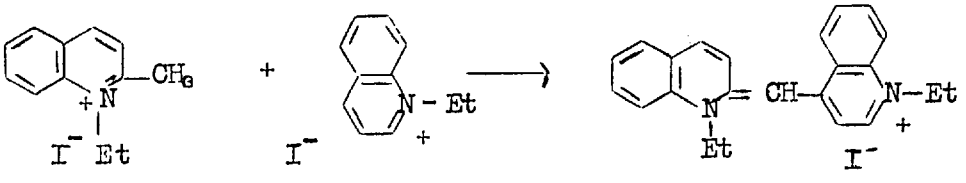
It appears that there are six available methods for the preparation of cyanines; these methods consist in treating a heterocyclic quaternary ammonium salt bearing an active methyl substituent with one of the following six types of reagents: (1) another heterocyclic quaternary salt, (2) an iodo-substituted quaternary salt, (3) an alkythio quaternary salt, (4) ethyl orthoformate or other poly-functional compounds, (5) a quaternary heterocyclic aldehyde, and (6) an o-formylaminoaryl disulphide. One or more examples of each method is given below:

(1) Condensation of an active methyl substituted heterocyclic quaternary salt with another quaternary salt.

This a historic method. A quaternary salt of lepidine or quinaldine was condensed with one of quinoline, in alcoholic solution, to give Cyanine Blue and Ethyl Red respectively.

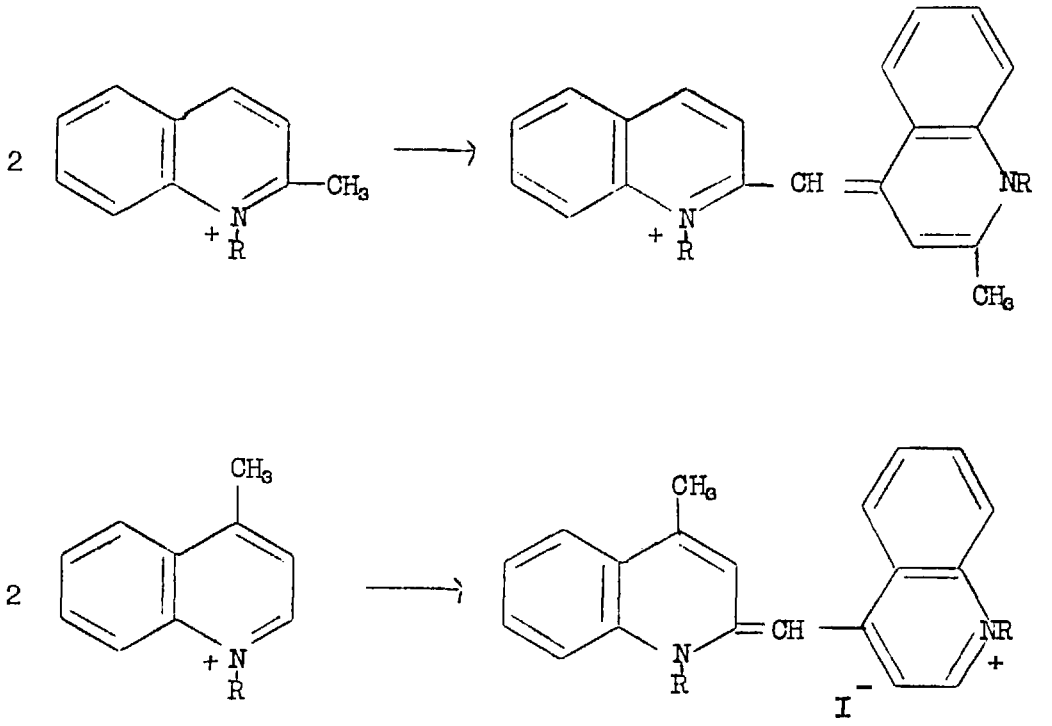


Cyanine Blue
(λ max 592,
554 mμ)



Ethyl Red

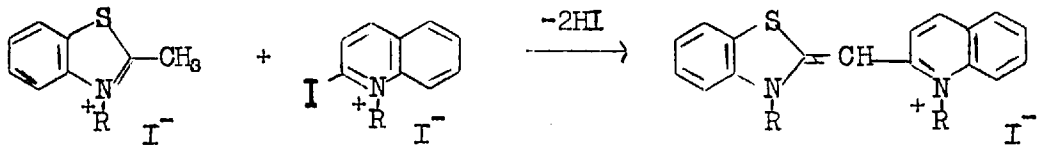
Further, a quinaldine alkiodide or a lepidine alkiodide was found to oxidize by itself under suitable conditions to yield an isocyanine dye. The essential feature of a isocyanine is the 4-2 linkage:-



The main structural variation that this route permits over the previous method is in extranuclear alkyl substitution.

(2) Condensation of an active methyl substituted heterocyclic quaternary salt with a similar reactive iodo-salt.

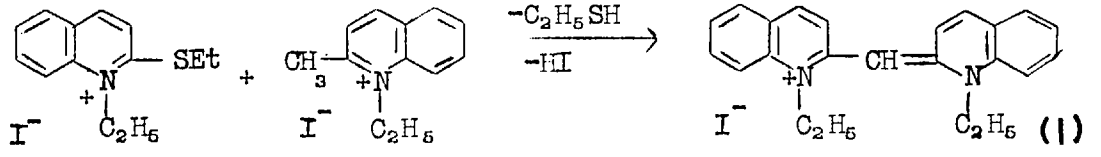
The two components interact in boiling absolute alcohol, in the presence of two equivalents of alkali.



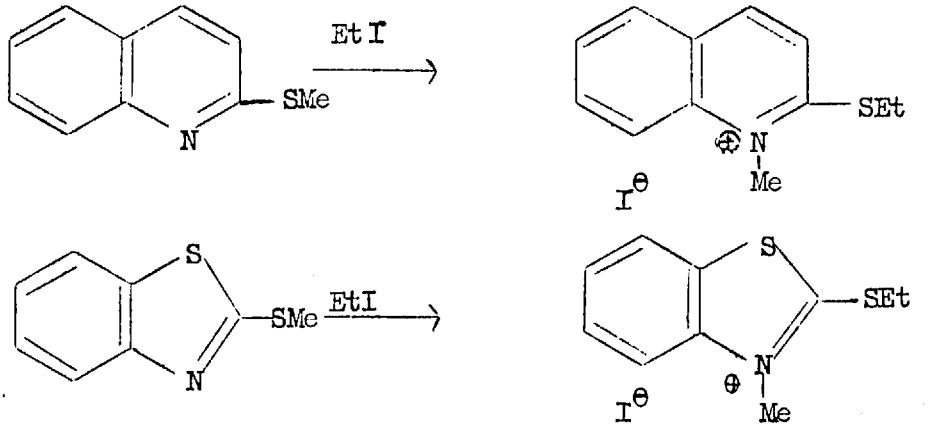
Both asymmetrical and symmetrical cyanines have been prepared this way. Unlike the 2,4'- and 4,4'- cyanines mentioned in the previous section, which had so long been known, the first 2,2'- cyanine (I) was only prepared in 1920, by condensing quinaldine methiodide with 2-iodo-quinoline methiodide.

(3) Condensation of a heterocyclic quaternary ammonium salt having an active methyl group with a similar salt having an active alkythio group.

On elimination of alkanethiol, a dinuclear methin cyanine is formed.[11]

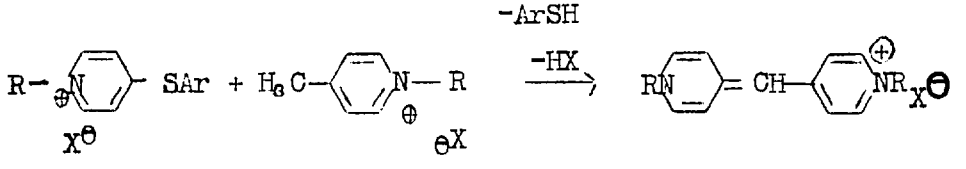


In the preparation of the necessary intermediates for this method, rearrangement of alkyl groups sometimes occurs as for example when ethyl iodide acts on 2-methylthioquinoline or on 2-methythio benzothiazole:- [12] [13]



To avoid complications, the alkyl groups in the quaternizing alkyl halide and the alkythio substituent should, therefore, be kept the same.

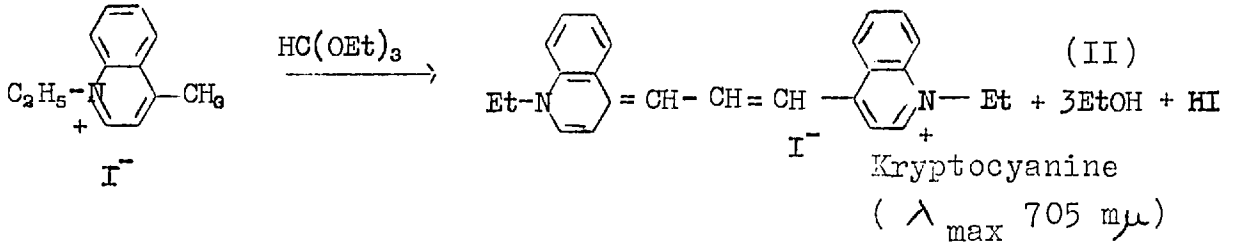
A further example of the condensation is the reaction of a 4-aryl-thiopyridinium salt with a 4-methylpyridinium salt in the presence of a strong base such as piperidine. This yields the 4,4' compound shown below:(14)



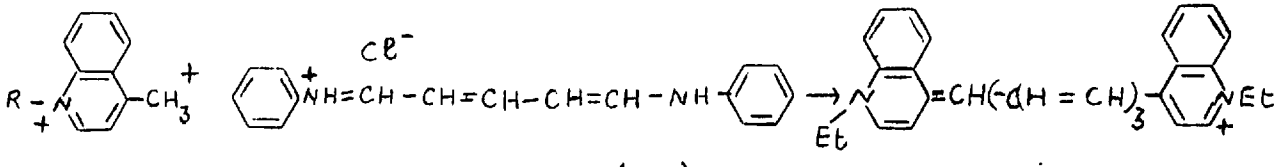
(4) <u>The reaction of ethyl orthoformate or other polyfunctional compounds with an active methyl quaternary salt.</u>

This is a good preparative method for carbo- or polycarbo-cyanines. The action of ethyl orthoformate on lepidine ethiodide in pyridine solution produces

Kryptocyanine (II) which is a historical near infrared sensitiser.



Other reactive one-carbon intermediates such as diphenyl formamidine are employed on occasion. There are also ways of introducing a longer methin chain. Thus glutaconaldehyde dianil hydrochloride reacts with two moles of lepidine ethiodide in the presence of alcoholic alkali, piperidine, or triethylamine, to give Xenocyanine. (III) (16).



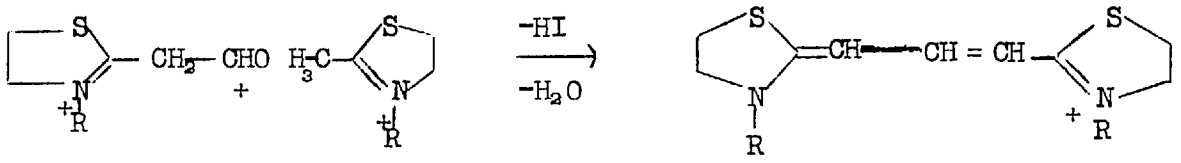
(III) Xenocyanine

The limitations to a progressive lengthening of the chain are the difficulty of preparation and the instability of the tetracarbocyanines and the still higher homologues.

(5) The reaction of a quaternary heterocyclic aldehyde with an active methyl compound.

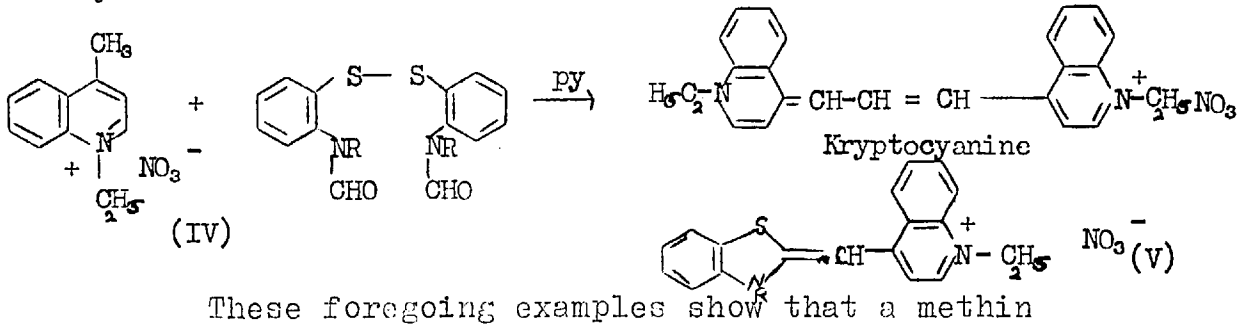
This type of reaction has also been widely studied. An example using an w-aldehyde and an active

methyl substituted heterocyclic salt in acetic anhydride or pyridine solution is:- (17) (18)



(6) <u>The reaction of an o-formylaminoaryl disulphide with an active methyl substituted quaternary salt.</u>

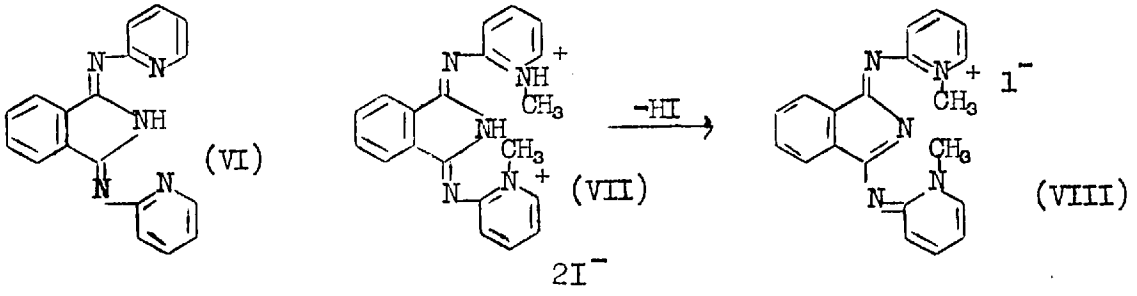
The action on lepidine ethonitrate in pyridine of the "disulphide" (IV) yields the asymmetrical cyanine (V). (19) (20) This product is accompanied by the symmetrical kryptocyanine (II) in which the central methin link is provided by the disulphide, presumably from a formyl substituent.



These foregoing examples show that a methin link in the cyanine dyes is always supplied by an active methyl substituent of a π-deficient-heteroaromatic quaternary salt.

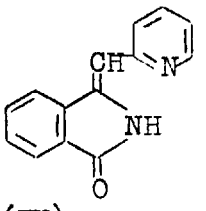
Scope of this thesis

During an investigation of the reactions of imidines [21], in particular the condensation reactions of 1,3-di-iminoisoindoline with primary amines [21a] the 3-unit product (VI) was obtained from 2-aminopyridine. Quaternisation of this with methyl iodide yielded a

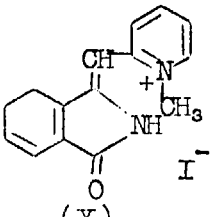


dimethiodide, the structure of which was shown as (VII) by hydrolytic degradation. It was appreciated [21b] that this salt might yield a cyanine-type dye (VIII) by loss of the elements of hydrogen iodide, although this was not demonstrated. It was merely recorded that treatment of the diquaternary salt with triethylamine produced no observable change, but that the possible conversion of this and related salts into cyanine dyes was being studied further.

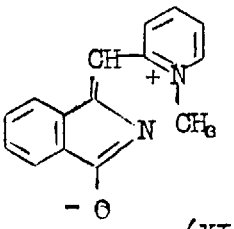
Subsequently, Barnes [22] in these laboratories found that 2-picoline could be condensed with 1-oxo-3-iminoisoindoline to give the product (IX)



(IX)



(X)



(XI)

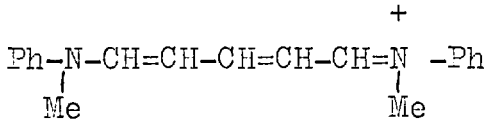
and that its methiodide could be made to lose the elements of hydroiodic acid by treatment with potassium hydroxide. The product was shown to have the zwitterionic structure (XI) which can be classed as a merocyanine. Further preparations in this direction from imidine intermediates also appeared feasible.

These several ideas have now been brought to fruition and it is an object of this thesis to describe the successful development of these cyanine syntheses, and the properties of the products, all of which possess the isoindolenine nucleus as part of the chromophoric chain.

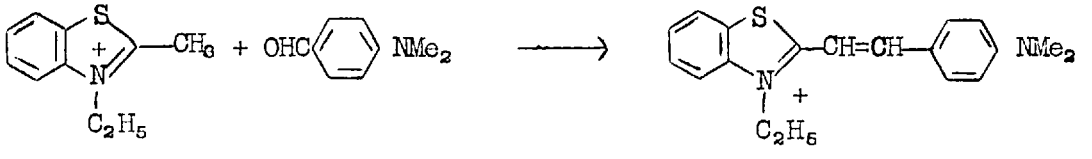
Chapter I. Hemicyanines with Terminal Unsubstituted Amino Groups

Introduction:

When one or both of the terminal nitrogen atoms of a cyanine-type dye is extranuclear, then it is called a "hemicyanine". A part of the carbon chain may be included in a ring system as part of the chromophoric chain. An example of the simplest kind of dye obtained is that by alkylation of the dianilide of glutaconic aldehyde.[23]

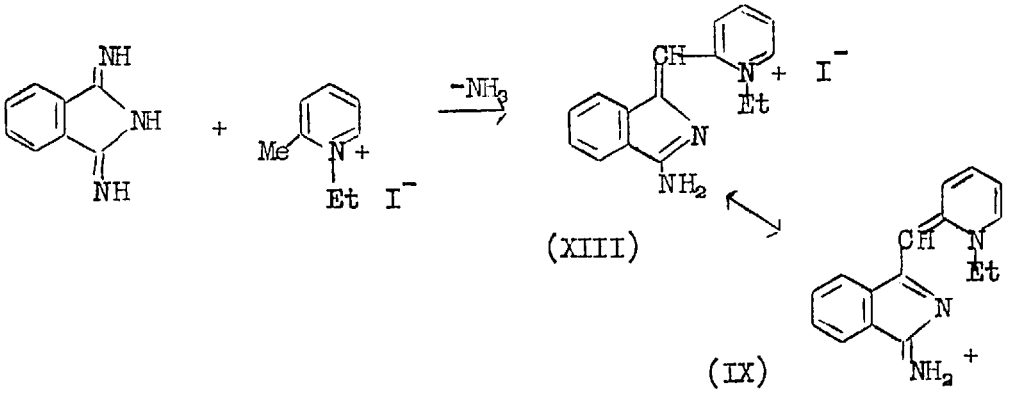


The reaction of a heterocyclic quaternary salt having a reactive methyl group with a p-dialkylaminobenzaldehyde in the presence of piperidine is a route which provides a number of hemicyanines of which (XII) is an example.[24]



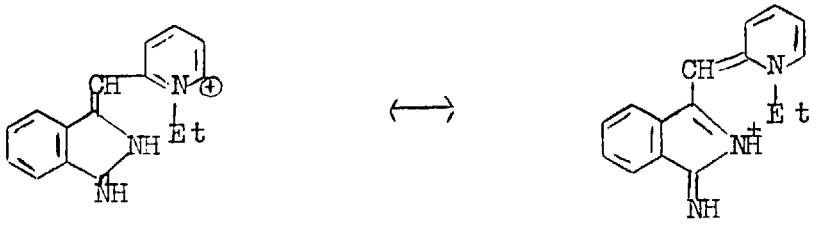
(XII)

We have used the more reactive 1,3-di-imino-isoindoline in place of an aldehyde and condensed it in boiling dry butanol with one molecular proportion of various reactive-methyl-substituted heterocyclic quaternary ammonium salts. Ammonia is evolved and coloured, sparingly-soluble products are obtained. Thus from 2-picoline ethiodide the product is (XIII).

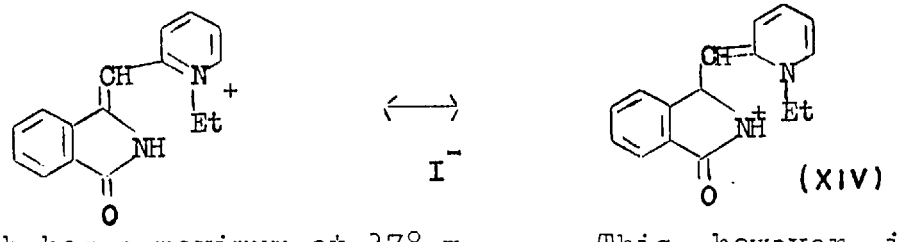


(XIII) (IX)

The evidence is briefly as follows. If the cationic resonance were just between the isoindolenine nitrogen atom and that of the linked heterocyclic base, the light absorptions would be comparable to those of the corresponding amides. For example, if the 2-picoline product had the following resonance structure,



then its light absorption characteristics would be expected to be similar to those of the amide (XIV)



(XIV)

which has a maximum at 378 mμ . This, however, is not so. The long wave-length maximum is actually 50 mμ further to the red. It seems reasonable, therefore, to account for this by means of the amino cyanine (hemicyanine) resonance structures (XIII) —— (IX).

4-Picoline ethiodide, 2,6-lutidine ethiodide, 2,4-lutidine ethiodide, quinaldine ethiodide, lepidine ethiodide, 2-methylbenzothiazole ethiodide and 2-amino-4-methyl pyrimidine ethiodide have each been successfully used in this way.

The gross structure of each product followed from the elementary analyses and method of preparation. As regards fine structure, it is considered that the products are best regarded as mesomeric salts, i.e., as hemicyanines, principally because of their long-wave-length light absorptions. Cyanines such as these, with a terminal unsubstituted amino group have not previously been reported. The compounds are soluble in water and

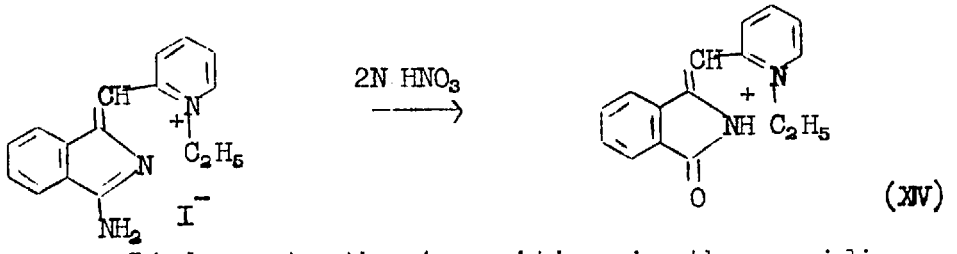
hot polar organic solvents but not in non-polar solvents in general. They crystallise with solvent of crystallisation, but can be obtained solvent-free from pyridine. Chromatography on alumina (Spence H) in isopropanol or chloroform is a good method of purification.

The best medium for their formation is butanol because in this the sparingly soluble hemicyanine salts precipitate out. Further condensation and the formation of dinuclear and other products is then prevented, which is not the case in basic solvents such as pyridine. The formation of the dinuclear cyanines will be discussed more extensively in Chapter 4. In boiling ethoxyethanol, the major condensation product is a bisquaternary salt (see Chapter 5).

A. Pyridine Series

Even though pyridine derivatives have been used only to a limited extent industrially as nuclei in cyanine preparations, their use in the first stage of this work was justified by their relative accessibility. It was soon established that 2- and 4-picoline ethiodide each readily condensed with 1 mol. of di-iminoisoindoline, with elimination of 1 mol. of ammonia to give compounds which after being recrystallized from ethanol have m.p.s about 250°. The 2-picoline derivative was resistant to

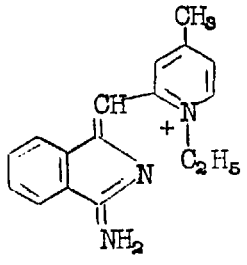
hydrolysis in boiling water as expected of an amidine-like salt. However, in warm dilute nitric acid, a product was formed which had identical light absorption with that of compound (XIV) which is the corresponding dinuclear cyanine with a terminal amide group Thus the hydrolysis involved the terminal amino grouping as shown:-

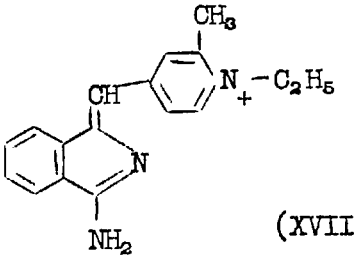


(XIV)

Linkage to the 4-position in the pyridine nucleus as in (XV) (P. 20) from 4-picoline rather than to the 2-position as in (XIII) causes a shift of the light absorption maximum of 14 mμ bathochromically.

2-6-Lutidine and 2,4-lutidine ethiodide also give similar condensation products with 1,3-di-iminoisoindoline. In the 2,6-lutidine derivative, the extranuclear methyl group in the 6- position is responsible for a 13 mμ hypsochromic shift in light absorption. The 2,4-lutidine derivative, unlike the preceding products, has two possible structures. Which of these is the more likely follows from a consideration of the light absorption in conjunction with the foregoing shifts.





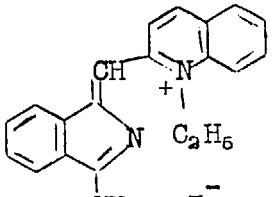
(XVII)

The absorption maximum at 432 mμ for the 2,4-lutidine condensation product falls in between the positions of the maxima for the 2- and 4-picoline condensation products at 428 mμ for the former (XIII) and 442 mμ for the latter (XV).

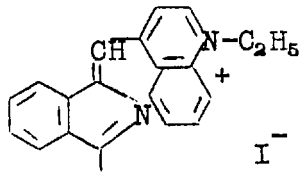
If the 2,4-lutidine product had a 2-linkage, it would absorb at about 428-13 = 415 mμ. A 4-linkage should give a maximum at about 442-13 = 429 mμ. The observed maximum at 432 mμ, therefore, strongly suggests that the 2,4-lutidine product has the structure (XVII) with a 4-linkage.

B. Quinoline Series

Quinaldine ethiodide and lepidine ethiodide have both been successfully condensed with 1,3-di-imino-isoindoline to give the corresponding hemicyanines. Like the pyridine compounds, these monoacid salts have melting points in the 250° region. The light absorptions of



(XVIII)



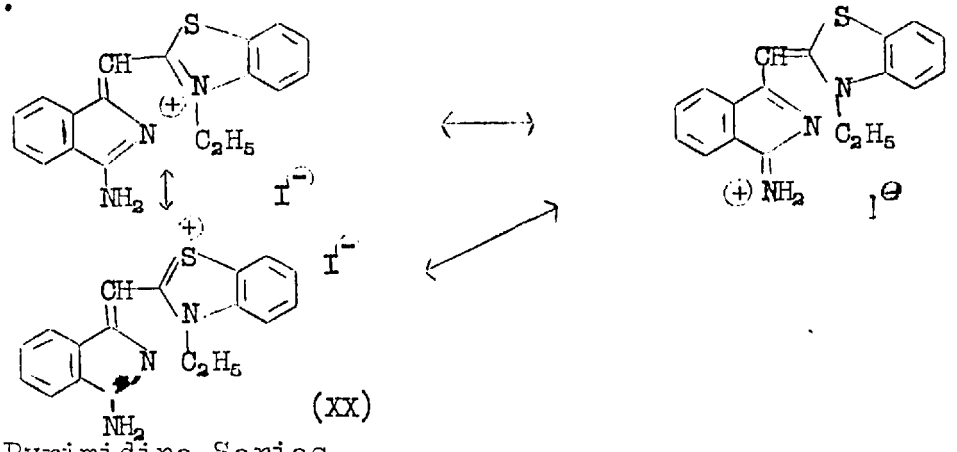
(XIX)

these compounds are interesting. When they are compared with the compounds of the pyridine series, the annelation of the benzene ring is seen to cause a bathochromic effect; in the compound with a 2-linkage there is a 27 mμ shift and in the 4-linked compound there is a 36 mμ shift. Similar to the pyridine series also, the 4-linked derivative (XIX) has a maximum absorption 13 mμ to longer wave-length than that of the 2-linked derivative (XVIII). The molecular extinction coefficients of the long wave-length absorptions of the quinoline compounds are more than double those for the corresponding pyridine derivatives. This means that the tinctorial value of the quinoline compounds is more than twice that of the pyridine derivatives.

C. Benzothiazole Series

The condensation of 2-methylbenzothiazole ethiodide with 1,3-di-iminoisoindoline in boiling butanol gave the corresponding hemicyanine. This condensation

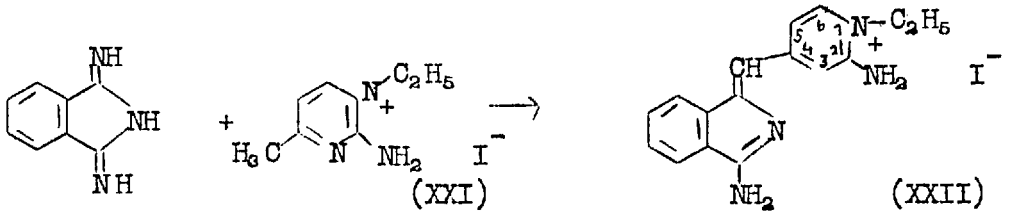
product has a long wavelength absorption maximum at 485 mμ which is the furthest position for these hemicyanines. The melting point is in the 300° region instead of the 250° region as with the pyridine and the quinoline derivatives. It appears that the benzothiazole product is more highly resonance stabilized and indeed it is possible to write an extra canonical form (XX) in this case.



(XX)

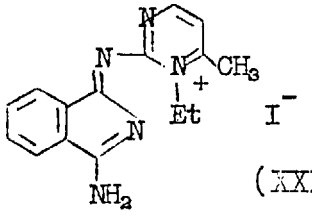
D. Pyrimidine Series

The effect of a second hetero nitrogen atom on the light absorption of the pyridine derivative (XXI) was examined by making a pyrimidine derivative (XXII). The particular pyrimidine quaternary salt employed in the preparation was chosen merely because of its accessibility.



(XXI) (XXII)

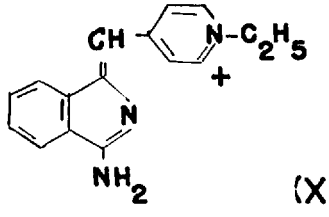
Because it contained both amino and methyl groups, there was uncertainty initially as to which group would condense with the imidine. Mild hydrolysis with boiling hydrochloric acid failed to degrade this hemicyanine; the hydrochloride was obtained. It, therefore, seemed very probable that the pyrimidine unit was joined to the isoindolenine ring through a methin link as in (XXII) rather than an aza link as in (XXIII). Subsequently, further evidence for this conclusion arose when it was found that amino substituted heterocyclic quaternary salts were unreactive towards the imidine in contrast to the methyl derivatives (see Chapter 3).



(XXIII)

The hemicyanine produced has a maximum absorption at 443 mμ which is at almost the same position as for the 4-picoline ethiodide derivative (XV). This provides some indication that the quaternary grouping in (XXII) is located on the 1-position rather than the 3-position. The latter orientation should produce an absorption maximum similar in position to that of the 2-picoline ethiodide derivative (XIII) at 428 mμ .

Protonation of the hemicyanine (XXII), as in the hydrochloride, shifts the absorption to shorter wavelength (400 mμ).



(XV)

Notes on experimental sections

(a) The experimental sections in the individual chapters of sections follow as closely as possible to the order of the discussions immediately preceding..

(b) All melting points recorded are "uncorrected".

(c) Light absorption data were measured in methanol, unless otherwise specified, on a Perkin Elmer Spectrocord Model 4000.

(d) Infrared measurements were determined on a Grubb Parson Type S 4. machine.

(e) Roman numerals are for identification of compounds.

(f) Arabic numerals written above the line of the text refer to the list of references.

Experimental Section

2-(1-Amino-3-isoindoleninylidene)methylpyridine ethiodide (XIII)

a-Picoline ethiodide (1.3 g.) and 1,3-di-iminoisoindoline (0.3 g.) were heated in n-butanol (50 ml.) under nitrogen for 17 hr. By the time ammonia gas was no longer evolved, the solution had become greenish. Evaporation of solvent to 25 ml. yielded a green powder. Recrystallization from methanol gave greenish black crystals, m.p. 248° (0.5 g., 82% based on isoindoline).

Found: C, 49.7; H, 4.8; I, 32.7%

Found: C, 49.7; H, 4.9; I, 32.6; N, 10.2; O, 3.9%.

$C_{17}H_{20}IN_3O$ requires

C, 49.9; H, 4.9; I, 31.0; N, 10.3; O, 3.9%

4-(1-Amino-3-isoindoleninylidene)methylpyridine ethiodide (XV)

r-Picoline ethiodide (1.3 g.) and 1,3-di-imino-isoindoline (0.4 g.) were heated in n-butanol (25 ml.) under nitrogen for 17 hr. A greenish solution resulted when ammonia gas ceased to be evolved. Evaporation of solvent to 20 ml. yielded a green precipitate. Recrystallization from methanol gave greenish flakes, m.p. 245-6°

(0.5 g., 80% yield based on isoindoline)

Found: C, 49.6; H, 4.6; I, 31.3; N, 10.5%

$C_{17}H_{20}IN_3O$ requires

C, 49.9; H, 4.9; I, 31.0; N, 10.3%

2-(1-Amino-3-isoindoleninylidene)methylquinoline ethiodide (XVIII)

Quinaldine ethiodide (3.2 g; .01 mol.) and 1,3-di-iminoisoindoline (0.7 g.; 0.005 mol.) were heated together in ethanol (100 ml.) for 4 hr. A brown precipitate was obtained, which recrystallized from methanol, gave brownish flakes, m.p. 250-251° (1.8 g., 80%).

Found: C, 56.2; H, 4.3; I, 29.6; N, 9.2%

$C_{20}H_{18}IN_3$ requires

C, 56.2; H, 4.3; I, 29.7; N, 9.8%.

4-(1-Amino-3-isoindoleninylidene)methyl-2-picoline ethiodide (XVII)

2,4-Lutidine ethiodide (2.7 g.) and 1,3-di-iminoisoindoline (1.4 g.) were heated under reflux in propanol (50 ml.) for 6 hr. during which evolution of ammonia was detected. The resulting green colour solution was cooled and a black precipitate was obtained, m.p. 233-237°, yield 1.7 g. The filtrate was allowed to pass

through an alumina column. Only a green band was found and it was eluted with methanol. The solution was evaporated to dryness, and the combined precipitates were recrystallized from nitromethane (soxhlet) to yield red-brown crystals, m.p. 253° (3.0 g., 87%).

Found: C, 51.6; H, 4.9; I, 33.1; N, 10.3%

Found: C, 52.5; H, 4.5; I, 31.0; N, 10.3%

$C_{17}H_{18}IN_3$ requires

C, 52.2; H, 4.6; I, 32.4; N, 10.7%

2-(1-Amino-3-isoindoleninylidene)methyl-6-picoline ethiodide

2,6-Lutidine ethiodide (2.7 g.) and di-imino-isoindoline (1.4 g.) were heated together in ethanol (50 ml.) for 6 hr. When chilled, the solution gave a black precipitate. Recrystallization from methanol gave greenish black crystals, m.p. 239-240° (0.5 g., 20%).

Found: C, 52.4; H, 4.7; I, 32.3; N, 10.0%

$C_{17}H_{18}IN_3$ requires

C, 52.2; H, 4.6; I, 32.4; N, 10.7%.

4-(1-Amino-3-isoindoleninylidene)methylquinoline ethiodide (XIX)

Lepidine ethiodide (3.0 g.) and 1,3-di-iminoisoindoline (1.4 g.) were heated together in butanol (50 ml.) for 2 hr. Ammonia was evolved and a brown precipitate formed during refluxing. The solution was cooled on ice and filtered. Recrystallization from methanol gave brown needles, m.p. 241° (4.2 g.).

Found: C, 56.0; H, 4.3; I, 29.6; N, 9.2%

$C_{20}H_{18}IN_3$ requires

C, 56.2; H, 4.25; I, 29.7; N, 9.8%.

2-(1-Amino-3-isoindoleninylidene)methylbenzothiazole ethiodide (XX).

1,3 Di-iminoisoindoline (1.4 g.) and 2-methyl benzothiazole ethiodide (3.0 g.) were heated together in boiling ethanol (50 ml.) for 1 hr. There was evolution of ammonia. Red precipitates, m.p. $>$ 360°, were collected and upon recrystallization from methanol, they yielded reddish-brown crystals, m.p. 300-302° (3.6 g., 90%).

Found: C, 48.8; H, 4.2; I, 27.5; N, 8.6; O. 3.6%

$C_{19}H_{20}IN_3OS$ requires

C, 49.0; H, 4.3; I, 27.3; N, 9.0; O,3.4%.

2-Amino-4-methylpyrimidine ethiodide (XXI)

2-Amino-4-methylpyrimidine (10.2 g.) and ethyl iodide (12.7 g.) were heated in a sealed tube with nitromethane (15 ml.) at 100° for 12 hr. The yellow precipitate (22.2 g.) was recrystallized from methanol-isopropanol giving light yellow needles, m.p. 182-183° (2.1 g., 87%).

Found: C, 31.4; H, 4.6; I, 47.9; N, 15.7%

$C_7H_{12}IN_3$ requires

C, 31.7; H, 4.6; I, 47.65; N, 15.85%.

2-Amino-4-(1-amino-3-isoindoleninylidene)methpyrimidine ethiodide (XXII)

1,3-Di-iminoisoindoline (2.8 g.) and 2-amino-4-methylpyrimidine ethiodide (1.4 g.) were refluxed in 1-nitropropane (100 ml.) for 48 hr. during which an orange precipitate formed and ammonia was evolved. The reaction mixture was cooled and 0.5 g. of orange precipitate was collected, m.p. 270-273°. Evaporation of solvent to 10 ml. yielded another 0.6 g. (second crop). The combined precipitates were recrystallized from methanol-water to give red needles, m.p. 250° (0.9 g., 52%).

Found: C, 46.8; H, 4.5; I, 28.4; N, 16.2%

$C_{17}H_{22}IN_5O$ requires

C, 46.5; H, 5.0; I, 28.9; N, 15.9%.

This compound was heated at 150° for 4 hr. in vacuum (weight loss 6.9%; required for loss in ethanol 7.6%).

Found: C, 45.8; H, 4.4% $C_{15}H_{16}IN_5$ requires

C, 45.8; H, 4.1%.

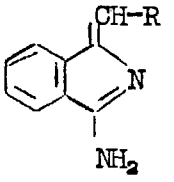
Attempted hydrolysis of 2-amino-4-(1-amino-3-isoindolen-inylidene)-methylpyrimidine ethiodide

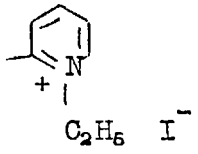
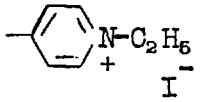
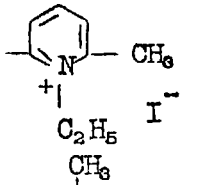
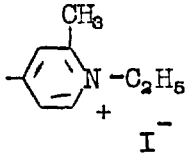
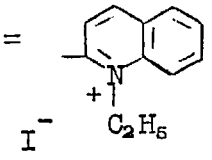
The hemicyanine (0.100 g.) was heated with conc. HCl (10 ml.) for 1 hr. on steam bath. Red colour persisted and upon evaporation to dryness, the precipitate was recrystallized from ethanol giving red crystals, m.p. 276-277° (0.063 g., 60%). The mixed m.p. with the original hemicyanine was depressed.

Found: C, 39.8; H, 4.4; I, 27.4% $C_{15}H_{19}ClIN_5O$ requires

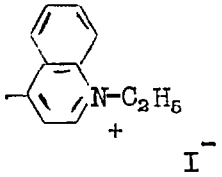
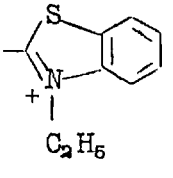
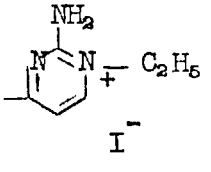
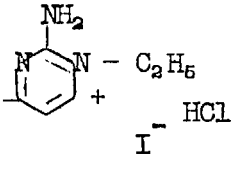
C, 40.2; H, 4.3; I, 27.4%.

Dinuclear Cyanine with Terminal Amino Group



	m.p.	mμ	ε
I; R = 	248°	207	29000
		252	20000
		428	19500
II; R = 	245-246°	217	24000
		252	29000
		442	29000
III; R = 	239-240°	207	28000
		280	3200
		415	16000
IV; R = 	253-253.5°	219	39000
		255	30000
		432	16000
V; R = 	250.251°	207	39000
		222	40000
		252	24000
		301	11000
		313	10000
		465	36000

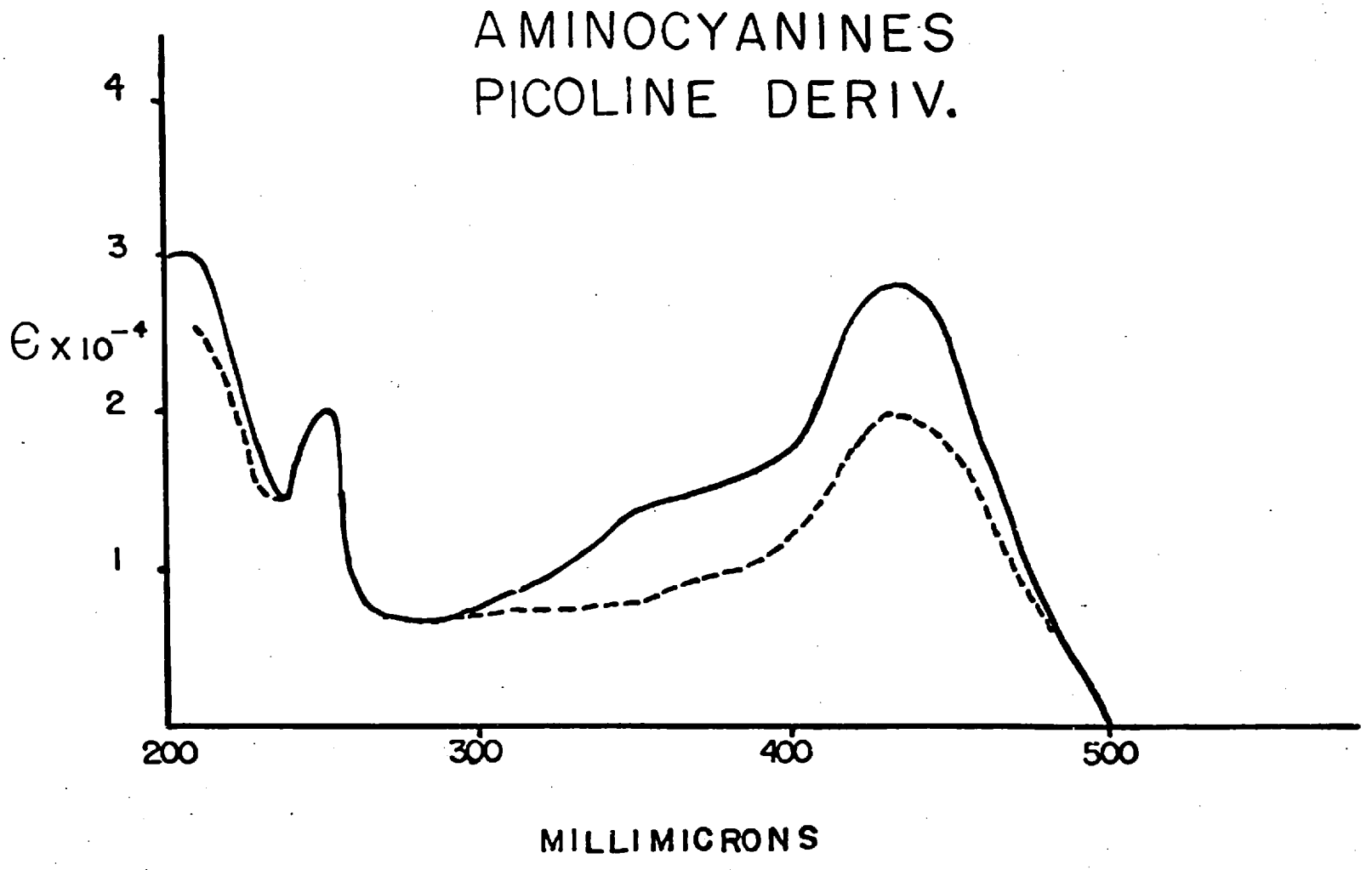
Dinuclear Cyanine with Terminal Amino Group (cont.)

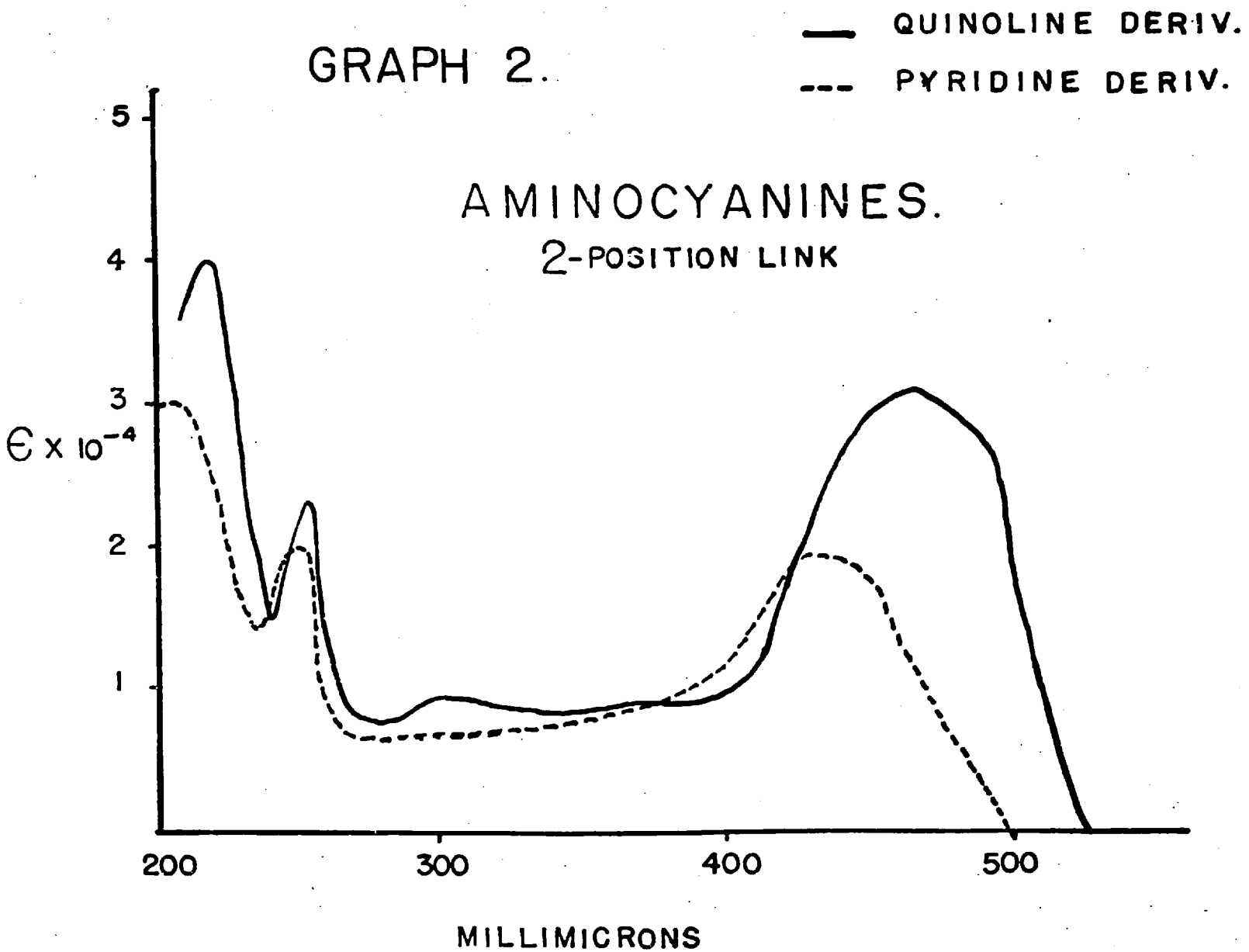
		m.p.	mμ	ε
VI; R =		241°	218	50000
			254	23000
			282	15000
			300	14000
			335	13000
			478	56000
VII; R =		300-302°	223	25000
			264	15000
			340	16000
			460	27000
			485	22000
VIII; R =		270°	220	37000
			270	10000
			280	10000
			310	13000
			398	28000
			443	9000
IX; R =		276-277°	220	49500
			268	9600
			278	9400
			315	14000
			384	54000
			400	48000

GRAPH I.

— 4-POSITION LINK

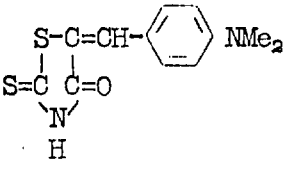
---- 2-POSITION LINK

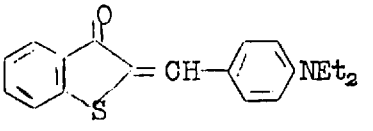



GRAPH 2.
QUINOLINE DERIV.
PYRIDINE DERIV.
AMINOCYANINES.
2-POSITION LINK
5
4
3
2
1
ε x 10⁻⁴
200
300
400
500
MILLIMICRONS

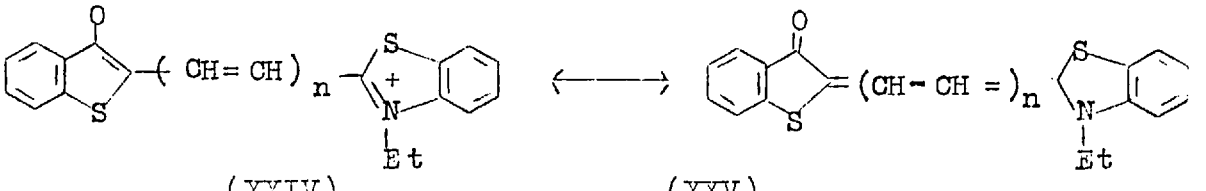
Chapter 2. Dinuclear Cyanines with Terminal Amide Groups

Hamer, following the observation that p-dialkylaminobenzylidene derivatives such as 5-p-dimethylaminobenzylidenerhodanine and 2-p-diethylaminobenzylidenethioindoxyl are good photographic sensitizers





proposed a generic term "merocyanine" for these compounds. One of these end groups is a disubstituted amine and the other end group contains a carbonyl group. Brooker [25] later studied dinuclear merocyanines and suggested that the colour of these dyes is associated with resonance between the following hybrids:



(XXIV) (XXV)

It was then that this class of dyes was defined by Brooker as possessing an extended amide system.

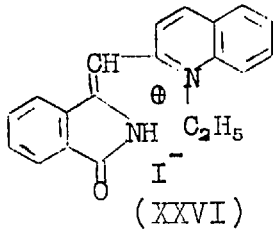
The zwitterionic structure (XXIV) normally ha~~ve~~s a higher energy than the covalent structure (XXV); but

both the heterocyclic rings have an additional double bond in the zwitterion structure, which gives each aromatic character, and the increased stabilization in the two rings offsets the energy of the charge separation more or less. The two canonical structures consequently have comparable energies so that a high degree of resonance is to be expected.

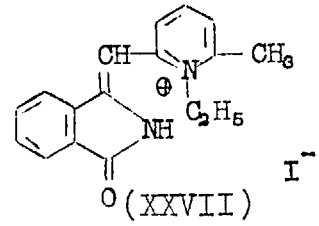
The methods of preparation are similar to those of cyanines but unlike cyanine dyes, which are quaternary ammonium salts soluble in general only in polar solvents, the merocyanines are zwitterionic compounds which dissolve in both polar and nonpolar solvents.(26)

Barnes (27) in studying compounds which are linked to other heterocycles through a methine bridge prepared 1-oxo-(2-pyridylmethylene)isoindoline and its quaternary salt, 1-methyl-2-(1-oxo-3-isoindolinylidene)-methylpyridinium iodide. The latter was treated with potassium hydroxide and the product shown to be a zwitterion, and it was pointed out that this was a merocyanine. In the present work, the oxoimine was condensed directly with quinaldine ethiodide and with 2,6-lutidine ethiodide to give the corresponding dinuclear cyanines (XXVI) and (XXVII). These condensations proceed much more readily than with the unquaternized methyl

heterocycles, as expected.

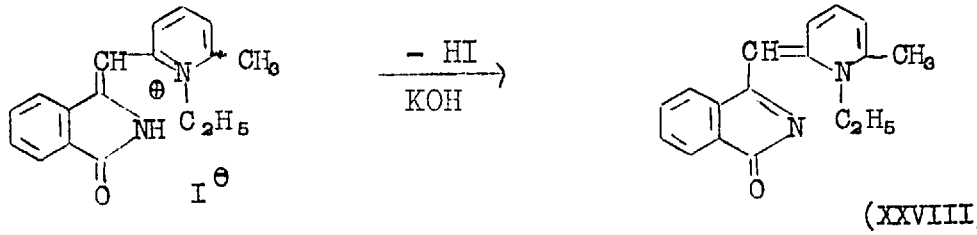


(XXVI)



(XXVII)

On treatment with potassium hydroxide, 1-ethyl-2-(1-oxo-3-isoindolinylidine)methylpyridinium iodide was converted into the following merocyanine (XXVIII).



(XXVIII)

These dinuclear cyanines with terminal amide groups (XXVI) and (XXVII) dissolve in polar solvents and are yellow crystalline solids with melting points in the region of 250°. They could be recrystallized from alcohol but retained solvent of crystallization. From dimethylformamide-benzene, however, crystals free of solvent were obtained. The infrared absorption characteristics supported the structure (XXVII). Thus, the NH stretching vibration was found at 3170 cm^{-1}, whilst a strong band at 1710 cm^{-1} was clearly the normal stretching frequency for

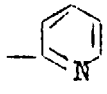
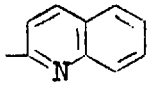
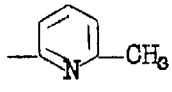
the amide carbonyl group in a 5-membered ring.

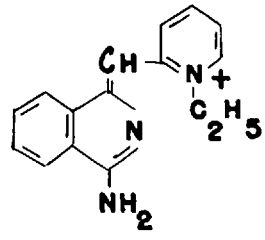
The effect on the light absorption of annelation of the aromatic nucleus can be seen from **PAGE 41**. The long-wavelength absorption has been shifted bathochromically from 378 mμ for pyridine derivative to 402 mμ for the quinoline derivative, a shift of 24 mμ ; the quinoline derivative has an absorption maximum in the visible region whilst the pyridine derivative has not. It is also interesting to note that the pyridine derivative has a high extinction band at 301 mμ whilst the quinoline derivative absorbs in this region at 320 mμ , a bathochromic shift of 19 mμ .

Methyl-substitution extranuclear to the pyridine nucleus, such as in the cyanine derived from 2.6-lutidine ethiodide, results in a broader absorption (**PAGE 41**) extending further into the visible region (a bathochromic shift giving a shoulder at 420 mμ), but the dominant absorption is at 386 mμ showing a bathochromic shift of 8 mμ when compared with the nonsubstituted cyanine which absorbs at 378 mμ .

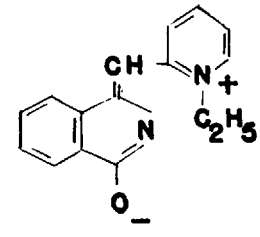
The data given in Table (1) show that the amide cyanine (XXIX) absorb at longer wavelengths than the parent bases (XXVIII), and that the amino cyanines (XXX) absorb at still longer wavelengths.

Table (1) Long-wavelength Absorption in mμ

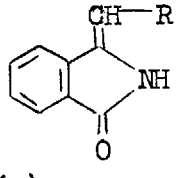
Type of Nucleus R	(i) Parent Base (XXVIII)	(ii) Amide Cyanine (XXIX)	(iii) Amino Cyanine (XXX)	(iv) Difference BETWEEN amino cyanine and amide cyanine	(v) Difference BETWEEN amide cyanine and parent base
	357	378	428	50	21
	378	402	465	63	24
	360	386	415	29	26



(XIII)

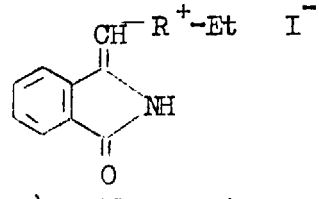


(XXXIII)



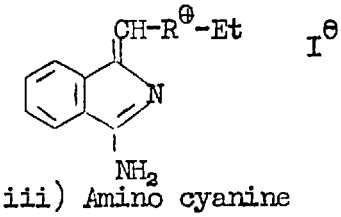
(i) Parent base

(XXVIII)



(ii) Amide cyanine

(XXIX)



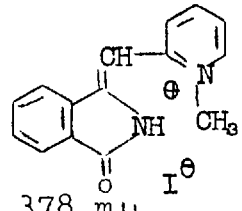
(iii) Amino cyanine

(XXX)

Compared with the corresponding aminocyanine (data obtained from Chapter 1), the amidecyanines show hysochromic shifts in the longest wavelength absorption of from 29 to 63 mμ , as indicated in column (iv) of Table (1).

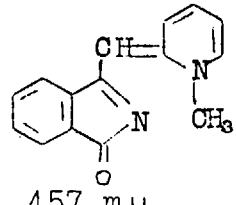
The merocyanines have longer wavelength absorption than their amide cyanine precursors and even the corresponding amino cyanines. This is possibly because the last are strictly hemicyanines with an aza link in the methin chain whilst the others are dinuclear types.

Table (2) Amide Cyanines and Merocyanine Long-wavelength Absorption Maxima in mμ



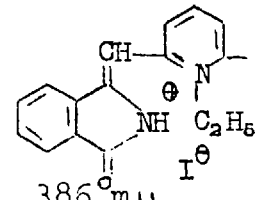
378 mμ

(XXXI)



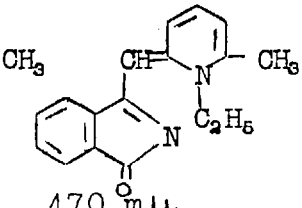
457 mμ

(XXXII)



386 mμ

(XXVII)



470 mμ

(XXVIII)

The difference in the position of maximum absorption between (XXXI) and (XXXII) is 79 mμ and between (XXVII) and (XXVIII) is 84 mμ . The extranuclear methyl causes a 13 mμ (470-457) bathochromic shift in the merocyanine and an 8 mμ (386-378) shift to longer wavelength

in the dinuclear cyanines.

The effect of solvent on light absorption for these two merocyanines is as follows: It is concluded that the present merocyanines are highly polar.

Table (3) Effect of Solvents on Merocyanine Absorptions.

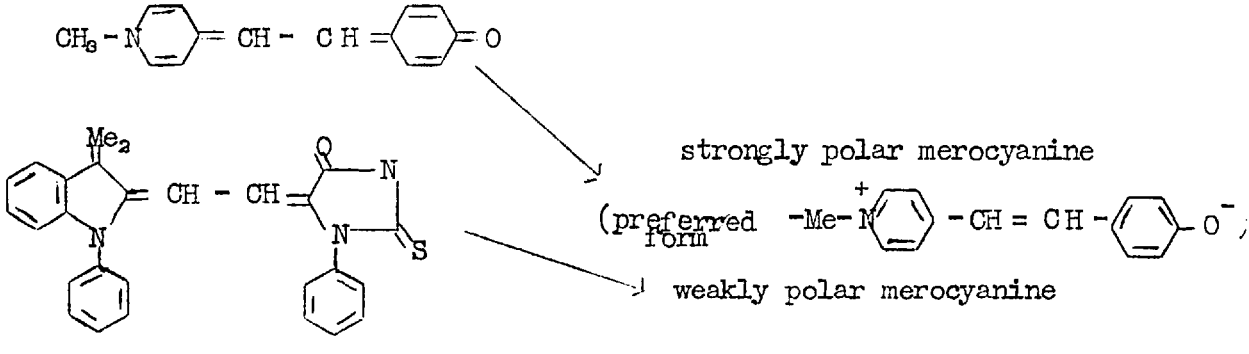
Type of Solvent	Absorption in mμ	
methanol	457	470
chloroform	486	503
solvent shift	29	33

There is a bathochromic shift on changing from a polar to a non-polar solvent. This is a 'reversed' solvent effect. According to Förster's arguments,[28] this means that the charge separation structure (XXXIII) is more stable than the covalent structure (XXXII) - not a situation encountered in merocyanines until Brooker's work in 1951 [29]. Altering the solvent to a less polar one destabilises the charge-separation form relative to the co-valent structure. The energy difference between the hybrids is

decreased. The resonance between these structures then becomes more perfect, there is less energy difference between ground and first excited states, and there is a bathochromic shift in the long-wavelength absorption.

The conclusion that the charge-separation form (XXXIII) has a lower energy content than the covalent structure means that the energy required to separate the charges is more than offset by the aromatic stabilisation of the pyridine ring.

The λ_{max} of a weakly polar merocyanine shifts to longer wavelengths on changing from a non-polar to a polar solvent. This effect has been ascribed to the formation of oriented solvent dipole layers around the polar atoms of the dye molecules. These oriented layers stabilize the contributing dipolar structure relative to the covalent structure so that these canonical forms become closer in energy. The result is again more perfect resonance with a shift in absorption to longer wavelengths, i.e. lower energies.[29] A strongly polar merocyanine and a weakly polar merocyanine are given below as examples:



Experimental Section

Preparation of 1-ethyl-2-(1-oxo-3-isoindolinylidene) methylquinolinium iodide tetrahydrate

Quinaldine ethiodide (1.2 g.) and 3-imino-1-oxo-isoindoline (0.4 g.) were refluxed in ethanol (4 ml.) for 4 hr. during which time a brown precipitate, m.p. 230° (1.4 g.) formed and ammonia was steadily evolved. The precipitate was recrystallized from ethanol, and then had m.p. 230°.

Found: C, 48.5; H, 4.6; N, 5.2%

Found: C, 48.5; H, 4.6; N, 5.2; I, 25.5%

$C_{20}H_{25}IN_2O_5$ requires

C, 48.0; H, 5.0; N, 5.6; I, 25.4%.

Preparation of 1-ethyl-2-(1-oxo-3-isoindolinylidene) methylpyridinium iodide

3-Imino-1-oxo isoindoline (1.8 g.) and 2.6-lutidine ethiodide (1.6 g.) were mixed in 50 ml. of butanol. The mixture was heated to dissolve the reagents and refluxed for 17 hr. during which evolution of ammonia was detected. The solution turned yellow and after 15 min. refluxing had turned greenish. Bumping occurred

after 2 hr. heating. At the end of 17 hr. heating, the solution was cooled and an orange precipitate (1.0 g.) was collected, m.p. 243-248°. Evaporation of solvent to 15 ml. afforded a second crop (0.5 g.). The combined precipitates were recrystallized from dimethylformamide-benzene yielding yellow crystals, m.p. 233-234° (1.3 g., 40%).

Found: C, 52.1; H, 4.4; I, 32.4; N, 7.5%

$C_{17}H_{17}IN_2O$ requires

C, 52.1; H, 4.4; I, 32.4; N, 7.1%.

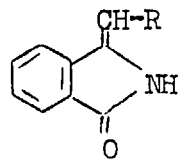
Generation of the corresponding merocyanine

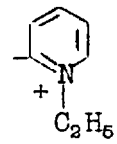
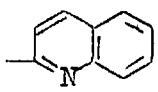
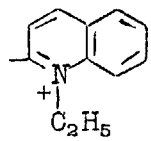
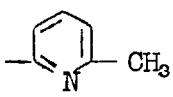
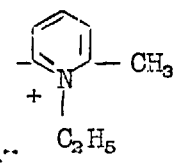
This dinuclear cyanine (0.5 g.) was dissolved in water (20 ml.) and aqueous 3 N-potassium hydroxide was added. The solution was warmed to 40°. After 5 min., an orange-coloured solid precipitated, m.p. 251-257° (0.2 g., 65%). Recrystallization from isopropanol gave red crystals, m.p. 260-260.5° (0.15 g.).

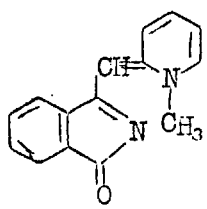
Found: C, 75.25; H, 6.3; N, 10.9; O, 8.7; Loss in wt. 3.4% at 150°; $C_{17}H_{16}N_2O\frac{1}{2}H_2O$ requires

C, 75.0; H, 6.1; N, 10.1; O, 8.6; Loss in wt. 3.2% for hemihydrate.

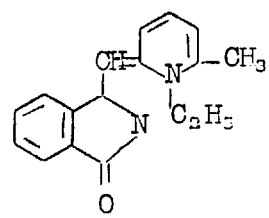
Light Absorption Data



	mμ	ε		mμ	ε
R = 	228	20,500	R =  I	222	8,830
	234	19,500		291	2,910
	275	11,300		301	2,150
	357	28,900		378	11,700
R = 	235	11,600	R =  I	220	17,500
	285	10,100		237	52,000
	378	11,700		241	54,000
				309	14,700
				320	17,000
				402	6,900
R = 	228	22,900	R =  I	220	19,200
	275	11,300		270	13,300
	360	33,000		386	10,100

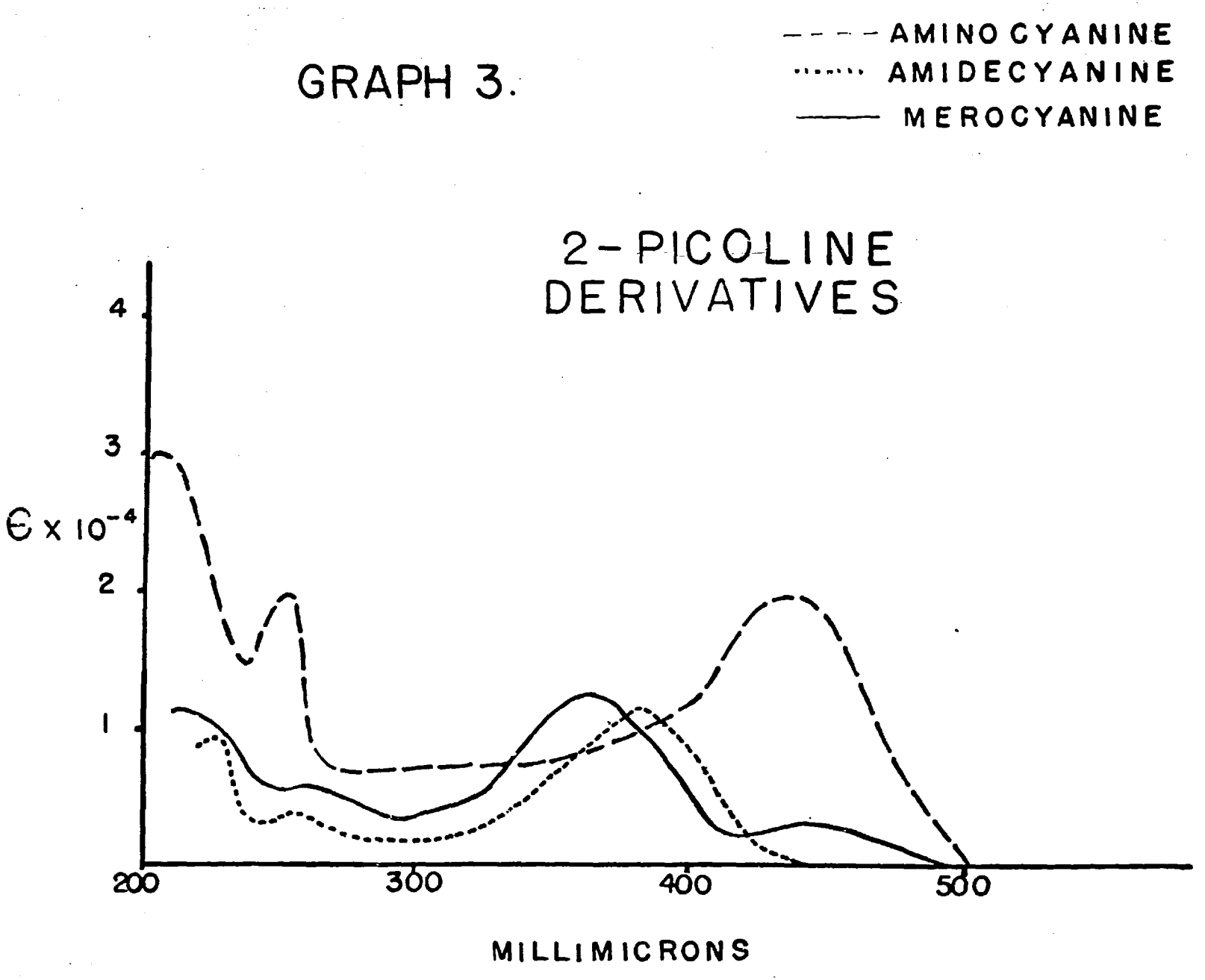


mμ	ε
227	11,900
262	6,500
362	12,600
457	3,000
In chloroform	
466	27,400
486	29,200

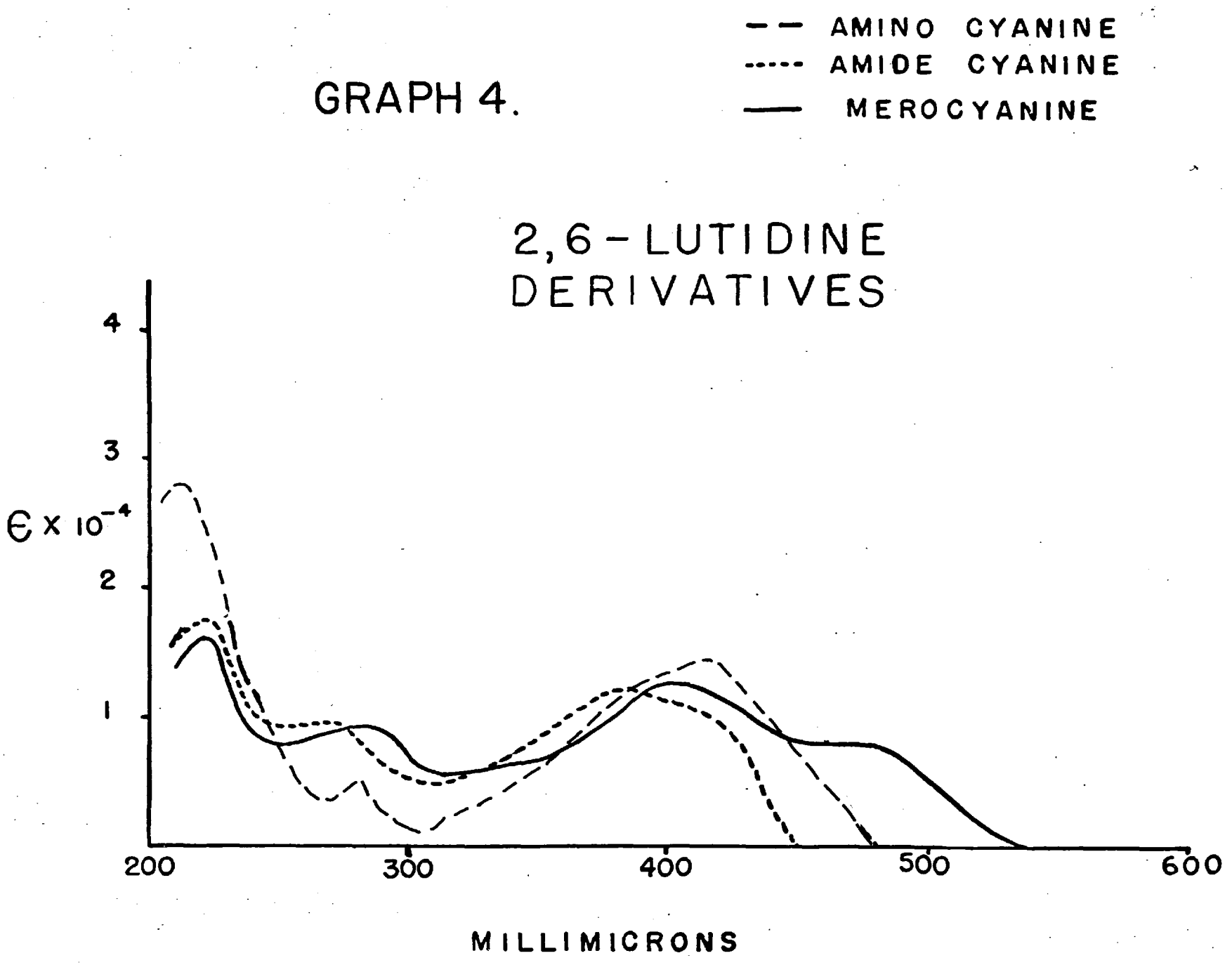


mμ	ε
220	15,800
271	10,000
400	12,600
470	7,500
503	12,000

GRAPH 3.

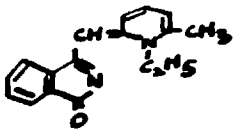

AMINO CYANINE
AMIDECYANINE
MEROCYANINE
2-PICOLINE
DERIVATIVES
4
3
2
1
ε x 10⁻⁴
200
300
400
500
MILLIMICRONS

GRAPH 4.

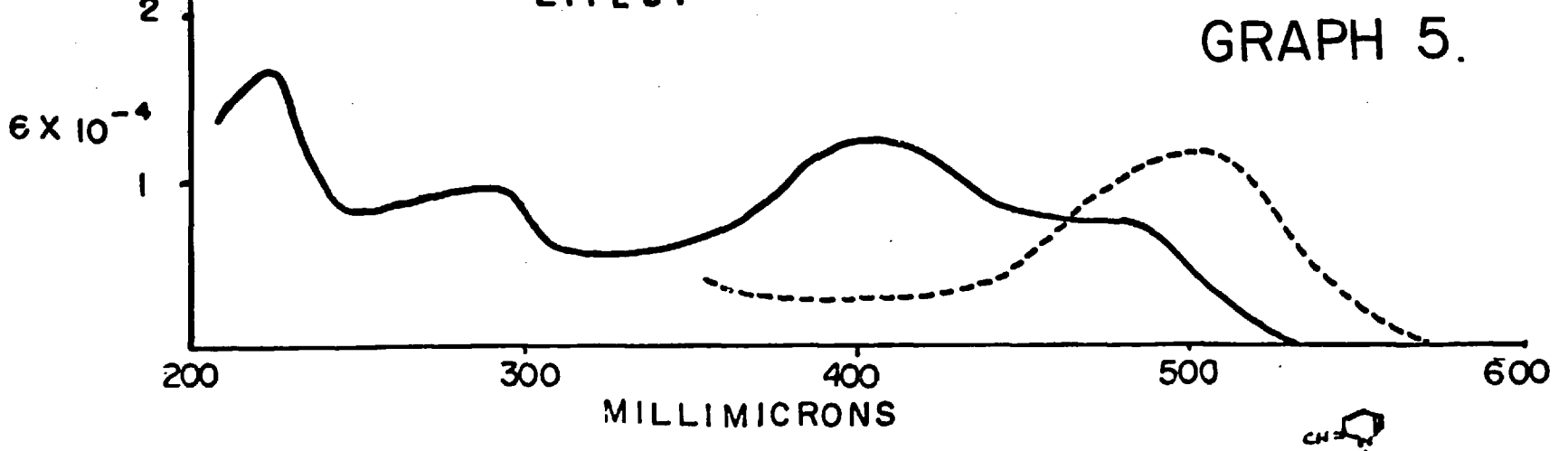

AMINO CYANINE
AMIDE CYANINE
MEROCYANINE
2,6-LUTIDINE
DERIVATIVES
4
3
2
1
ε X 10⁻⁴
200
300
400
500
600
MILLIMICRONS

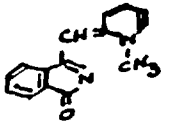
MEROCYANINES

SOLVENT EFFECT

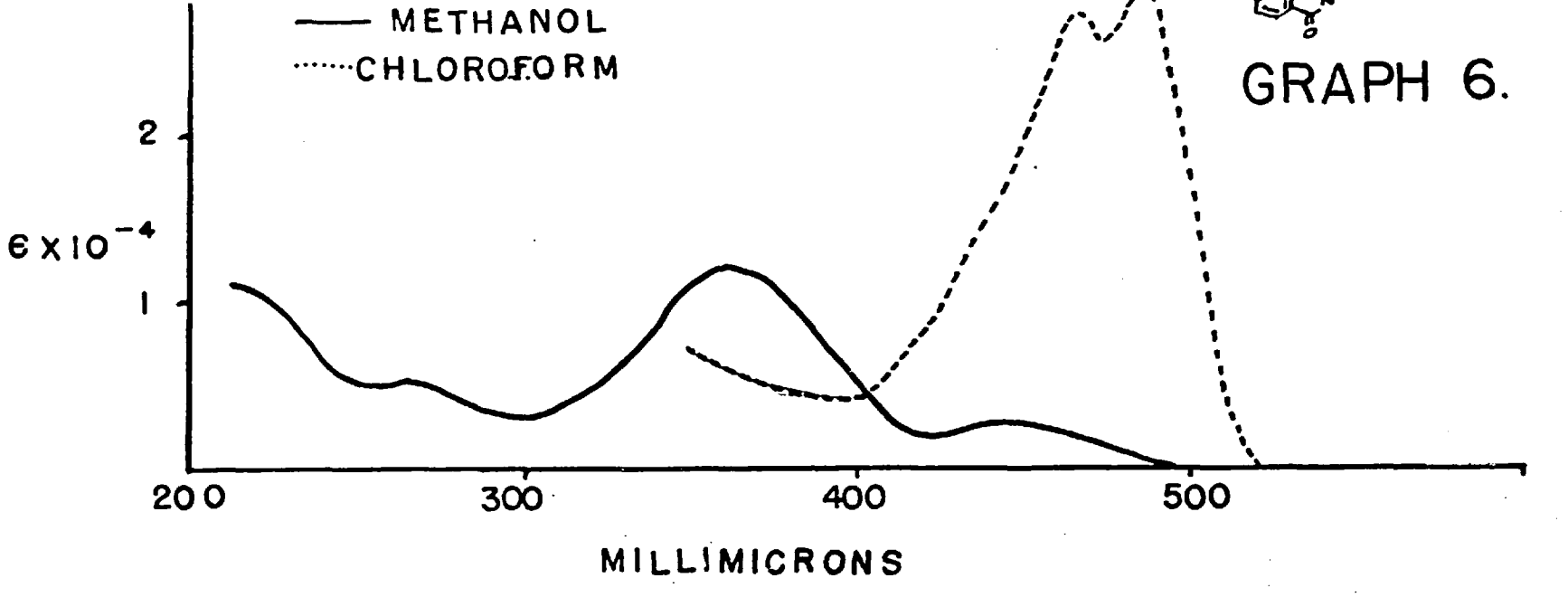


GRAPH 5.



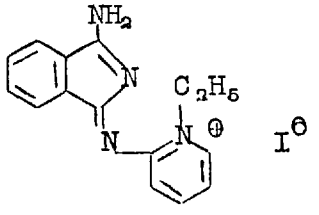


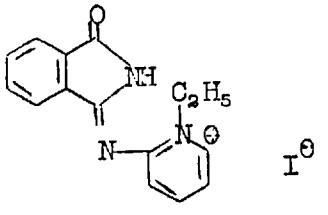
GRAPH 6.



Chapter 3. The Reaction of Amino Substituted Quaternary Salts with Heterocyclic Imines

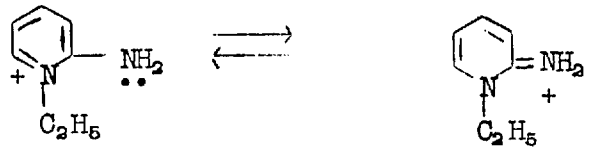
The ease of condensation of active methyl quaternary ammonium salts with heterocyclic imines, which was reported in Chapter 1 and Chapter 2, led to some attempts at condensing amino substituted quaternary salts with 1,3-di-iminoisoindoline and with 3-imino-1-oxo-isoindoline. It was hoped that hemicyanines and di-nuclear cyanines might be obtained which had an extra-nuclear aza link as shown in the following two examples:



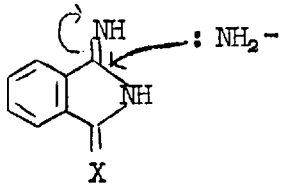


When 2-aminopyridine ethiodide was heated with 1,3-di-iminoisoindoline in boiling butanol for 40 hr., the amino substituted quaternary ammonium salt was recovered in 80% yield after being recrystallized from isopropanol. Similarly 3-imino-1-oxoisoindoline failed to react. In this case, the heterocyclic imine was recovered nearly

quantitatively. This lack of reactivity of the amino substituted quaternary salt could be attributed to resonance delocalization of the positive charge, thus:-

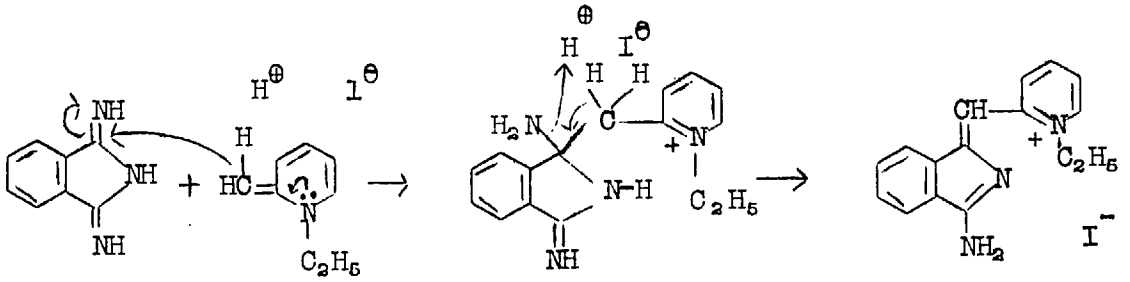


The availability of the lone pair on the amino group is thereby much reduced, evidently sufficiently to prevent nucleophilic attack on the imine -

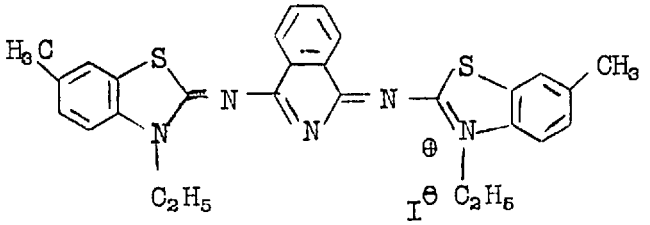


X may be = O
or = NH

On the other hand, the reactivity of methyl-substituted heterocyclic quaternary salts with an imidine depends on the ease of formation of the corresponding methylene base, which is the nucleophilic attacking reagent:-

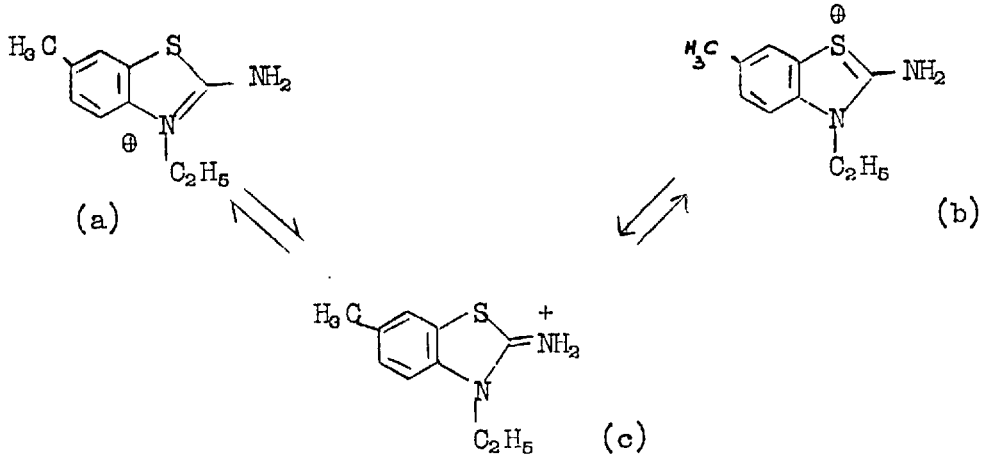


When 2-amino-6-methylbenzothiazole ethiodide was mixed with 1,3-di-iminoisoindoline in methanol at room temperature, the hydriodide of the dinuclear cyanine was formed. This dye has an isoindolenine unit as part of the chromophoric path.



+ HI (XXXIV)

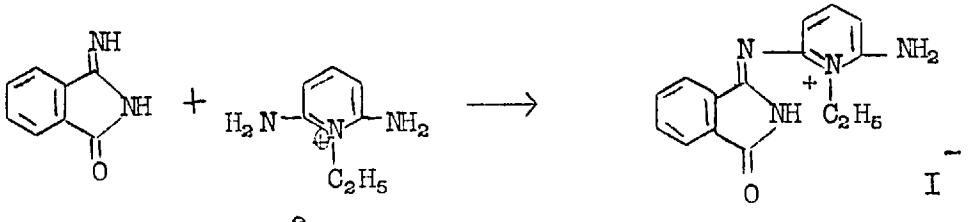
The reactivity of the 2-aminobenzothiazole ethiodide contrasts with the inertness of the 2-amino-pyridine ethiodide. The greater reactivity may possibly be explained by the fact that the positive charge can be shared, by resonance, with a third atom (sulphur) as follows:-



The resultant loss of availability of the lone pair on the exocyclic amino group will not be so marked as in the pyridine case, and it is evidently insufficient to prevent reaction with 1,3-di-iminoisoindoline.

The next reaction studied was with 2,6-diaminopyridine ethiodide. The preparation of this salt gave some difficulty. When the two reactants, 2,6-diaminopyridine and ethyl iodide were heated together in either alcohol or nitrobenzene, only the hydroiodide was obtained. The required ethiodide was obtained by dissolving the reactants in nitroethane and allowing the reaction to proceed at room temperature.

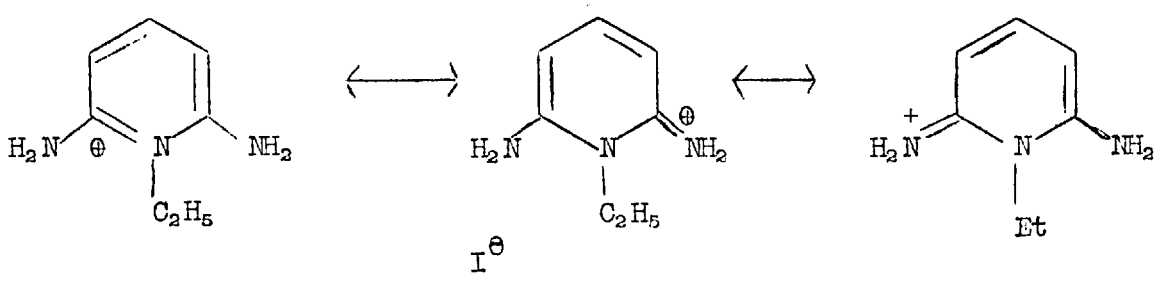
2,6-Diaminopyridine ethiodide condensed smoothly with 3-imino-1-oxoisoindoline to give the dinuclear aza-cyanine (XXXV). This has a terminal amide group and an extranuclear amino group.



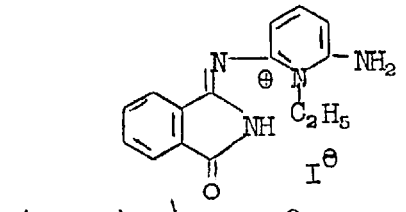
$I^{\ominus}$ (XXXV)

In the diaminopyridine ethiodide, the positive charge is presumably distributed over three atoms (the 3 N s). Consequently, as in the benzothiazole case,

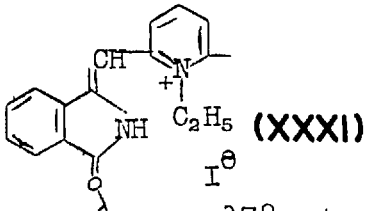
amino group reactivity is not sufficiently diminished to prevent condensation with the imidine.



The new dinuclear azacyanine (XXXV) has a maximum absorption at 382 mμ and an inflexion at 400 mμ. It differs little from the dinuclear cyanine (XXXI), which lacks the exocyclic amino substituent.



(XXXV) λ_{max} 382 mμ

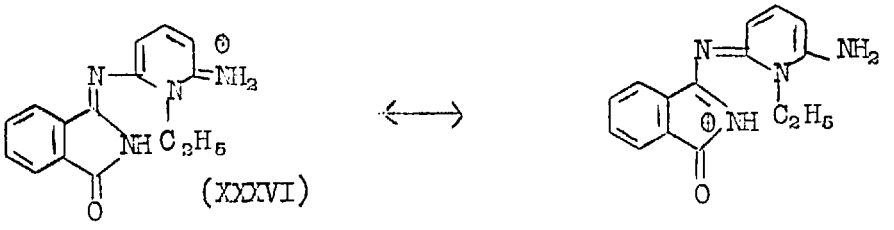


(XXXI)

λ_{max} 378 mμ

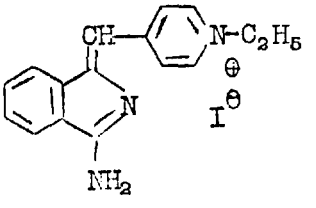
Since the substitution of an aza link for a methin link is known to have a hypsochromic effect, it is perhaps at first sight surprising to find that this aza cyanine absorbs at a slightly longer wavelength. However, a longer resonance path can be drawn for this azacyanine by making use of the extra amino substituent. On this basis, the dye could be

regarded as a hemicyanine type and there would be seven atoms between the two extreme nitrogen atoms involved in the cationic resonance:-



(XXXVI)

The nearest comparable dye becomes (XV), but the absorption of this at 442 mμ is hardly approached, presumably because of the resonance dispersion of the positive charge within the pyridine nucleus of (XXXVI).



(XV)

$\lambda_{max.}$ 442 mμ

Experimental Section

Preparation of 2-aminopyridine ethiodide

2-Aminopyridine (4.7 g.) and ethyl iodide (4 ml.) were warmed together on the steam bath and the solution was then kept in the dark for 17 hr. The solid product was crushed with ether, and recrystallized from acetone to give yellow needles, m.p. 145°, (10.1 g., 81%)

Found: C, 33.6; H, 4.5; I, 50.9; N, 11.3%

$C_7H_{11}IN_2$ requires

C, 33.6; H, 4.4; I, 50.75; N, 11.2%

Preparation of 2,6-diaminopyridine ethiodide

2,6-Diaminopyridine (5 g., m.p. 121-122°, recrystallized from chloroform) and ethyl iodide (5 ml.) were dissolved in methanol (100 ml.) and the resulting solution was heated under reflux on the steam bath for 40 hr. The solution was evaporated to dryness under reduced pressure and a yellow precipitate was collected. This became gummy but after being dried in a desiccator for 2 hr., it could be recrystallized from acetone-chloroform and then had m.p. 190-192° (6 g., 60%).

Found: C, 25.2; H, 3.2; I, 53.5; N, 17.9%

$C_5H_8IN_3$ requires

C, 25.3; H, 3.4; I, 53.5; N, 17.7%.

Another attempt to prepare the ethiodide was made by heating 2,6-diaminopyridine (1.9 g.) and ethyl iodide (2.7 g.) in nitrobenzene (5 ml.) on the steam bath for 10 min. and then keeping the solution in the dark for 48 hr. Yellow needles formed (2.1 g.) m.p. 102-108°. Recrystallization from ethanol-ether gave colourless needles, m.p. 192-193° (1.3 g., 35%).

Found: C, 25.6; H, 3.4; I, 53.2; N, 17.2%

$C_5H_8IN_3$ requires

C, 25.3; H, 3.4; I, 53.5; N, 17.7%

The m.p. was not depressed by admixture with the previously prepared sample.

Preparation of 2,6-diaminopyridine ethiodide

2 6-Diaminopyridine (5.0 g.) and ethyl iodide (7 g.) were mixed in nitroethane (50 ml.) with constant shaking (15 min.) until all the pyridine derivative was completely dissolved. The solution was kept in the dark for 17 hr. Yellow needles formed (4.0 g.). Evaporation

of solvent to 5 ml. yielded a second crop 3.0 g., m.p. 206-210°. Recrystallization from methanol-ether gave yellow needles, m.p. 218-219° (6.1 g., 52%).

Found: C, 31.7; H, 4.5; I, 47.2; N, 15.8%

$C_7H_{12}IN_3$ requires

C, 31.7; H, 4.6; I, 47.9; N, 15.8%.

This compound has been further characterized as its picrate, as follows:

Preparation of 2,6-diamino-1-ethylpyridinium picrate

2,6-Diaminopyridine ETHIODIDE (0.5 g.) was dissolved in 3 ml. of water, and 5 ml. of saturated picric acid was added. This solution was warmed on the steam bath for 5 min. and then cooled in ice. The yellow precipitate was collected and recrystallized from isopropanol to give yellow needles, m.p. 151-152° (0.3 g., 75%).

Found: C, 42.3; H, 4.1; N, 22.8% $C_{13}H_{14}N_6O_7$ requires

C, 42.6; H, 3.85; N, 22.9%

Preparation of 6-Amino-1-ethyl-2-(1-oxo-3-isoindolinylidene aminopyridinium iodide

2,6-Diaminopyridine ethiodide (m.p. 218-219°, 1.3 g.) and 3-imino-1-oxoisoindoline (m.p. 203°, 0.7 g.)

were refluxed in propanol (50 ml.) for 12 hr. An orange colour appeared after a few minutes and evolution of ammonia was detected during the heating. The reaction mixture was cooled in ice and an orange coloured precipitate, m.p. 291-292° (turning brownish-red, yield 1.6 g., 80%) was collected. Recrystallization from ethanol-water gave yellow needles, m.p. 301-301.5° (1.4 g. 78%).

Found: C, 44.95; H, 4.3; I, 31.4; N, 13.9; O, 6.0
Loss in wt. 3.1% at 150°. $C_{15}H_{15}IN_4 . \frac{1}{2} H_2O$ requires
C, 44.7; H, 4.0; I, 31.5; N, 13.9; O, 6.0;
Loss in wt. 2.9% for hemihydrate.

Hydrolysis of 6-Amino-1-ethyl-2-(1-oxo-3-isoindolinylidene)-aminopyridinium iodide

The preceding product (0.1005 g.) was dissolved in concentrated hydrochloric acid by gentle warming on the steam bath for 10 min. The solution was then cooled in ice, and yellow needles of the starting material, m.p. and mixed m.p. 302° (0.08 g.) were collected. The precipitate and filtrate were again mixed and butanol (5 ml.) was added, and boiled for 30 min., addition of concentrated hydrochloric acid (5 ml.) being made every 10 min. When the solution was cooled, colourless needles of phthalimide separated, m.p. and mixed m.p. 230-232° (0.016 g.,

0.5 mol.). The filtrate was extracted with benzene. After evaporation of the benzene solution, the residue was taken up with water (10 ml.) and picric acid solution (5 ml.) was added. After 10 min. the yellow precipitate was filtered off (0.0428 g., 0.6 mol.). It had m.p. 149-151° and a mixture with the authentic picrate, m.p. 151-152° showed no depression.

Attempted condensation of 2-aminopyridine methiodide with 3-imino-1-oxoisoindoline

2-Aminopyridine methiodide, m.p. 148-149° (2.0 g.) and 3-imino-1-oxoisoindoline (1.2 g.) were heated for 15 hr. in butanol (100 ml.). Only traces of ammonia were evolved during refluxing which was continued for 9 hr. The solution was then cooled and a yellow precipitate was obtained. It had m.p. 171-174° (0.5 g.). A second crop was also recovered (1.1 g.). The product was recrystallized from isopropanol giving colourless needles, m.p. 148-149°.

Found: C, 30.7; H, 3.8; I, 53.3; N, 11.6%

$C_6H_9IN_2$ requires

C, 30.5; H, 3.8; I, 53.8 N, 11.9%.

Attempted condensation of 2-amino-6-methylpyridine methiodide with 3-imino-1-oxoisoindoline

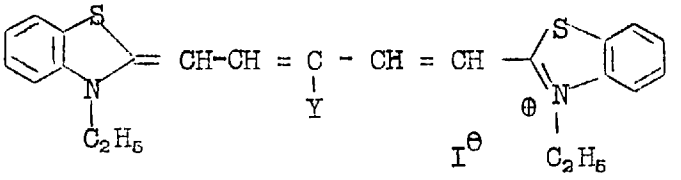
2-Amino-6-methylpyridine ethiodide (2.5 g.) and 3-imino-1-oxoisoindoline (1.5 g.) were heated together in butanol for 24 hr. On cooling a colourless precipitate (1.3 g.) was collected, m.p. 203-205°. Recrystallization from isopropanol gave colourless needles, m.p. 203-205° (1.2 g.).

Found: C, 65.3; H, 4.1% $C_8H_6N_2O$ requires
C, 65.7; H, 4.2%

The admixture with 3-imino-1-oxoisoindoline gave no depression and the recovery was 81%.

Chapter 4. Pentamethincyanines

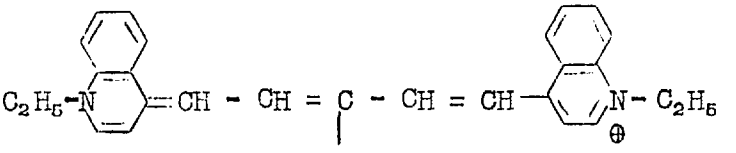
When a cyanine has five carbon atoms between the two terminal nuclei, it is defined as a pentamethincyanine or a dicarbocyanine. An example of a symmetrical pentamethincyanine with benzothiazole nuclei and one with lepidine nuclei are shown below.



Y = H

Y = H λ_{max} = 648 mμ (XXXVII)

Y = Br λ_{max} = 645 mμ



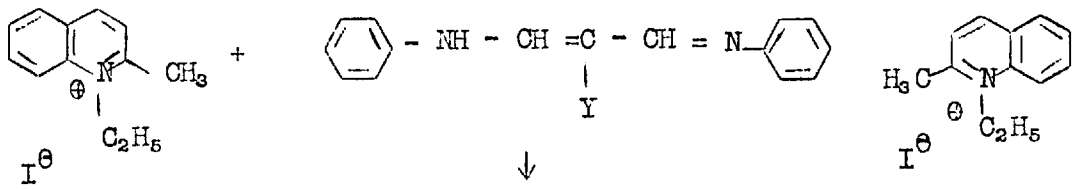
Y = H (XXXVIII)

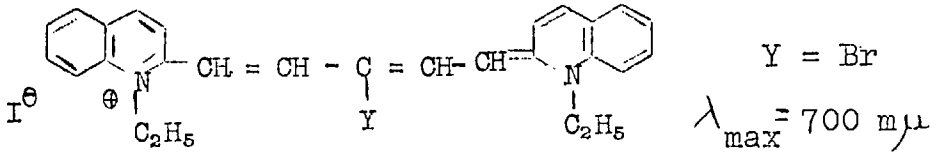
Y = H λ_{max} = 810 mμ

Y = Br λ_{max} = 800 mμ

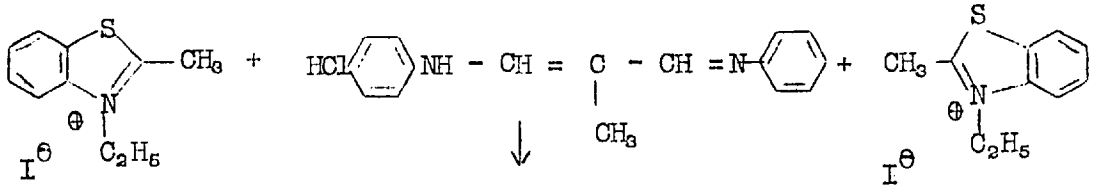
The first pentamethincyanines known were meso-substituted, e.g. (Y = Cl, Br, or NO_2). They were synthesized by condensing one mol. of a-chloroanilinoacralde-

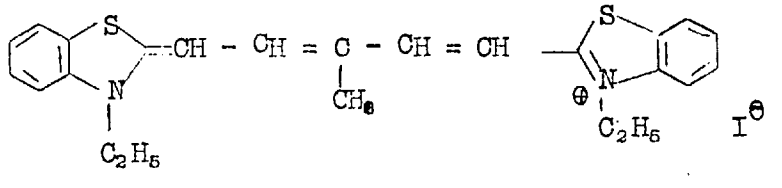
hyde anil or the corresponding a-bromo or a-nitro-compound, with two mols. of a quaternary salt having a reactive methyl group.





In some instances the acid salts of these anils were used. (30) Analogous dyes with meso-methyl substituents have also been prepared.

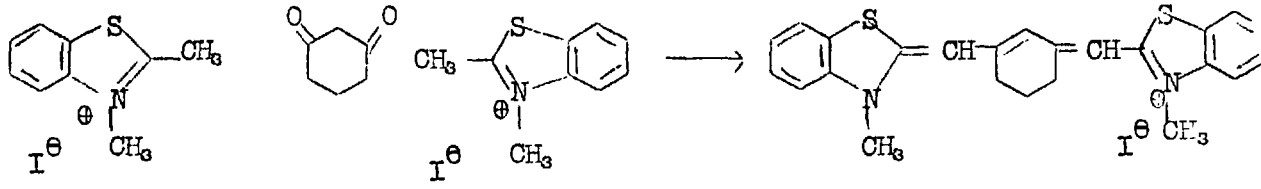




λ_{max} 650 mμ

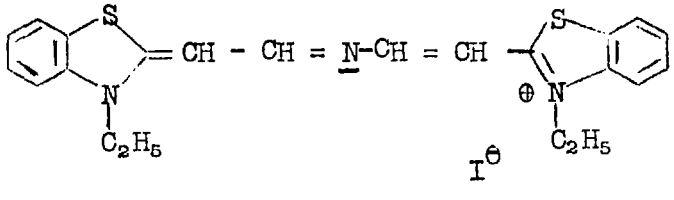
Similarly the lepidine derivative (XXXVIII) with Y = CH_3 has been obtained. The absorption maximum here is 818 mμ (730 mμ inflexion).

A homocyclic ring has been introduced as a part of the pentamethin chain by condensing a quaternary salt having a reactive methyl group with a cyclohexane 1,3-dione or a 3-alkylthiocyclohex-2-enone.(31)



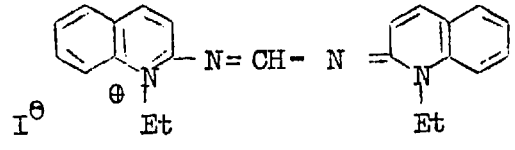
It was reported that this bridging of a pentamethin chain had a hypsochromic effect upon the light absorption.

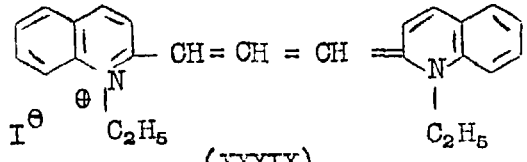
Substitution of an aza link in the polymethine chain has been found to produce a hypsochromic shift.



$\lambda_{max.}$ = 554 mμ

The above azacyanine absorbs at 554 mμ which is 94 mμ to shorter wavelength than the parent methin linked compound (XXXVII) which absorbs at 648 mμ. The diazacyanine,



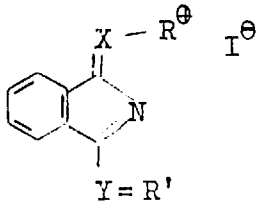


(XXXIX)

1,1'-diethyl- α, γ -diaza-2,2'-carbocyanine iodide is reported as having λ_{max} 343 mμ whilst the corresponding trimethincyanine (XXXIX) has λ_{max} 605 mμ, so the hypsochromic shift is 262 mμ, almost three times that caused by the one aza link in the previous example.(32)

As mentioned in Chapter 1, the hemicyanines with terminal amino groups react further with active methyl-substituted heterocyclic quaternary-ammonium-salts and also with 2-amino-6-methylbenzothiazole ethiodide to form dinuclear azapentamethincyanines. These have an isoindolenine nucleus as part of the chromophoric path. There is then both a chain bridge and an aza link in the molecules of these new cyanines. Yet their light absorptions are comparable to those of the pentamethincyanines. Possible reasons for the absence of the expected double hypsochromic shift are discussed in Chapter 6.

Cyanines with heterocyclic rings as part of the chromophoric path have not been reported before. In this chapter cyanines with the following structure are discussed.

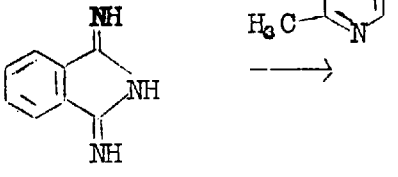


X and Y can be -N= or -CH=.
R⁺ and R' may be the same or different heterocyclic nuclei.

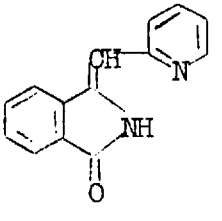
This chapter is divided into three sections. The first section is concerned with the monazacyanines (X=Y= -CH=) which are prepared by condensing two mols. of an active-methyl substituted quaternary salt with one mol. of 1,3-di-iminoisoindoline. The second section concerns the diazacyanines (X= -CH=; Y = -N=) which are prepared from the hemicyanine (Chapter 1) and a reactive amino-substituted-quaternary salt. The third section covers the triazacyanines (X = Y = -N=) prepared via the reaction of two mols. of an amino-substituted heterocyclic base with 1,3-di-iminoisoindoline. Only one amino-substituted quaternary salt, 2-amino-6-methylbenzothiazole ethiodide, was found to be sufficiently reactive to condense directly with di-iminoisoindoline.

Section A. Symmetrical Monazapentamethincyanines

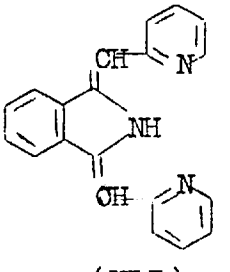
Barnes [22] found that 2-picoline interacted with di-iminoisoindoline only under rather vigorous conditions. The main product was then unexpectedly (XL) presumably because of competitive hydrolysis by moisture in the reagents. Tri-cyanocyaphenine was also isolated, probably as a result of the self-condensation of phthalonitrile formed by thermal dissociation of di-iminoisoindoline. The hoped-for three-unit compound (XLI) was not obtained.



(XLII)

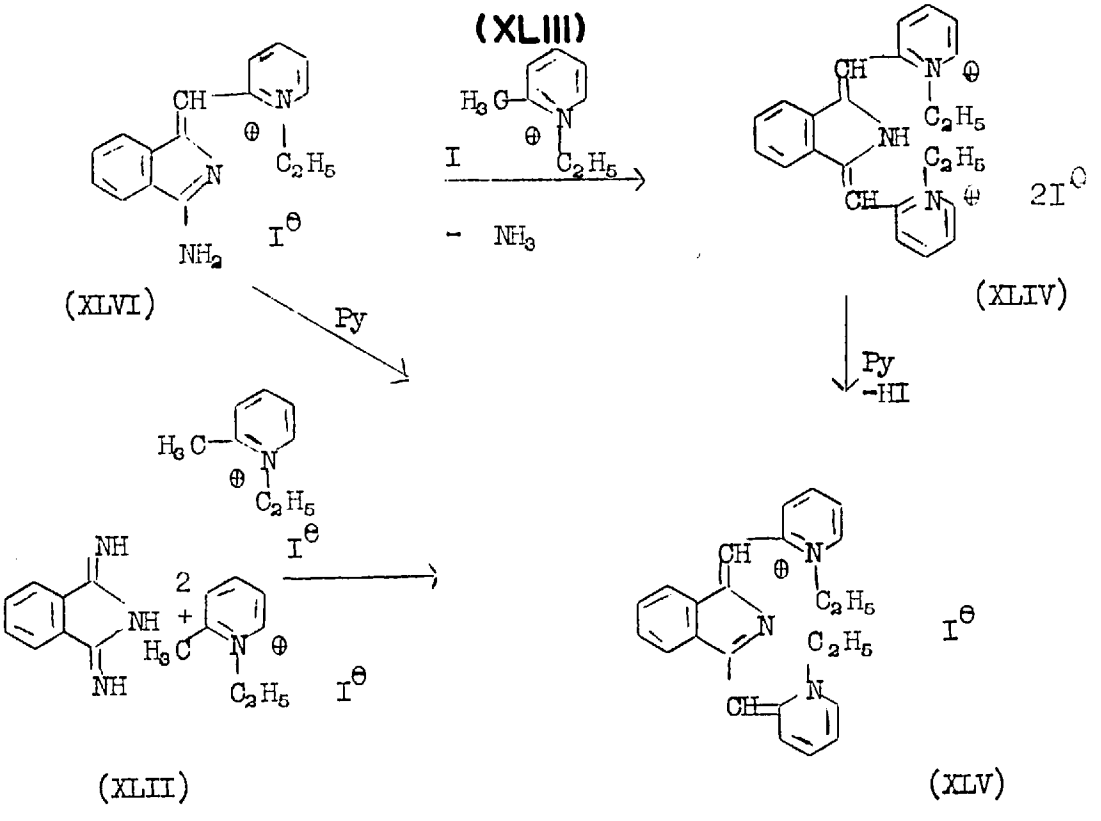


(XL)



(XLI)

Following the observation (Chapter 1) that one mol. of an active methyl substituted quaternary heterocyclic salt reacted readily with 1,3-di-iminoisoindoline, experiments were made to condense the unsubstituted amino group of the first-formed hemicyanine with a second mol. of the methyl-substituted-quaternary-salt. In boiling ethoxyethanol the reaction of (XLVI) with (XLIII) gave


(XLIII)
(XLVI)
(XLIV)
(XLII)
(XLV)
Py
Py
-HI
- NH3
2I⊖

the bisquaternary salt (XLIV) of the three-unit condensation product (with elimination of ammonia). When this new product was treated with pyridine, the dinuclear cyanine (XLV) was obtained. This dinuclear cyanine was also obtained directly in 70% yield when the hemicyanine (XLVI) and 1,3-di-iminoisoindoline were heated in boiling pyridine with 2-picoline ethiodide.

4-Picoline ethiodide, 2,6- and 2,4-lutidine ethiodide, lepidine ethiodide, and 2-methylbenzothiazole ethiodide were each used in similar condensations with the appropriate hemicyanine.

These dinuclear monazacyanines are sparingly soluble in alcohol and pyridine, and they can be recrystallized from these solvents. The crystals have a marked bronzy metallic sheen and contain alcohol or water of crystallization. The cyanine (XLV) is not hydrolysed by boiling concentrated hydrochloric acid but forms a hydrochloride. This has a light absorption identical with the bisquaternary salt, and on recrystallization from pyridine the original cyanine could be again generated. Chromatography on an alumina column is a powerful tool for purification of these compounds which have intense light absorption maxima in the visible region giving blue coloured solutions in methanol.

The long-wavelength absorption maxima (with extinction coefficients) for the hemicyanines (Chapter 1) and the dinuclear cyanines are listed in Table 4. In general the dinuclear cyanines have long-wavelength absorption maxima about 200 mμ further to the red than the corresponding hemicyanines and the tinctorial values are much higher.

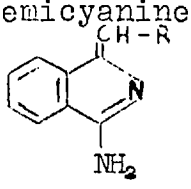
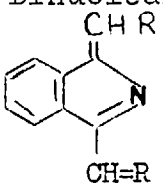
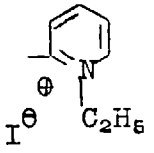
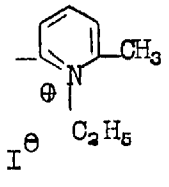
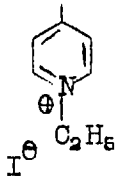
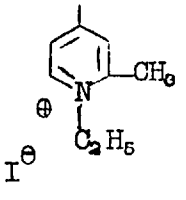
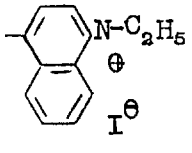
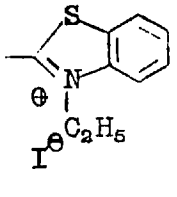
A few detailed points in this work are considered under the following sub-headings:-

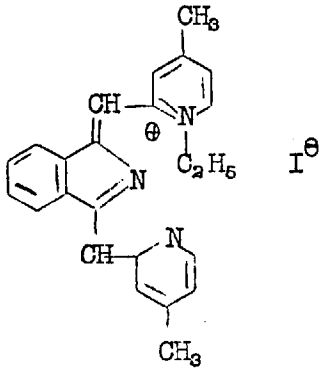
The Pyridine Series

The cyanine derived from 2-picoline has λ_{max} 615 mμ, E = 58,000 whilst that from 4-picoline has λ_{max} 660 mμ, E = 115,000. This structural change causes a 45 mμ bathochromic shift and the extinction coefficient has doubled. Strong absorption at 370 mμ is also developed.

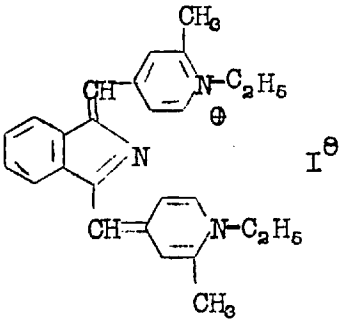
The cyanine derived from 2,4-lutidine has more than one possible structure. However, it has already been concluded from light absorption data that the 4-methyl group of 2,4-lutidine ethiodide condenses with diiminoisoindoline, rather than the 2-methyl group. Consequently the structure (XLVII) for the cyanine is regarded as most likely to be correct. Support comes

Table 4

Type of Nucleus, R	Hemicyanine 	Dinuclear 	Comparison between dinuclear cyanine and hemicyanine
	428 mμ E_1 = 16,000	615 mμ E_2 = 58,000	187 mμ E_2/E_1 = 3.5
	415 mμ E_1 = 16,000	618 mμ E_2 = 56,000	203 mμ E_2/E_1 = 3.5
	442 mμ E_1 = 29,000	660 mμ E_2 = 115,000	218 mμ E_2/E_1 = 4.0
	432 mμ E_1 = 16,000	645 mμ E_2 = 58,000	213 mμ E_2/E_1 = 3.5
	478 mμ E_1 = 56,000	735 mμ E_2 = 180,000	257 mμ E_2/E_1 = 3.2
	485 mμ E_1 = 22,000	621 mμ E_2 = 178,000	136 mμ E_2/E_1 = 5.8



(XLVIII)



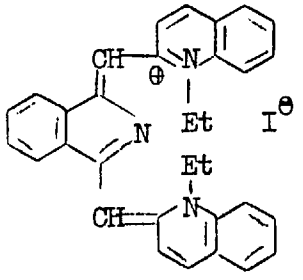
(XLVII)

from further light absorption information. It is seen in Graph **7** and **8** that especially in the ultraviolet region there are two kinds of absorption envelope. One type is characteristic of 2,6-lutidine derivative and the 2-picoline derivative, and the other type is characteristic of the 2,4-lutidine derivative and the 4-picoline cyanine. A strongish absorption band at 372 mμ is present for both the 4-methylpyridine derivative and the 2.4-dimethyl-pyridine derivative with E = 91,700 and 30,000 respectively. No marked absorption band appears at this position in the spectra of the 2,6-lutidine and 2-picoline derivatives. This leads one to believe that the 2,4-lutidine derivative has a 4-position linkage (XLVII) rather than the 2-position linkage (XLVIII). Further support for this conclusion comes from qualitative

observations on the rates of reaction. The preparation of the 4-methylpyridine derivative (XLIX) required 10 hr. of refluxing for completion, the 2-methylpyridine derivative (XLIV) required over 20 hr., whilst the preparation of 2,4-lutidine derivative was completed in 12 hr.

Quinoline Series

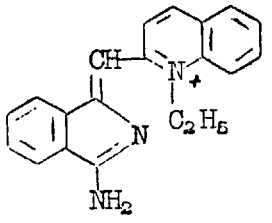
Although lepidine ethiodide reacted similarly to the methyl pyridinium salts to form the dinuclear azacyanine, quinaldine ethiodide failed to give the azacyanine (L).



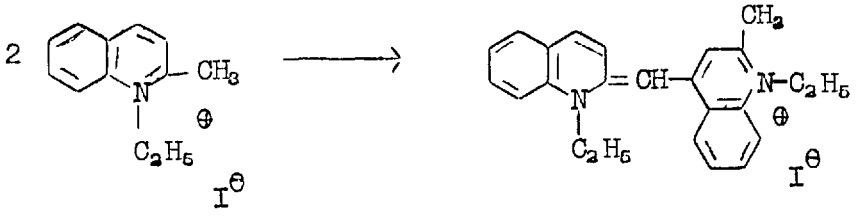
(L)

Instead, the self condensation product (LI) was obtained which has characteristic maxima at 486 and 520 mμ, (literature values are 490 and 523 mμ). (32)

An alternative route to the desired azacyanine (L) was also tried. This consisted in condensing the



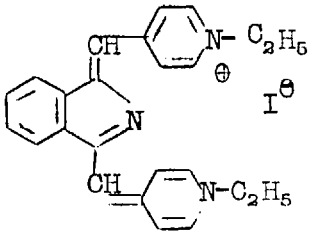
(XVIII)



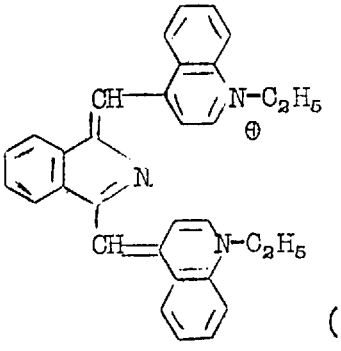
(LI)

amino group of the hemicyanine (XVIII) with 1 mol. of quinaldine ethiodide. The experiment was also abortive. It gave the self-condensation product (LI), and the original hemicyanine (XVIII) was recovered.

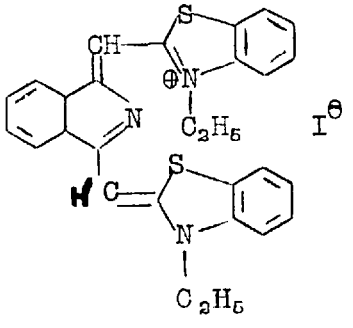
The product from lepidine ethiodide (LII) has λ_{max} 735 mμ, E = 180,000 which is the longest wavelength absorption of all the cyanines studied here. The 4-picoline derivative (XLIX) has λ_{max} 660 mμ, E = 115,000. The effect of annelating a benzene ring with the pyridine nucleus in this case is a 75 mμ bathochromic shift, and the extinction coefficient has about doubled. In the corresponding hemicyanines reported in Chapter 1, annelation of an aromatic nucleus causes either a 30 mμ or a 45 mμ bathochromic shift depending on whether the pyridine ring is attached to the rest of the molecule by the 2- or the 4-position respectively. The bathochromic shift in the dinuclear cyanine (LII) is about twice that in the corresponding hemicyanine (XVIII).



(XLIX)



(LII)



(LIII)

Experimental Section

1,3-Di-(2'-pyridylmethylene)isoindoline 1',1'-diethiodide. (XLIV)

2-Piccline ethiodide (5.0 g.) and 1,3-di-imino-isoindoline (3.0 g.) were heated together in boiling ethoxyethanol (100 ml.) for 17 hr. during which ammonia was evolved. The reaction product precipitated on cooling, m.p. 272-275°, (5.0 g.). Recrystallization from methanol-water gave red needles, m.p. 263-264°, (4.6 g., 63%) of the dihydrate.

Found: C, 44.7; H, 4.1; I, 40.0; N, 6.6; O, 4.7%

$C_{24}H_{19}I_2N_3O_2$ requires

C, 44.7; H, 4.5; I, 39.3; N, 6.5; O, 4.9%.

The three unit cyanine, bis-(1-ethylpyridine-2)-β,δ-(o-phenylene)-γ-azapentamethincyanine iodide, (0.3 g.) was heated with ethyl iodide (0.5 ml.) in nitroethane (5 ml.) in a sealed tube at 120° for 12 hr. A greenish black precipitate was obtained. This compound melted at 121-124°. Recrystallization from water gave red needles, m.p. 263°, (0.2 g.). No depression was observed in a mixed m.p. with the bisquaternary salt prepared above.

Preparation of bis-(1-ethylpyridine-2)- β, δ -(o-phenylene)- γ -azapentamethincyanine iodide (XLV).

a-Picoline ethiodide (m.p. 129-130°, 43%) was obtained by heating a-picoline (9.3 g.) in boiling ethyl iodide (2 ml.).

2-Picoline ethiodide (1.0 g.) and 1,3-di-imino-isoindoline (0.3 g.) were heated in boiling pyridine (20 ml.) for 26 hr. The solution became viscous and green. The solution was evaporated to dryness and the residue redissolved in pyridine. A crystalline precipitate (XLV), m.p. $>400^{\circ}$, (1.0 g. 83%) was obtained.

Found: C, 60.0; H, 5.2; I, 26.6; N, 8.7%

$C_{24}H_{24}I\,N_5$ requires

C, 60.0; H, 5.0; I, 26.4; N, 8.7%.

Note: Ammonia was still evolving at the end of 20 hr. refluxing in pyridine.

This compound was also prepared from 2-(1-amino-3-isoindoleninylidene)methylpyridine ethiodide (XIII); (XIII)(1.95 g.) and 2-picoline ethiodide (1.30 g.) were heated together in boiling pyridine (50 ml.) for 26 hr. The solution remained green in colour and ammonia was still detected after 20 hr. of refluxing. The solution gave a

bronzy precipitate, m.p. $>400^{\circ}$, (2.5 g.) when cooled. It was identified as the monazapentamethincyanine (λ_{max} 407, 615 mμ).

Preparation of 1,3-di(4'-pyridylmethylene)isoindoline 1',1'-diethiodide

4-Picoline ethiodide (2.5 g.) and 1,3-di-iminoisoindoline (0.7 g.) were heated together in pyridine (50 ml.) for 10 hr. during which ammonia was evolved. The solution was cooled in ice and a blackish-brown precipitate was collected, m.p. 330-334°, (1.0 g.). The precipitate was recrystallized from methanol giving bronzy needles, m.p. 295-295.5° (0.8 g.)

Dihydrate:

Found: C, 44.5; H, 4.5; I, 39.3; N, 6.4; O, 4.5;
wt. loss 5.3% @ 150°

$C_{24}H_{29}I_2N_3O_2$ requires

C, 44.7; H, 4.5; I, 39.3; N, 6.5; O, 5.0 .
wt. loss 5.6% for dihydrate.

Preparation of bis-(1-ethylpyridine-4)- β, ε -(o-phenylene)- γ -azapentamethincyanine iodide(XLIX).

The filtrate from this reaction was allowed to pass through an alumina column. Development with

isopropanol gave a yellow, a blue, and a green band (ratio of widths, 1:5:3); each of which was eluted. The blue solution was evaporated to dryness and the solid recrystallized from ethanol to give bronzy blue needles, m.p. 244-245° (0.5 g.)

Hemihydrate:

Found: C, 59.0; H, 5.0; I, 26.3; N, 8.1; O, 1.4%

$C_{24}H_{25}IN_3O_{.5}$ requires

C, 58.8; H, 5.1; I, 25.9; N, 8.5; O, 1.6%.

The yellow solution was evaporated to dryness giving a yellow precipitate which was identified as 1,3-di-(4'-pyridylmethylene)isoindoline-1',1'-diethiodide (λmax 509, 659 mμ). The green solution product was identified as the hemicyanine (XV), λmax 442 mμ.

Preparation of bis-(1-ethyl-6-methylpyridine-2)- β, δ - (o-phenylene)- γ -azapentamethincyanine iodide.

2,6-Lutidine ethiodide (2.6 g.) and 1,3-diiminoisoindoline (1.4 g.) were heated under reflux in propanol (100 ml.) for 24 hr. during which evolution of ammonia was detected. The solution was evaporated to dryness under reduced pressure and the solid was dissolved in chloroform (250 ml.). Chromatography of this solution

on alumina (Spence H) and elution with chloroform afforded a blue, a green and an orange band. Rechromatographing the blue solution on alumina column gave a blue solution which was later evaporated to dryness under reduced pressure. Recrystallization of the product from ethanol yielded 0.1 g., m.p. 248-249°.

Found: C, 61.3; H, 5.7; I, 24.6; N, 8.2%

$C_{26}H_{28}IN_3$ requires

C, 61.3; H, 5.5; I, 24.9; N, 8.2%.

Preparation of bis-(1-ethyl-2-methylpyridine-4)- β, δ -(o-phenylene)- γ -azapentamethincyanine iodide. (XLVII)

2.4-Lutidine ethiodide (2.6 g.) and 1,3-diiminoisoindoline (1.4 g.) were heated under reflux in butanol (50 ml.) for 12 hr. during which evolution of ammonia was detected. The solution was cooled and a black precipitate, (1.8 g.), m.p. 250-275°, was obtained. This black precipitate was recrystallized from ethanol to give brown needles (0.4 g.), m.p. 245-246°. This was identified as the hemicyanine, 4-(1-amino-3-isoindolenylidene)methyl-2-picoline ethiodide (XVII) by elementary analysis and light absorption.

Found: C, 51.6; H, 4.9; I, 33.1; N, 10.3%

$C_{17}H_{18}IN_3$ requires

C, 52.2; H, 4.5; I, 31.0; N, 10.3%.

(λ_{max} 219, 255, 432 mμ).

Chromatography of the filtrate on alumina (Spence H) and elution with chloroform afforded a blue, and a green band. Rechromatographing the blue solution on alumina column gave a blue solution and after it was evaporated to dryness, the precipitate was crystallized from ethanol to give bronzy needles, m.p. 258° (0.3 g.).

Ethanolate:

Found: C, 60.5; H, 5.8; I, 22.5; N, 7.5; O, 2.6%

$C_{28}H_{34}IN_3O$ requires

C, 60.5; H, 6.1; I, 22.85; N, 7.6; O, 2.9%.

Preparation of bis-(1-ethylquinoline-4)- β, δ -(o-phenylene)- γ -azapentamethincyanine iodide (LII).

Lepidine ethiodide (3.0 g.) and 1,3-di-imino-isoindoline (0.7g.) were heated in pyridine for 8 hr. Strong evolution of ammonia gas was detected. The brownish black solution was evaporated to a few ml. and a viscous solution resulted. Attempted crystallization

from ethanol and ethyl cyanoacetate failed.

When the methanol solution was allowed to pass through an alumina column and the chromatogram was eluted with isopropanol, a blue solution was obtained. This solution was evaporated to dryness. Recrystallization from methanol gave blue needles, m.p. 283-284° (0.7 g.)

Monohydrate:

Found: C, 63.7; H, 5.2; I, 20.9; N, 6.6%

$C_{32}H_{30}IN_3O$ requires

C, 64.1; H, 5.0; I, 21.2; N, 7.0%.

Elution of the column with methanol gave a greenish-brown solution. The precipitate from this solution was recrystallized from methanol giving crystals, m.p. 240-241° (0.9 g.). This was identified as the hemicyanine (XIX), λ_{max} 335, 478 mμ.

The hemicyanine (XIX)(0.8 g.) and lepidine ethiodide (0.6 g.) were heated together in pyridine (50 ml.) for 8 hr. A gum resulted when the solution was evaporated to 5 ml. Chromatography on an alumina column gave a blue and a reddish-brown band. The blue solution was identified as that of the three-unit cyanine (λ_{max} 415, 475, 735 mμ). The solution was evaporated to dryness and the precipitate had m.p. 282-284° (no depression with

admixture of a sample of the monazapentamethincyanine (LII) obtained from previous preparations.

Preparation of bis-(1-ethylbenzothiazole-2- β - δ -(o-phenylene)- γ -azapentamethincyanine iodide (LIII).

2-Methylbenzothiazole ethiodide (2.7 g.) and 1,3-di-iminoisoindoline (0.7 g.) were heated together in ethoxyethanol (50 ml.) for 40 hr. A dark brown solution was obtained, with evolution of ammonia. When the resulting solution was cooled, the greenish black crystals were collected. Recrystallisation from methanol gave reddish brown needles, m.p. 334° (0.6 g., 20%)

Found: C, 56.8; H, 4.2; I, 21.1; N, 7.2%

$C_{28}H_{24}IN_3S_2$ requires

C, 56.7; H, 4.4; I, 21.4; N, 7.1%.

Attempted preparation of the corresponding monazapentamethincyanine (L) from quinaldine ethiodide.

Quinaldine ethiodide (3.0 g.) and 1,3-di-iminoisoindoline (0.7 g.) were heated together in boiling pyridine for 5 hr. Ammonia was evolved during the heating. The purple precipitate, m.p. 250-254° (1.5 g.), was collected after the solution had cooled. Recrystallization

from methanol-butanol gave brown needles but these were still impure (elementary analysis). Rechromatography on alumina gave brown needles, m.p. 251-255° (1.0 g., 33% based on quinaldine ethiodide).

Found: C, 60.9; H, 5.5; I, 25.6%

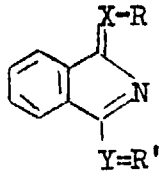
$C_{25}H_{29}IN_2O$ requires

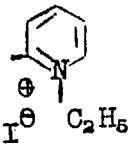
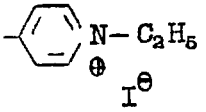
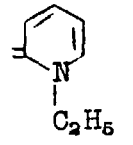
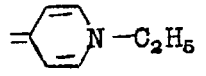
C, 61.2; H, 5.9; I, 25.9%.

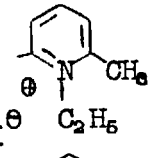
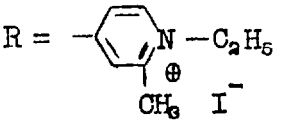
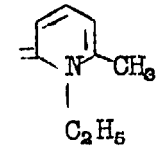
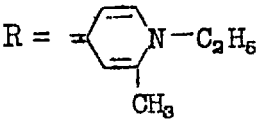
The compound has λ_{max} 221, 258, 335, 486, 520 mμ. Ethyl red with 2-methyl substituent on one of the quinoline nuclei was reported to have λ_{max} 517 mμ (9) was discussed in page 4.

A further attempt to condense 2-(1-amino-3-isoindoleninylidene)methylquinoline ethiodide (XX) with quinaldine ethiodide also failed, and again the Ethyl Red derivative was isolated, (identified by light absorption λ_{max} 486, 520 mμ).

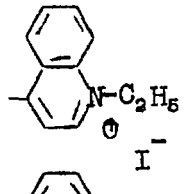
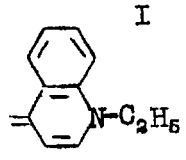
Absorption Data

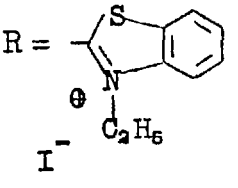
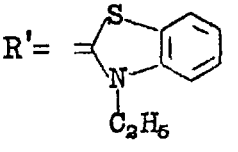


	mμ	E		mμ	E
X = CH	285	45,000	X = CH	222	66,000
Y = CH	285	24,000	Y = CH	278	45,000
R = 	317	22,000	R = 	372	91,700
	385	17,400			
R' = 	407	13,000	R = 	660	115,000
	615	58,000			

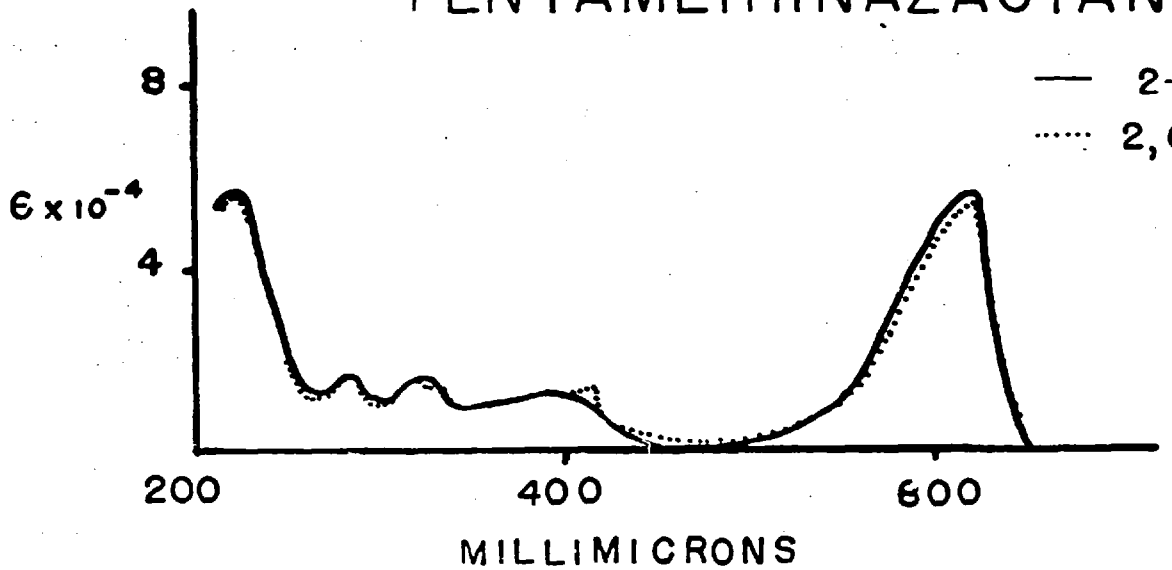
X = CH	215	42,000	X = CH		
Y = CH	286	19,000	Y = CH		
R = 	317	17,700	R = 	222	50,000
	388	15,800		268	26,000
R = 	418	12,500	R = 	372	30,000
	618	56,000		645	58,000

Absorption Data (cont.)

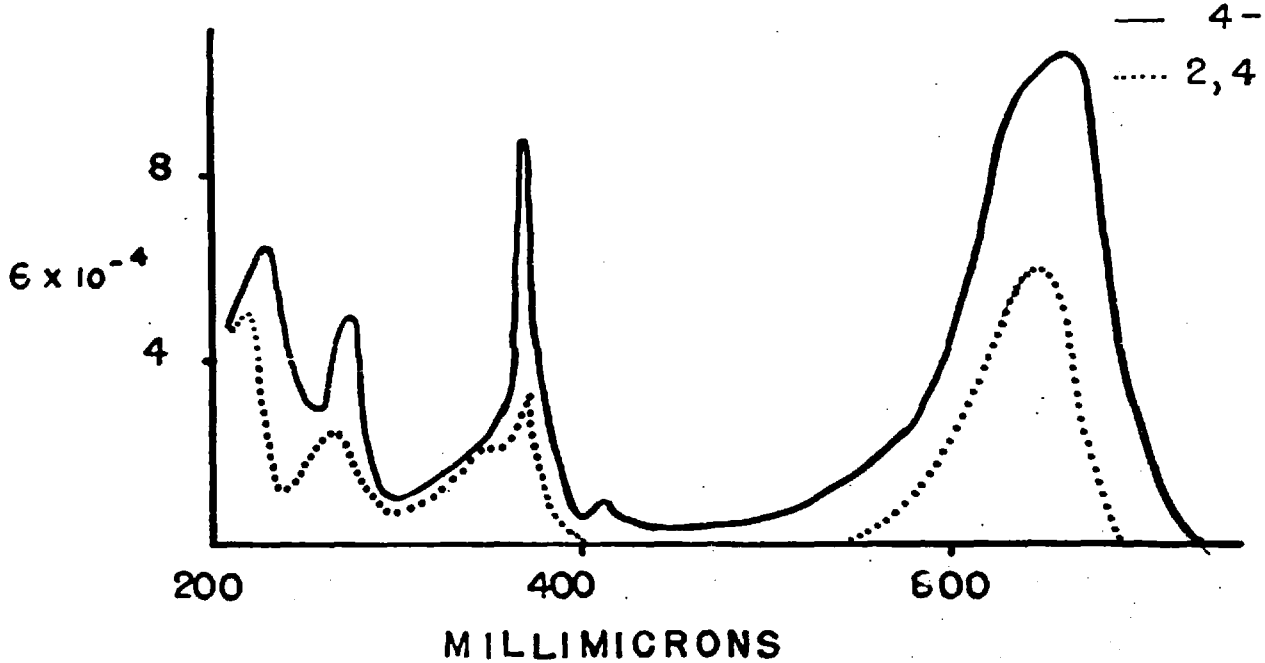
	mμ	E
X = CH	225	76,000
Y = CH	272	35,000
R = 	304	20,000
	334	14,000
R'= 	415	82,000
	475	18,000
	735	180,000

	mμ	E
X = CH	220	39,000
Y = CH	257	22,000
R = 	293	11,500
	330	23,000 (inflexion)
	342	39,000
R'= 	380	18,000 (inflexion)
	402	21,500
	426	24,000
	576	28,500
	621	78,000

PENTAMETHINAZACYANINES

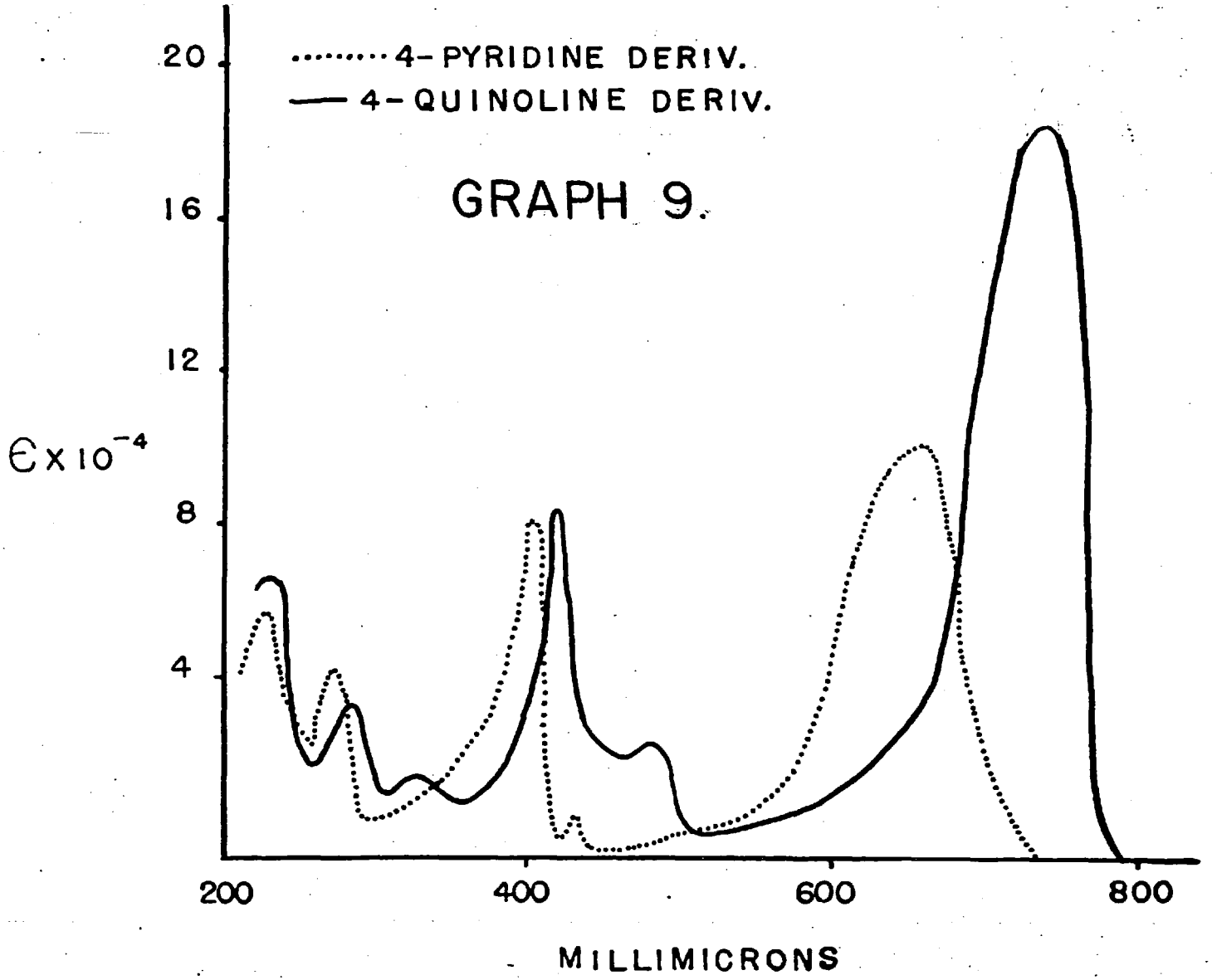


GRAPH 7.



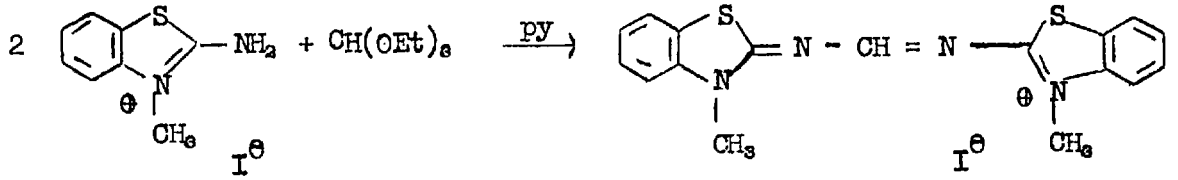
GRAPH 8.

PENTAMETHINMONAZACYANINES.

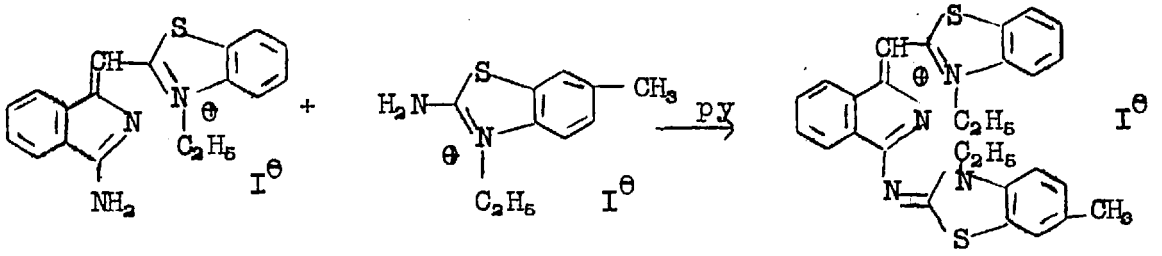


Section B. Asymmetrical Diazacyanines.

The formal substitution of two of the methine groups in the polymethine chain of a cyanine by two nitrogen atoms gives a compound called a diazacyanine. a,a'-Diazatrimethincyanines have been prepared by reacting ethyl orthoformate with two mols of amino-substituted-heterocyclic-quaternary-ammonium salts in pyridine.[33]

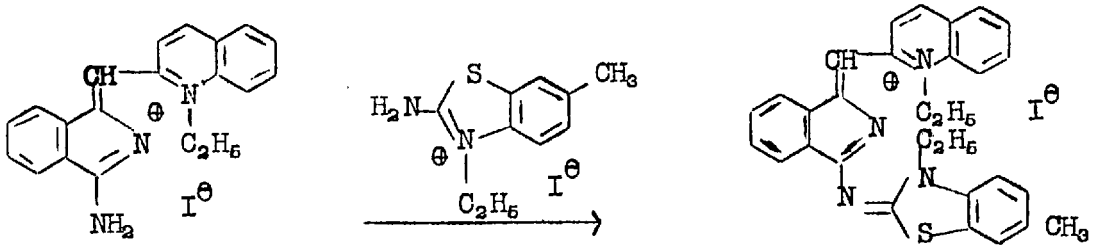


In this connection, 2-amino-6-methylbenzothiazole ethiodide was successfully condensed in boiling pyridine with 2-(3-amino-1-isoindoleninylidene)methylbenzothiazole ethiodide to give (1-ethyl-6-methylbenzothiazole-2)(1'-ethylbenzothiazole-2')β,δ-(o-phenylene)α,γ-diazapentamethincyanine iodide (LIII).



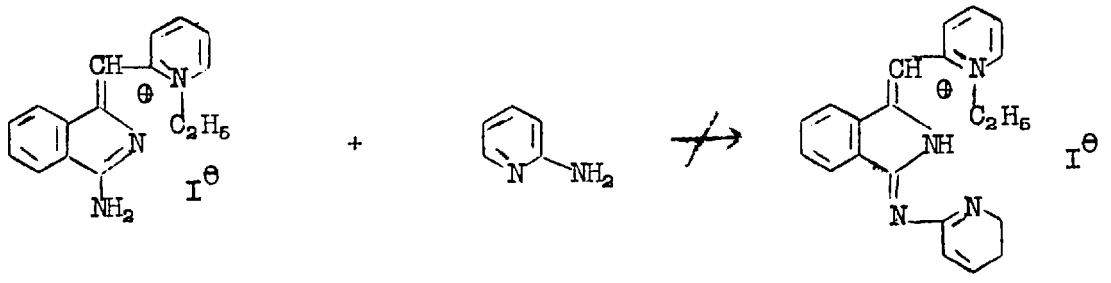
(XX) (LIII)

The resistance of the quinaldine hemicyanine (XVIII) to further reaction with a mol. of quinaldine ethiodide was mentioned in Section 1 of this Chapter. Nevertheless the compound (XVIII) condensed in boiling pyridine with 2-amino-6-methylbenzothiazole ethiodide to yield the diazapentamethincyanine iodide (LIV).



(XVIII) (LIV)

An attempt to condense 2-aminopyridine with the picoline hemicyanine (XIII) failed even in pyridine as a reaction medium. Seventy per cent. of the hemicyanine (XIII) was recovered.



(XIII)

The terminal amino group in the hemicyanines is somewhat unreactive presumably because of the cationic resonance, (it bears a partial positive charge) (Chapter 3). Reaction is only to be expected with groups which have a high electron availability.

The light absorptions of these two asymmetrical diazapentamethincyanines are shown in Graph (10). The similarity between the longest wavelength (first order) absorption bands of these two compounds indicates that the degree of positive charge resonance in the two molecules is of the same order.

This accords with Brooker's finding that in the polymethincyanines the 2-benzothiazole and quinaldine nuclei are almost equivalent chromphorically.[34]

Experimental Section.

The preparation of (1-ethyl-6-methylbenzothiazole-2)(1'-ethylbenzothiazole-2)β,δ(o-phenylene)α,γ-diazapentamethincyanine iodide (LIII).

2(3-Amino-1-isoindoleninylidene)methylbenzothiazole ethiodide (0.4 g.) and 2-amino-6-methylbenzothiazole ethiodide (0.3 g.) were heated in pyridine (20 ml.) The brown solution gradually changed to a violet colour during 2 hrs. heating and a violet precipitate appeared on the sides of the flask. The solution was cooled after 4 hrs. refluxing, and the precipitate, m.p. 400° (0.5 g., 70%), was recrystallized from methanol to give violet flakes, m.p. 230-232°.

Methanolate:

Found: C, 54.5; H, 4.6; I, 19.7; N, 8.8%

$C_{29}H_{29}IN_4S_2O$ requires

C, 54.4; H, 4.6; I, 19.8; N, 8.8%.

This compound was also recrystallized from pyridine when it formed violet needles, m.p. 265-267°, of the hemihydrate.

Hemihydrate:

Found: C, 54.6; H, 4.2; I, 20.5; O, 1.5%

$C_{28}H_{25}IN_4S_2 \cdot \frac{1}{2}H_2O$ requires

C, 54.5; H, 4.2; I, 20.5; O. 1.3%.

The preparation of (1-ethyl-6-methylbenzothiazole-2)(1'-ethylquinoline-2')β,ξ(o-phenylene)α,γ-diazapentamethincyanine iodide (LIV).

2-(3-Amino-1-isoindoleninylidene)methylquinoline ethiodide (0.9 g.) and 2-amino-6-methylbenzothiazole ethiodide (0.5 g.) were heated in butanol (50 ml.) for 17 hr. The mixture did not dissolve and so the butanol was evaporated and replaced by ethoxyethanol (50 ml.). The boiling solution was left refluxing for 4 hr. On cooling the resulting solution gave violet-coloured flakes. They recrystallized from ethanol giving violet flakes, m.p. 249-250° (0.3 g., 25%).

Found: C, 59.6; H, 4.5; I, 21.1; N, 9.4%

$C_{30}H_{27}IN_4S$ requires

C, 59.8; H, 4.5; I, 21.1; N, 9.3%.

Attempted condensation of 2-aminopyridine and 2(1-amino-3-isoindoleninylidene)methylpyridine ethiodide.

2(3-Amino-1-isoindoleninylidene(methylpyridine ethiodide (1.9 g.) and 2-aminopyridine (0.5 g.) were heated under reflux in pyridine (50 ml.) for 14 hr. There was no detectable evolution of ammonia. When the solution had been evaporated to dryness, the precipitate

was recrystallized from ethanol. The starting hemicyanine, 2(1-amino-3-isoindoleninylidene)methylpyridine ethiodide was obtained, m.p. and mixed m.p. 255-257° (1.3 g., 70%).

Hydrolysis of (1-ethyl-6-methylbenzothiazole-2) (1'-ethylquinoline-2')β,δ(o-phenylene)α,γ-diazapentamethincyanine iodide (LIV).

(1-Ethyl-6-methylbenzothiazole-2)(1'-ethylquinoline-2')β,δ(o-phenylene)α,γ-diazapentamethincyanine iodide (0.603 g.) was dissolved in concentrated hydrochloric acid (15 ml.) and the solution was warmed on the steam bath for 20 min. The violet colour gradually discharged to an orange coloured solution. On cooling, light yellow needles separated, m.p. 233-234° (0.091 g.) The filtrate was evaporated to dryness and taken up in 15 ml. of boiling water. The solution was cooled in ice and another crop, m.p. 229-231° (0.085 g.) was collected. The m.p. of a mixture with phthalimide was depressed. The light absorption in methanol is as follows: λ_{max} 207, 241, 320, 402 mμ which was identified as that of 2(1-oxo-3-isoindolinylidene)methylquinoline ethiodide. The filtrate was warmed with 5 ml. of saturated picric acid solution and a yellow precipitate, m.p. 142-145° (0.230 g.) was collected. The admixture with authentic

2-amino-1-ethyl-6-methylbenzothiazole picrate gave no depression in melting point.

Preparation of 2-amino-6-methylbenzothiazole.

p-Toluidine (5 g.) was mixed with a homogeneous paste of cupric chloride (19 g.), potassium thiocyanate (17 g.) and glacial acetic acid (8 g.). The paste was warmed to 40° and kept for 15 min. The colour changed from a brownish black to yellow. After adding one litre of boiling water in three increments, the filtrate was neutralized with ammonia. The precipitate was recrystallized from ethanol and then had m.p. 135° (5.0 g.) (Literature m.p. 134°).

Preparation of 2-amino-6-methylbenzothiazole ethiodide.

2-Amino-6-methylbenzothiazole (6.0 g.) was heated on the steam bath with ethyl iodide (2 ml.) for 4 hr. Recrystallization from methanol gave colourless flakes, m.p. 241-43° (7.1 g., 61%).

Found: C, 37.6; H. 4.3; I, 39.6; N, 9.2%

$C_{10}H_{13}IN_2S$ requires

C, 37.5; H, 4.1; I, 39.6; N, 8.8%.

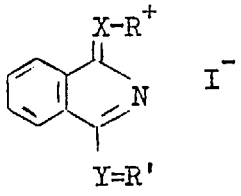
This compound was further characterised as its picrate as follows:

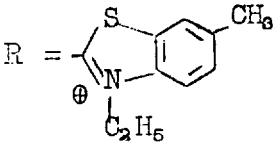
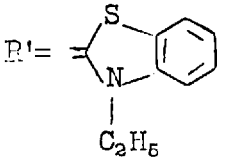
Preparation of 2-amino-1-ethyl-6-methylbenzothiazole picrate.

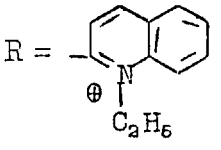
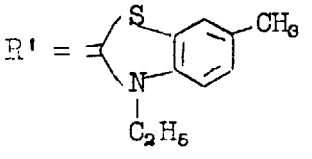
2-Amino-6-methylbenzothiazole ethiodide (1.0 g.) was dissolved in ethanol-water (5-15 ml.) and to it a saturated picric acid solution (5 ml.) was added. After 15 min., the precipitate was filtered off. The yellow precipitate, m.p. 140-142°, was recrystallized from water giving yellow needles, m.p. 144-145° (0.67 g.).

Found: C, 47.6; H, 3.7; N, 16.3% $C_{16}H_{15}N_5O_7S$ requires C, 45.6; H, 3.6; N, 16.6%.

Light Absorption Data

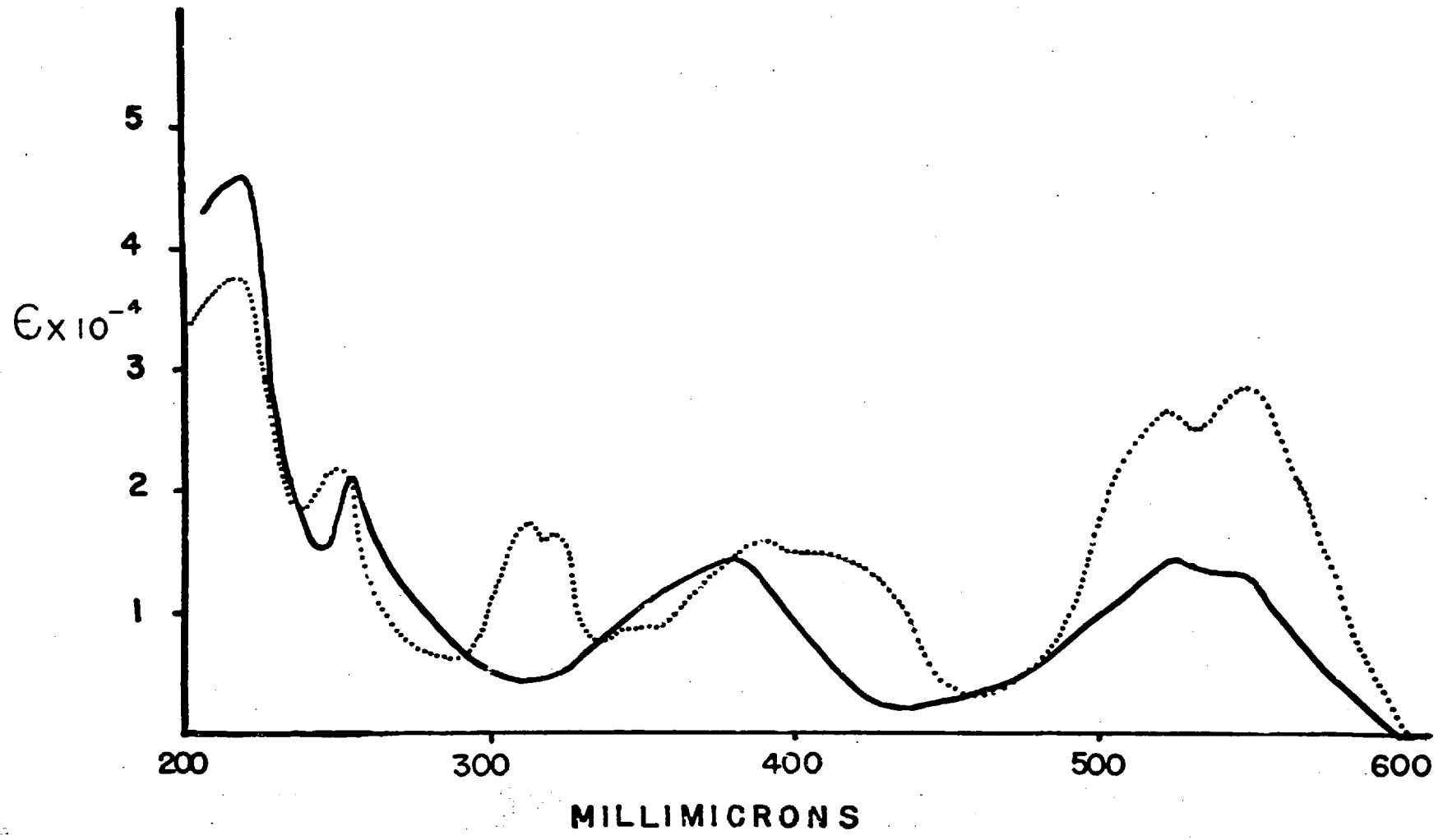


	mμ	E
X = N	217	38000
Y = CH	251	22000
R = 	278	8200
	313	17000
	322	16600
	345	8000
R'= 	390	16500
	426	14500
	527	**26400**
	552	**28500**

	mμ	E
X = CH	220	51000
Y = N	264	21000
	380	12700
	525	14500
R = 	550	14200 (inflexion)
R' = 		

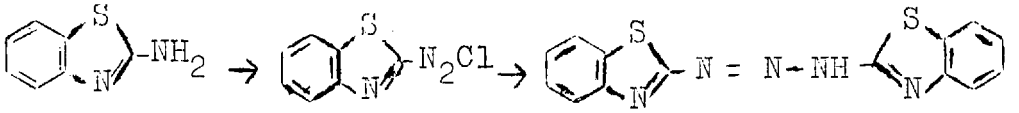
ASYMMETRICAL PENTAMETHINDIAZACYANINES

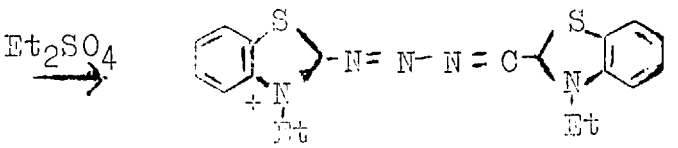
GRAPH 10.



Section C. Triazapentamethincyanines.

A triazatrimethincyanine has been prepared via a diazonium salt intermediate (LV) as follows:- (35)





However, a triazapentamethincyanine with alternate aza and methin links has not been reported before.

During a study of the reactions of 1,3-diiminoisoindoline with primary bases,(21) it was shown that two mols. of 2-aminopyridine condensed smoothly with the imidine to give a 3-unit compound (VI). This with methyl iodide gave a dimethiodide (VII) which, it was thought, might yield a triazapentamethincyanine by loss of the elements of hydrogen iodide. However, the conversion was not demonstrated.

This transformation has now been successfully accomplished and the work has been extended. 4-Aminopyridine, 2-amino-4-methylpyridine, 2-amino-6-methylpyridine, and 2-amino-4-methylbenzothiazole have all been

condensed with 1,3-di-iminoisoindoline in boiling butanol solutions to give the corresponding symmetrical three-unit products.

The 4-aminopyridine derivative (LVI) has m.p. $> 400^{\circ}$ whilst the other four derivatives all melt below 200°. Because this high melting product was so insoluble, no attempts were made to make the corresponding triazacyanine.

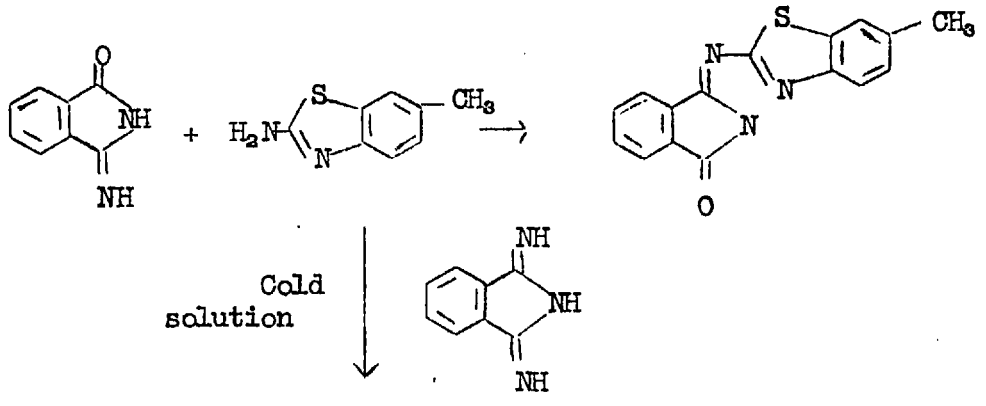
2-Amino-6-methylbenzothiazole was found to be especially reactive towards the imidine. Under mild conditions an adduct (LVII) was obtained without elimination of ammonia. The infrared spectrum confirmed the presence of NH_2 groups (max. at **3349- & 3155 cm^{-1}**). Only once before has similar behaviour been encountered, in the reaction between m-phenylenediamine and the imidine.[36] The present adduct (LVII) was rather more stable and in boiling butanol gave the 3-unit condensation product rather slowly, with evolution of ammonia. In a comparative experiment, 2-amino-6-methylbenzothiazole ethiodide was found to condense readily with 3-imino-1-oxoisoindoline and not yield an adduct in this case.

The second stage in making the triazapentamethincyanines involves quaternization of the correct two nitrogen centres. The 2-aminopyridine derivative (VI)

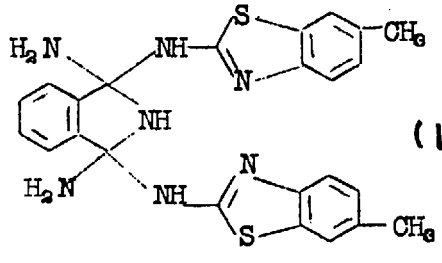
quaternized smoothly with ethyl iodide in a sealed tube at 100°.[21] However, the methyl-substituted-pyridine derivative (LVIII) gave unexpected difficulties. Using similar conditions, i.e. in a sealed tube with an excess of ethyl iodide, a monoethiodide dihydroiodide (LIX) was obtained. Many other reaction conditions were tried and a further account is given in Chapter 5. Successful quaternization to give the desired product was only achieved in nitroethane as solvent, with ethyl iodide at 100° in a sealed tube for 4 hr.

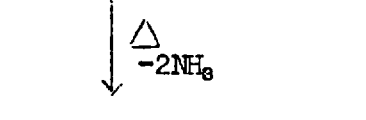
The third stage concerns the removal of the elements of hydrogen iodide. The strong base, sodium ethoxide, gave only 20% yield of the cyanine but when pyridine was used a high yield, 70-80% was obtained.

The red product obtained by heating the 2-amino-6-methyl-benzothiazole-three-unit-product (XXXIV) with an excess of ethyl iodide in a sealed tube at 100° showed, on elementary analysis, 24% iodine. It appeared that the bisquaternary salt was unstable, and indeed on recrystallization from methanol the iodine content dropped further to 19% which is that required for the corresponding triazacyanine methanolate (LX). Later, the light absorption data confirmed that the final product was the triazacyanine.

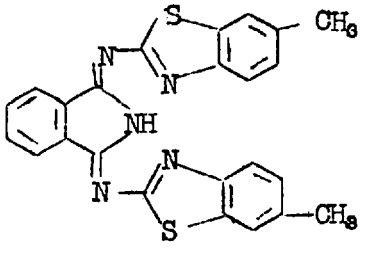


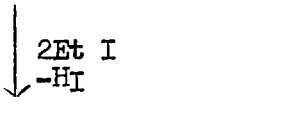
(LVII)





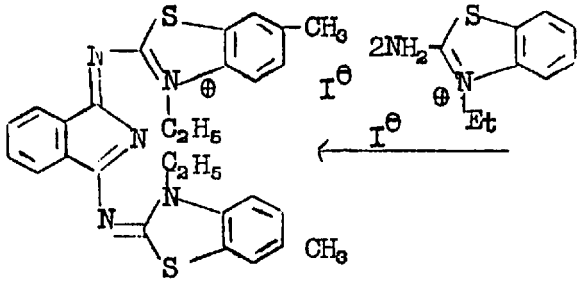
(XXXIV)





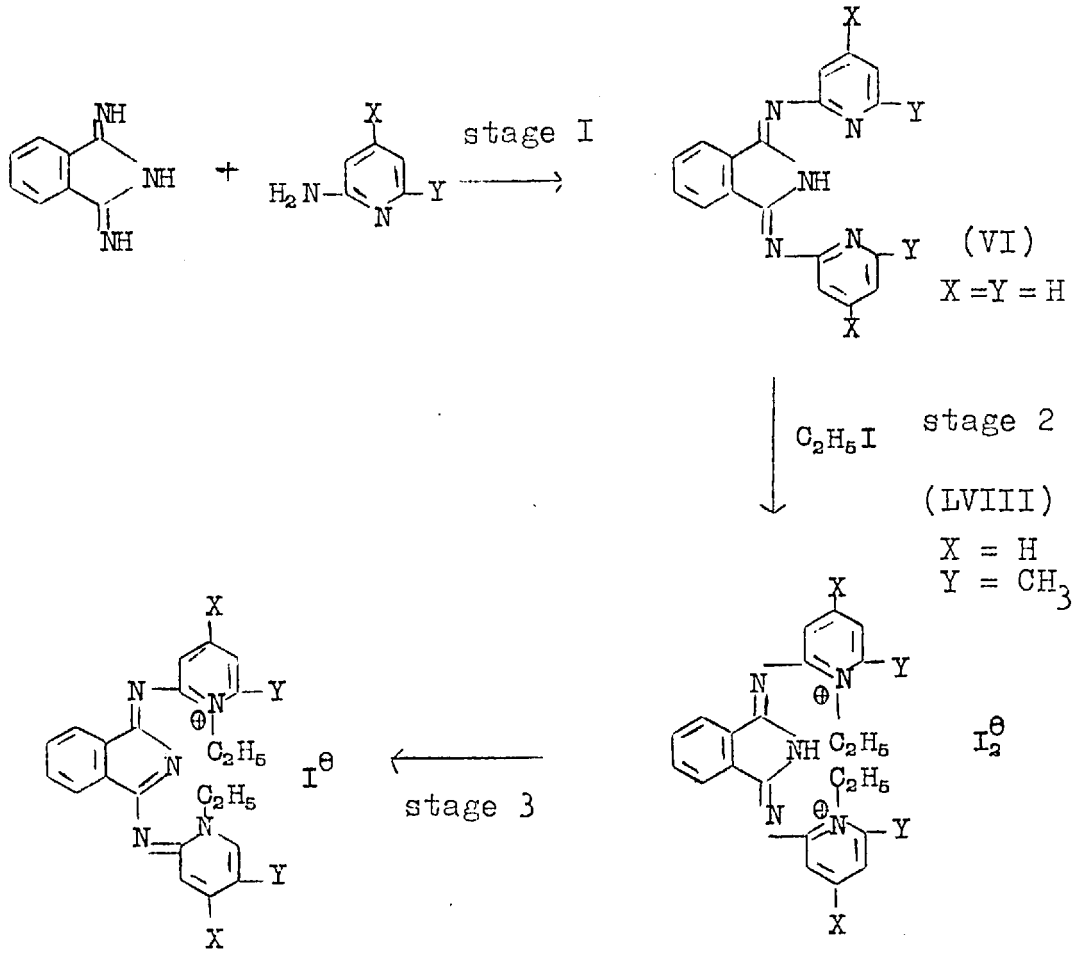
(LXI)

(LX)



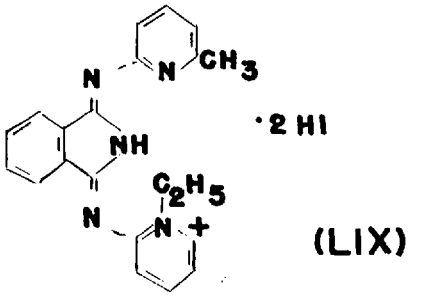
A preparation of the 2-amino-6-methylbenzothiazole triazacyanine (LX) was successfully achieved by mixing methanol solutions of the two amino-substituted-quaternary-ammonium-salt (LXI) and 1,3-di-iminoisoindoline and allowing the combined solution to stand in the dark at room temperature. An 85% yield was obtained in 24 hr. This is in marked contrast to 2-aminopyridine ethiodide which has no tendency to react with 1,3-di-iminoisoindoline even in boiling butanol for 40 hr. (Chapter 3).

The long-wavelength absorption maxima of the 3-unit condensation products, the bisquaternary salts and the cyanines are tabulated in Table V. For the pyridine derivatives, there is only a few mμ shift to the red when a 3-unit condensation product became quaternized, but on changing to the triazacyanine, the long-wavelength maxima shift from the ultraviolet to the visible by 65-74 mμ Similarly the 2-amino-6-methylbenzothiazole derivative shows a 55 mμ bathochromic shift for the change from the 3-unit product to the cyanine.



X, Y may be -H or $-CH_3$

Preparative method for triazapentamethincyanine with extranuclear methyl groups



(LIX)

Experimental Section

Condensation of 1,3-di-iminoisoindoline with 2-aminoquinoline.

2-Aminoquinoline (1.4g.) and 1.3-di-iminoisoindoline (0.7 g.) were heated in dry butanol (20 ml.) for 17 hr. A yellow precipitate was obtained when the solution was cooled. The product was extractively crystallized from carbon tetrachloride to yield yellow flakes, m.p. 197-198°, (0.9 g., 48%).

Found: C, 78.1; H, 4.0; N, 17.7% $C_{26}H_{17}N_5$ requires C, 78.2; H, 4.3; N, 17.5%.

Hydrolysis of 1,3-di(2-quinolylimino)isoindoline.

The three-unit condensation product, 1,3-di(2-quinolylimino)-isoindoline, (0.6 g.) and dilute hydrochloric acid were mixed and the solution was heated to boiling. On cooling, phthalimide separated, m.p. and mixed m.p. 229-230°. Saturated picric acid solution (5 ml.) was added and the yellow precipitate collected, m.p. 256-258° (0.201 g., 1.6 mol.). 2-Aminoquinoline picrate is reported to have m.p. 258°.

Condensation of 3-imino-1-oxoisoindoline and 2-amino-6-methylbenzothiazole.

3-Imino-1-oxoisoindoline (2.4 g.) and 2-amino-6-methylbenzothiazole (2.6 g.) were heated in butanol (50 ml.) for 4 hr. The yellow precipitate, m.p. 268-272° (4.0 g.), was recrystallized from ethanol giving yellow needles, m.p. 288° (2.9 g., 65%).

Found: C, 65.0; H, 3.8; N, 14.3%

Found: C, 65.6; H, 3.9; N, 14.5% $C_{16}H_{11}N_3OS$ requires C, 65.5; H, 3.8; N, 14.3%.

Condensation of 4-aminopyridine and 1,3-di-iminoisoindoline

4-Aminopyridine (1.6 g.) and 1,3-di-iminoisoindoline (1.45 g.) were refluxed together in ethanol (50 ml.) for 24 hr. Ammonia gas was still being evolved after 24 hrs. heating. The solvent was evaporated under reduced pressure, and butanol (50 ml.) added: in 2 hr. a light green precipitate had formed. When the solution was cooled in ice, more of a greyish precipitate, m.p. $> 400°$ (2.8 g.), was obtained. Recrystallization from quinoline gave a colourless powder, m.p. $> 400°$.

Found: C, 71.8; H, 4.4; N, 22.9; O, 0.8%

$C_{18}H_{13}N_5.1/8H_2O$ requires

C, 71.8; H, 4.4; N, 23.1; O, 0.7%.

The Adduct from 1,3-di-iminoisoindoline (0.145 g.) and 2-amino-6-methylbenzothiazole (0.300 g.) were separately dissolved in ethanol (5 ml. each), and the two solutions mixed together. On standing for 17 hr. a colourless precipitate was collected (0.031 g.), m.p. 125-133° (with evolution of gas).

Found: C, 59.9; H, 5.4; N, 19.0; O, 3.1%.

$C_{24}H_{23}N_7S_2.C_2H_5OH$ requires

C, 60.1; H, 5.6; N, 18.9; O, 3.1%.

The m.p. was depressed by 2-amino-6-methylbenzothiazole.

The infrared spectrum showed two strong peaks at 3349 and 3155 cm^{-1} indicating the presence of $-NH_2$ groups. The 3155 cm^{-1} peak was more prominent when the compound was examined in a potassium chloride plate.

The adduct was initially obtained when a butanol solution containing the benzothiazole and the imidine in two to one mol. ratio was heated under reflux for 15 min. A colourless precipitate appeared and later changed gradually from a pale green to a dark green in 30 min. of

heating. Then, on further heating, the precipitate redissolved evolving ammonia to give a brownish-yellow solution. After 4 hr. heating, the three-unit condensation product, 1,3-di-(6-methyl-2-benzothiazoleimino)-isoindoline, began precipitating out of the solution.

Condensation of 2-amino-6-methylbenzothiazole with 1,3-di-iminoisoindoline.

2-Amino-6-methylbenzothiazole (1.2 g.) and 1,3-di-iminoisoindoline (0.6 g.) were heated in boiling butanol (50 ml.). The solution turned greenish in 30 min. and ammonia was strongly evolved. After 3 hrs. refluxing an orange precipitate appeared. After cooling the solution in ice, the solid, m.p. 274-278°, was collected and recrystallized from ethanol to afford orange coloured needles, m.p. 289° (0.8 g., 56%).

Found: C, 66.5; H, 4.2; N, 16.0% $C_{24}H_{17}N_5S_2$ requires C, 66.1; H, 3.85; N, 15.7%.

When this compound was heated with dilute hydrochloric acid a colourless precipitate was obtained which was identified as phthalimide, m.p. and mixed m.p. 230°.

Attempted quaternization of 1,3-di(6-methyl-2-benzothiazolylimino)isoindoline with ethyl iodide.

The base (0.503 g.) and ethyl iodide (1 ml.) were heated in a sealed tube at 100° for 10 hr. The red coloured precipitate, m.p. 330-340° (0.701 g.) was recrystallized from nitrobenzene-ethyl acetate giving red coloured flakes, m.p. 343-345° (0.598 g.). The light absorption spectrum of this compound (λ_{max} 414, 457 (infl.), 500, 535 mμ) was identical with that of the following cyanine.

Preparation of bis-(1-ethyl-6-methylbenzothiazole-2) β,δ (o-phenylene) α,γ,ε -triazapentamethincyanine iodide

1,3-Di-iminoisoindoline (0.3 g.) and 2-amino-6-methylbenzothiazole ethiodide (1.3 g.) were heated together in boiling ethanol(8 ml.) for 4 hr., during which ammonia was evolved. After evaporation of solvent to 2 ml., a red flaky precipitate, m.p. 268-274° (1.0 g., 80%) was obtained. Elementary analysis showed 24.24% iodine. The required iodine content for the bisquaternary salt is 33.78% and the cyanine requires 20.36%. After recrystallizations from methanol the iodine figure had dropped to 18.9% which corresponds to that required

for the cyanine methanolate ($C_{28}H_{26}IN_5S_2.CH_3OH$ requires 19.4% iodine).

In another preparation methanol solutions of 1,3-di-iminoisoindoline (0.3 g.) and 2-amino-6-methylbenzothiazole ethiodide (1.3 g.) were mixed and kept at room temperature. A red flaky precipitate, m.p. 285° (0.2 g., 13%) was collected after half an hour. A second crop was collected after the solution had been kept in the dark for 24 hr. (1.1 g., 71%).

Found: C, 53.1; H, 4.8; I, 19.2; N, 10.4; O, 2.6%

$C_{28}H_{26}IN_5S_2.CH_3OH$ requires

C, 53.1; H, 4.6; I, 19.4; N, 10.7; O, 2.6%.

Hydrolysis of bis-(1-ethyl-6-methylbenzothiazole-2)α,γ ϵ-triaza-β,δ-(o-phenylene)pentamethincyanine iodide.

The triazacyanine (0.5042 g.) was dissolved in ethanol (15 ml.), concentrated hydrochloric acid (15 ml.) was added, and the solution was heated on the steam bath for 40 min. The colour discharged to a pale yellow and on cooling a colourless precipitate was collected, m.p. 233-234° (0.91 g., in two crops). The filtrate was evaporated to dryness and the residue was redissolved in boiling water (15 ml.) and a cold picrate acid solution

(5 ml.) was added. The yellow precipitate (0.271 g.) had m.p. 140-142° not depressed by the authentic picrate, m.p. 144-145°.

1-3-Di-(2-pyridylimino)isoindoline diethiodide.

2-Aminopyridine (4.0 g.) and 1,3-di-iminoisoindoline (3.0 g.) were dissolved in butanol (50 ml.) and refluxed for 10 hr., during which ammonia was evolved. Evaporation under reduced pressure and crystallization of the greenish residue, m.p. 170-183°, from ethanol gave yellow needles, m.p. 183°, (4.2 g.). 1,3-Di-(2-pyridylimino)isoindoline was reported to have a m.p. of 182°.

This three-unit product (1.0 g.) and ethyl iodide (1 ml.) was heated in a sealed tube at 100° for 10 hr. to give a red precipitate, m.p. 250° (1.6 g., 78%). Recrystallization from ethanol gave red needles, m.p. 251° (1.3 g.).

Found: C, 42.9; H, 4.1; I, 41.3; N, 11.6%.

$C_{22}H_{23}I_2N_5$ requires

C, 42.2; H, 3.8; I, 41.5; N, 11.45%.

Conversion of 1,3-di-(2-pyridylimino)isoindoline diethiodide to the corresponding triazapentamethincyanine iodide.

1,3-Di-(2-pyridylimino)isoindoline diethiodide (0.06 g.) was dissolved in dry ethanol (10 ml.) to which sodium ethoxide (.007 g.) was previously added. There was a slight deepening in colour and the solution was warmed on the steam bath for 5 min. The solution was evaporated under reduced pressure to 3 ml. and no precipitation was observed when the solution was cooled in ice. Upon addition of cyclohexane (6 ml.), yellow needles were obtained. Recrystallization from methanol-cyclohexane afforded yellow needles, m.p. 189° (0.01 g., 20%), of the cyanine methanolate:

Found: C, 53.2; H, 4.7; I, 24.6; N, 13.1%

$C_{23}H_{26}IN_5O$ requires

C, 53.6; H, 5.0; I, 24.7; N, 13.6%.

Alternatively, the diethiodide (0.3 g.) was warmed with pyridine (10 ml.) and a deepening of colour was observed. After evaporating the solvent to dryness under reduced pressure, the residue was recrystallized from methanol. Yellow needles were obtained (0.165 g., 65%), m.p. and mixed m.p. 189-190° with the above cyanine.

Preparation of 1,3-di-(4-methyl-2-pyridylimo)isoindoline.

2-Amino-4-methylpyridine (2.2 g.) and 1,3-di-iminoisoindoline (1.4 g.) were refluxed in butanol (50 ml.) for 24 hr. A greenish yellow precipitate was recovered when the solution was cooled in ice. Recrystallization from methanol gave yellow needles, m.p. 159-160° (2.1 g., 60%).

Found: C, 73.0; H, 5.3; N, 31.6%

$C_{20}H_{17}N_5$ requires

C, 73.4; H, 5.2; N, 21.4%.

Hydrolysis of 1,3-di-(4-methyl-2-pyridylimino)isoindoline.

1,3-Di-(4-methyl-2-pyridylimino)isoindoline (0.5 g.) was boiled in dilute hydrochloric acid (10 ml.) for 5 min. On cooling, colourless needles of phthalimide separated, m.p. and mixed m.p. 230-231° (0.09., 0.54 mol.) The filtrate was treated with saturated picric acid solution (5 ml.) and the yellow precipitate formed was recrystallized from water to give yellow needles, m.p. 227-229° (2-amino-1-ethyl-4-methylpyridine picrate has m.p. 225-227°).

1,3-Di-(4-methyl-2-pyridylimino)isoindoline diethiodide.

1,3-Di(4-methyl-2-pyridylimino)isoindoline (3.3 g.) and ethyl iodide (3 ml.) were added to nitroethane (15 ml.). The mixture was heated in a sealed tube at 100° for 4 hr. The orange precipitate, m.p. 233-235° (4.0 g.) was recrystallized from nitroethane to give orange needles, m.p. 253-254° (2.3 g., 30%) of the monohydrate.

Found: C, 42.2; H, 4.0; I, 40.5; N, 10.6%

$C_{24}H_{27}I_2N_5.H_2O$ requires

C, 42.2; H, 3.6; I, 40.6; N, 11.2%.

Generation of the corresponding triazapentamethincyanine iodide from the above bisquaternary salt.

1,3-Di-(4-methyl-2-pyridylimino)isoindoline diethiodide (m.p. 254°, 1.0 g.) was heated in pyridine (50 ml.) for 10 min. and the solution was cooled in ice. Orange-red coloured crystals were found and upon recrystallization from pyridine the cyanine formed red coloured needles, m.p. 225° (0.4 g., 50%).

Found: C, 56.6; H, 5.0; I, 24.8; N, 13.9%

$C_{24}H_{26}IN_5$ requires

C, 56.4; H, 5.1; I, 24.8; N, 13.7%.

Preparation of 1,3-di-(6-methyl-2-pyridylimino)isoindoline.

1,3-Di-iminoisoindoline (3.0 g.) and 2-amino-6-methylpyridine (4.4 g.) were heated together in butanol (100 ml.) for 6 hr., during which ammonia was evolved. After the solution had been cooled in ice, a greenish yellow precipitate, m.p. 120-125°, (5.1g., 75%) was obtained. Recrystallization from methanol-water gave yellow needles, m.p. 148-150° (4.5 g., 66%).

Found: C, 73.4; H, 5.2; N, 20.9% $C_{20}H_{17}N_5$ requires C, 73.4; H, 5.2; N, 21.4%.

Hydrolysis of 1,3-di-(6-methyl-2-pyridylimino)isoindoline.

The three-unit condensation product (0.5 g.) was treated with dilute hydrochloric acid (10 ml.) and boiled for 3 min. On cooling, phthalimide separated, m.p. and mixed m.p. 232-233° (0.08 g., 0.5 mol.). The filtrate was evaporated to dryness and the precipitate was taken up in 10 ml. of boiling water. On cooling, another crop of phthalimide (0.02 g.) was collected. To the filtrate, a saturated picric acid solution (5 ml.) was added and in 10 min. the yellow precipitate, m.p. 220-223° (0.2 g.) was collected. Recrystallization from dimethyl ketone gave yellow prisms, m.p. 228-229°

(2-amino-6-methylpyridinium picrate melts at 226-228°).

Quaternization of 1,3-di-(6-methyl-2-pyridylimino)isoindoline.

The three-unit condensation product (0.5 g.) and ethyl iodide (1 ml.) were heated to 105° in nitromethane (10 ml.) in a sealed tube for 4 hr. Addition of ether to the resulting red coloured solution gave a red precipitate, m.p. 195-200° (0.8 g.). This red precipitate after recrystallization from ethanol afforded orange-yellow needles, m.p. 205-205.5° (0.5 g., 60%) of the bisquaternary salt.

Found: C, 43.2; H, 3.6; N, 11.1% $C_{22}H_{23}I_2N_5$ requires C, 43.2; H, 3.8; N, 11.5%.

Recrystallization from water afforded orange coloured needles of the hydrate, m.p. 205°.

Found: C, 42.9; H, 3.6; I, 40.7; N, 11.4; O, 1.4; loss in wt. at 150° 1.5%.

$C_{22}H_{23}I_2N_5.\frac{1}{2}H_2O$ requires

C, 42.6; H, 3.9; I, 40.9; N, 11.3; O, 1.3; wt. loss for hemihydrate, 1.5%.

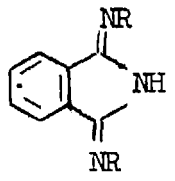
Generation of the corresponding triazapentamethincyanine iodide.

1,3-Di-(6-methyl-2-pyridylimino)isoindoline diethiodide (1.0 g.) was heated in pyridine (50 ml.) for 10 min. and the solution cooled in ice. Orange-red coloured crystals were obtained. Recrystallization from pyridine gave orange coloured needles, m.p. 185-187° (0.2 g.).

Found: C, 56.7; H, 4.9; I, 24.4; N, 13.3%

$C_{24}H_{26}IN_5$ requires

C, 56.4; H, 5.1; I, 24.8; N, 13.7%.

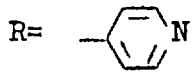


(LVI)

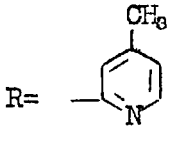
(61) ethanol

R= 

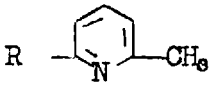
mμ	ε
231	31,300
274	19,800
284	18,500
330	16,900
345	18,300
364	20,500
383	21,800

R= 

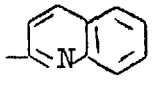
mμ	ε
217	95000
248	54000
257	50000
303	16000

R= 

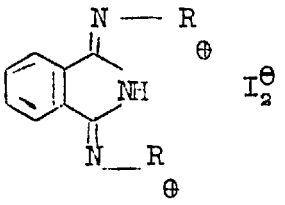
mμ	ε
228	25,000
270	18,100
294*	9,000
335*	8,500
348	13,300

R 

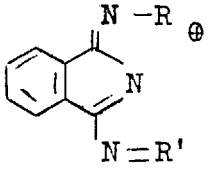
mμ	ε
230	25000
273	18000
340	15000
355	17000

R= 

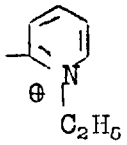
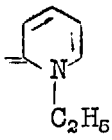
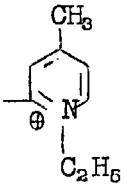
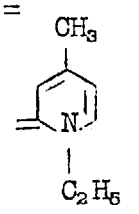
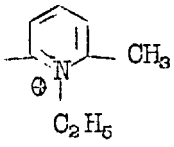
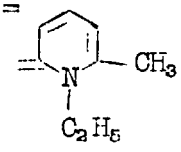
mμ	ε
210	42000
235	35000
340	17000

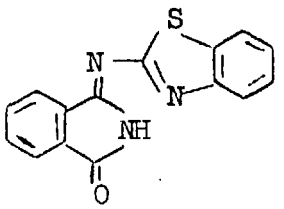


$I_2^{\ominus}$

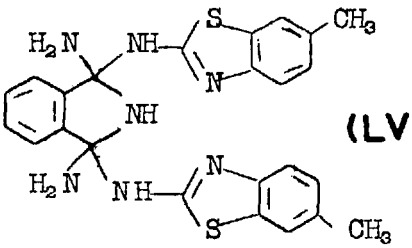


$I^{\ominus}$

		mμ	
R =		222	45000
		290	14000
		340	18000
R =		233	30,000
		270	15,000
		320	11,000
R =		220	45500
		290	23400
		346	24000
R =		220	34,000
		290	18,000
		346	19,500
		405	22,000
R =		225	43000
		294	27000
		350	27000
R =		220	43,000
		332	27,000
		429	27,000

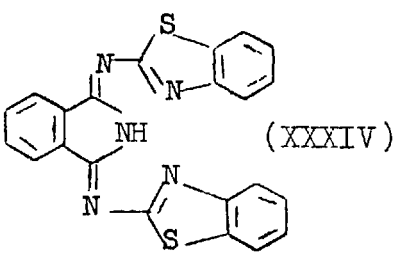


mμ	ε
222	31000
228	28000
260	13000
275	10000
372	17000



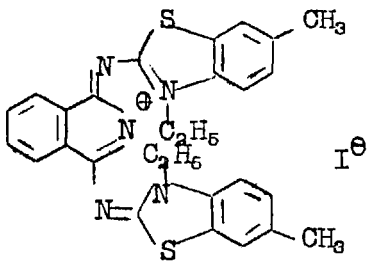
(LVII)

mμ	ε
207	9300
221	9600
224	11000
260	5000
306	1400
320	1300



(XXXIV)

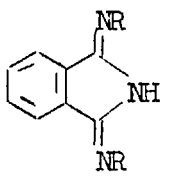
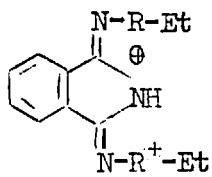
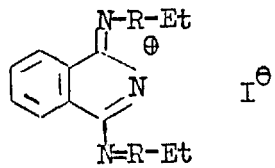
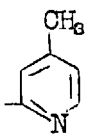
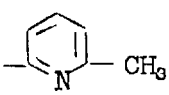
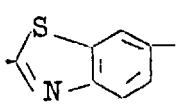
mμ	ε
220	8400
232	15000
281	8300
291	7500
318	3400
362	8200
376	8600
397	8100
421	7600
448	7100
480	4300



(LX)

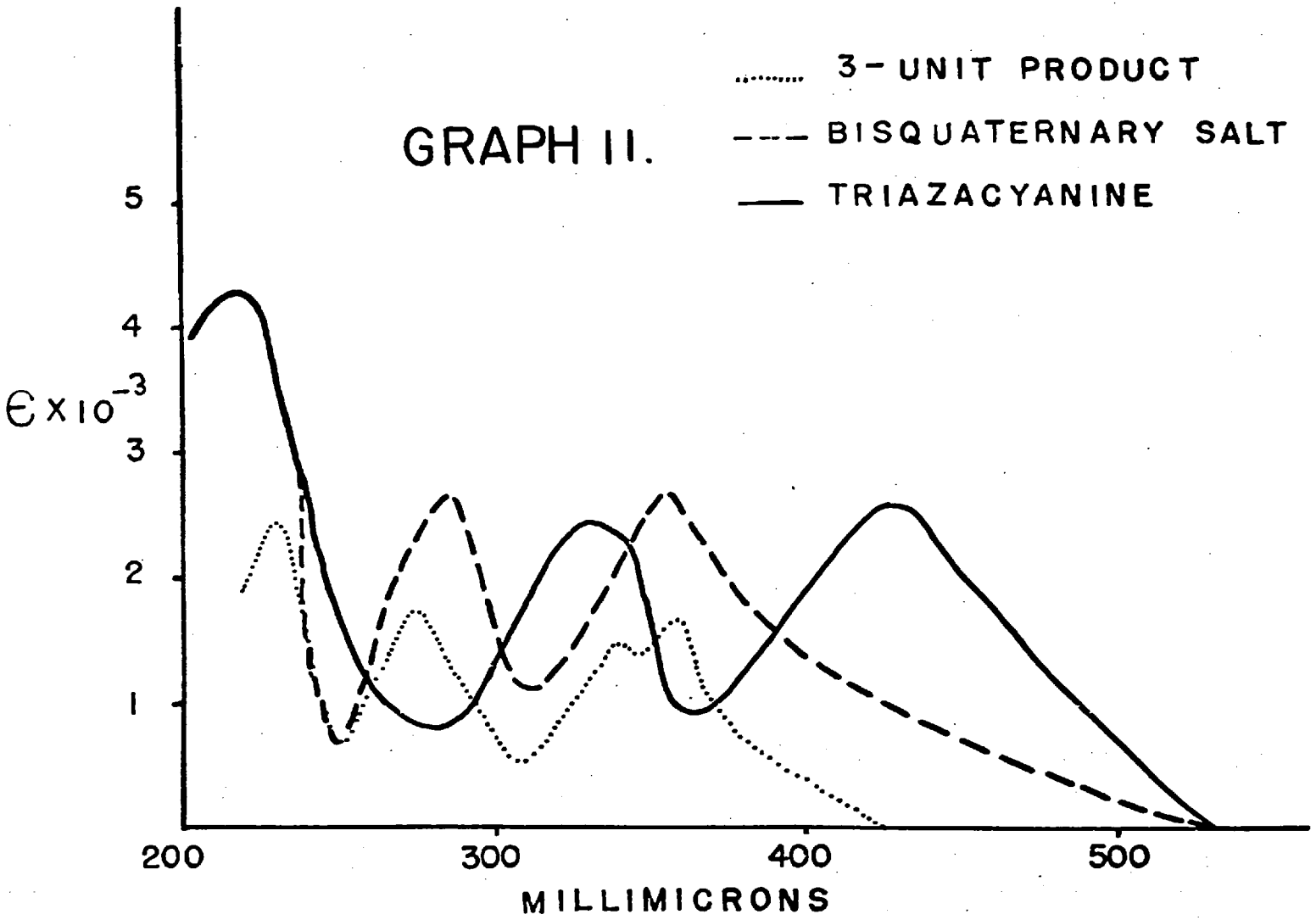
mμ	2 x ε
251	40000
276	16900
292	19000
302	19000
370	25000
392	31000
414	27000
467	27000
500	42000
535	34000

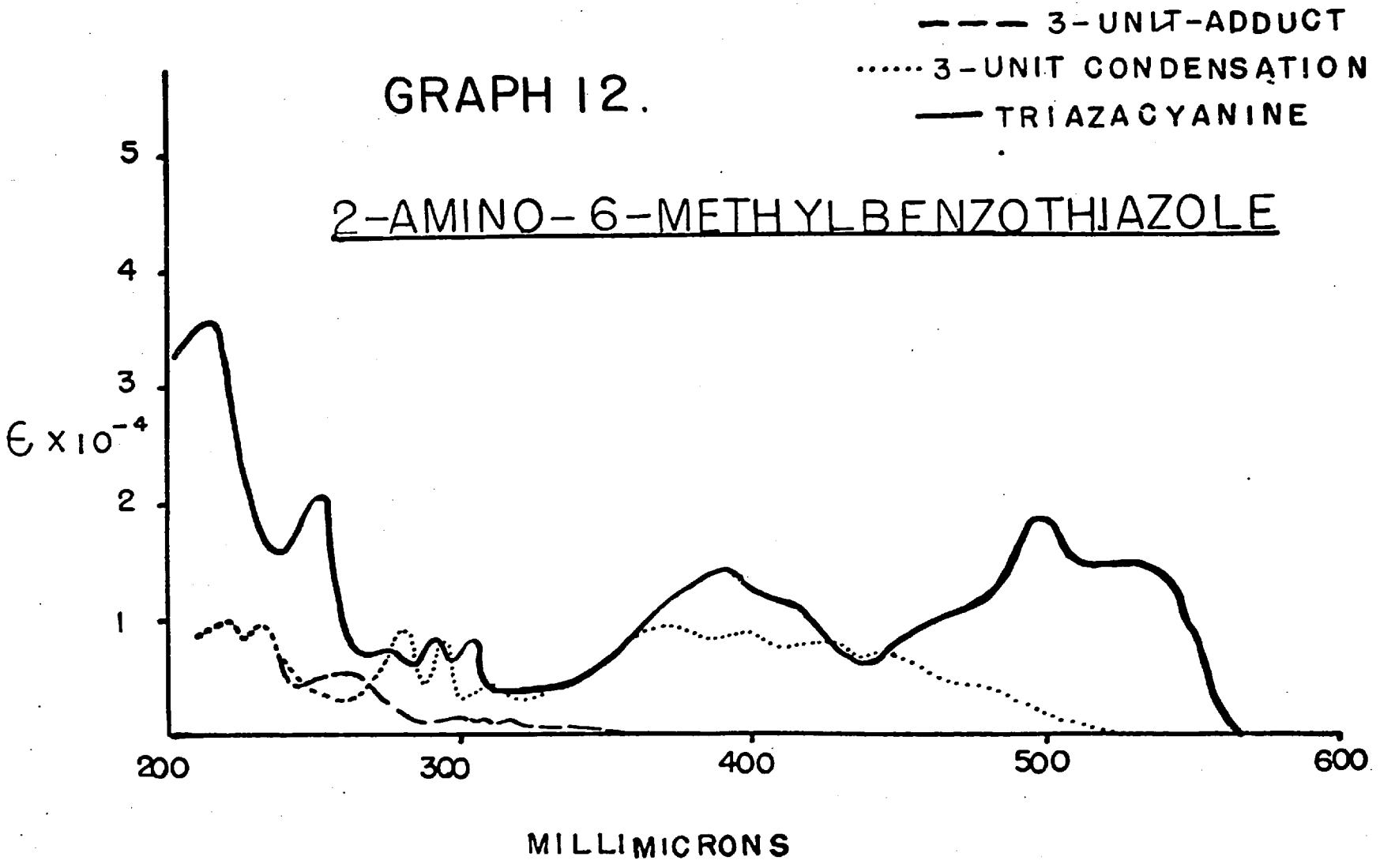
Table V. Long-wavelength Absorption maxima, mμ

Type of Nucleus R	3-unit product 	bisquaternary salt 	Triazacyanine 
	340	346	405
	355	350	429
	480	-	535

PENTAMETHINTRIAZACYANINE

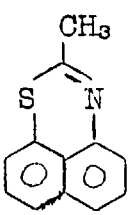
2-AMINO-6-METHYLPYRIDINE DERIV.



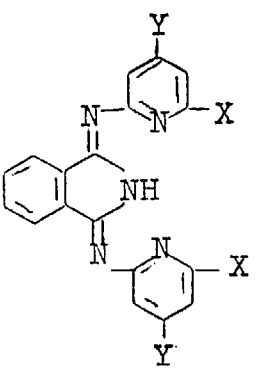

GRAPH 12.
3-UNIT-ADDUCT
3-UNIT CONDENSATION
TRIAZACYANINE
2-AMINO-6-METHYLBENZOTHIAZOLE
5
4
3
2
1
ε x 10⁻⁴
200
300
400
500
600
MILLIMICRONS

Chapter 5. Quaternization reactions.

Quaternization of a tertiary amine either aromatic-heterocyclic or aliphatic in nature is one of the main operations in cyanine synthesis; the former is for cyanines and the latter for hemicyanines. It has been shown that simple quaternary ammonium salts are more readily obtained than quaternary salts of larger molecules having more than two rings. 2-Methylperinaphtho-1,3-thiazine (LXI) resisted quaternary salt formation. In contrast, quinaldine and benzothiazole, for example, are easily quaternized.(37)



(LXI)



X and Y maybe H or CH_3

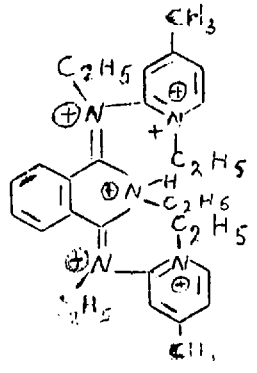
(LXII)

In the present work, the quaternisation of three-unit condensation products (LXII) was performed to produce the corresponding bisquaternary salts. These were needed for two different purposes. Firstly, it was hoped to generate azacyanines from them by loss of the elements of hydrogen iodide. This objective was successfully realised

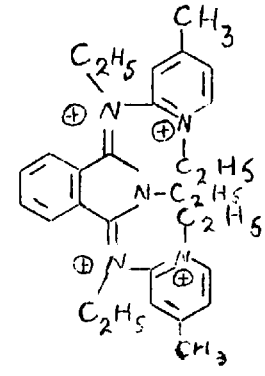
(Chapter 4, Section C.). The second purpose was to activate the extranuclear methyl groups so that they might be condensed with another mol. of 1,3-di-imino-isoindoline or other difunctional reactive compound to form a macrocyclic bisquaternary salt. It was hoped from such products to obtain macrocyclic cyanines (again by loss of the elements of hydrogen iodide). This will be discussed in Chapter 6. In the present Chapter, some abnormalities in the quaternization reactions with ethyl iodide are described.

The three-unit condensation product (LXII; X = CH_3, Y = H), when refluxed with ethyl iodide at atmospheric pressure gave the monoethiodide. In a sealed tube at 100° for 4 hr. with an excess of ethyl iodide, the monoethiodide dihydriodide was formed, which was converted into the monoethiodide by pyridine. The bisquaternary salt (LXIII) was finally obtained by heating the three-unit (LXII) in nitroethane with 2 mols. of ethyl iodide in a sealed tube at 100° for 4 hr. The other three-unit condensation product (LXII; X = H, Y = CH_3) gave the diethiodide (LXIII) in an excess of ethyl iodide in a sealed tube at 100° for 4 hr., and when nitroethane was used a penta-ethiodide was produced. Surprisingly, the penta-ethiodide was recovered unchanged after 1 hr. in

boiling pyridine: it had been expected to lose the elements of hydrogen iodide:-



$I_5^{\ominus}$



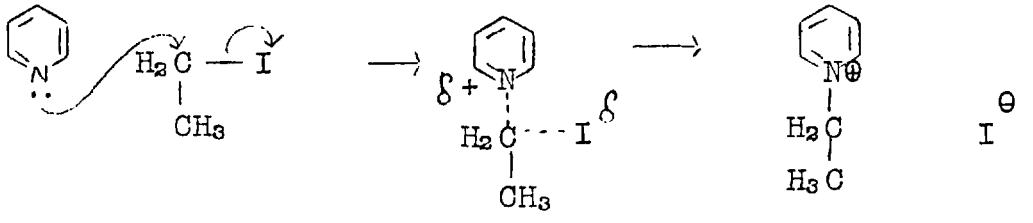
$I_4^{\ominus}$

On acid hydrolysis, N-ethylphthalimide and a picrate with m.p. 193-194° were obtained. 2-Aminopyridine ethopicrate melts at 183-184° and the mixed m.p. was depressed. Hence this picrate with m.p. 193-194° may be the unknown 2-ethylaminopyridine ethopicrate, which would be expected from the hydrolysis.

From these two sets of experiments it seems that a methyl substituent on the 6-position (x) tends to inhibit bisquaternary-ammonium-salt formation, presumably sterically. The inductive effect of the methyl group should assist quaternization, but it has been pointed out that steric effects are often dominant in determining $S_N 2$ reactivity.(38)

The introduction of polar nitroethane (dipole moments: nitroethane, 3.19; ethanol (vapour), 1.68;

ethyl iodide, 1.78)[39] has overcome this steric effect. Possible explanations of the assistance by polar solvents of such nucleophilic displacement reactions have been discussed. It has been pointed out that a polar solvent would tend to stabilize the resultant polar product and would also remove energy from the intermediate activated complex, thus preventing the intermediate from reverting to the starting material.[40] [41]



Experimental Section.

Quaternization of 1,3-di-(6-methyl-2-pyridylimino)-isoindoline.

a. Quaternization in an excess of ethyl iodide (at atmospheric pressure.

1,3-Di-(6-methyl-2-pyridylimino)isoindoline (analytical purity, 1.5 g.) and ethyl iodide (redistilled, 1 ml.) were heated on a steam bath under reflux overnight (14 hr.). Evaporation of the ethyl iodide under reduced pressure gave a red precipitate (2.0 g.), m.p. 227-229°. Recrystallisation from ethanol gave brownish flakes (1.5 g.) m.p. 231-232°. 1,3-Di-(6-methyl-2-pyridylimino)iso-indoline monoethiodide monohydrate.

Found: C, 52.4; H, 4.9% $C_{22}H_{20}IN_5.H_2O$ requires C, 52.7; H, 4.8%.

b. Quaternization in a sealed tube in excess of ethyl iodide.

1,3-Di-(6-methyl-2-pyridylimino)isoindoline (1.5 g.) and ethyl iodide (2 ml.) were heated for 17 hr. at 100°. A brown-coloured precipitate, m.p. 200°, was obtained. Recrystallization from ethanol gave brown

needles (2.5 g.), m.p. 204-205°, of the monoethiodide dihydriodide.

Found: C, 35.5; H, 2.9; I, 52.1; N, 8.9%

$C_{22}H_{22}I N_5.2HI$ requires

C, 35.8; H, 3.3; I, 51.4; N, 9.5%.

When the compound was recrystallized from pyridine the monoethiodide, m.p. 233-233.5°, was obtained.

Found: C, 54.1; H, 4.5; I, 26.6; N, 14.4%

$C_{22}H_{22}IN_5$ requires

C, 54.7; H, 4.6; I, 26.25; N, 14.5%.

The light absorption was the same as that of the product from the reaction of ethyl iodide at atmospheric pressure (λ_{max} 223, 265, 330 mμ).

c. Quaternization in nitromethane with an excess of ethyl iodide in a sealed tube.

The 3-unit condensation product (**LXII**)(0.5 g.), ethyl iodide and nitromethane (5 ml.) were heated in a sealed tube at 105° for 4 hr. The red-coloured product (0.8 g.), m.p. 195-200°, was recrystallized from ethanol to yield yellow needles (0.3 g.), m.p. 205-205.5° of diethiodide.

Found: C, 43.2; H, 3.6; N, 11.2%

$C_{22}H_{23}I_2N_5$ requires

C, 43.3; H, 3.8; N, 11.5%.

The second crop was obtained from the filtrate, and recrystallization from ethanol gave red-coloured needles (0.2 g.), m.p. 237-238°. This product has a light absorption spectrum identical with that of the monoethiodide prepared previously. (λ_{max} 265, 330 mμ), and the mixed m.p. was depressed with the diethiodide. Presumably it is the monoethiodide.

D. Quaternization with an excess of methyl iodide in nitromethane in a sealed tube.

The 3-unit product (0.6 g.), methyl iodide (redistilled, 1 ml.) and nitromethane (5 ml.) were heated in a sealed tube at 100° for 4 hr. A brown precipitate (1.0 g.), m.p. 190-200° was obtained, which after recrystallization from methanol formed yellow needles (0.7 g.), m.p. 205°.

Found: C, 42.9; H, 3.5; I, 40.7; N, 11.4; O, 1.4;
loss in weight @ 150°, 1.5%.

Dimethiodide hemihydrate, $C_{22}H_{23}I_2N_5 \cdot \frac{1}{2}H_2O$ requires

C, 42.6; H, 3.9; I, 40.9; N, 11.3; O.1.3;
loss in weight for $\frac{1}{2}H_2O$, 1.5%.

A mixture with the product from ethyl iodide and nitromethane in a sealed tube, showed no depression in m.p.

A successful preparation of the diethiodide was reported in Chapter 4, Section 3, by using nitroethane as a solvent in a sealed tube for 4 hr.

Quaternization of 1,3-di-(4-methyl-2-pyridylimino)-isoindoline.

The three-unit product (3.3 g.), ethyl iodide (5 ml.) and ethanol (20 ml.) were heated in a sealed tube at 105° for 10 hr., and a brown precipitate (0.72 g.) was obtained. It had m.p. 267-269°, and upon recrystallization from nitropropane gave brown needles, m.p. 265-266°.

Found: C, 32.5; H, 3.7; I, 57.4; N, 7.2; 7.8; 7.7%

Pentaethiodide: $C_{30}H_{42}I_5N_5$ requires

C, 32.5; H, 3.8; I, 57.3; N, 6.3%.

After this compound had been boiled in pyridine for 30 min. and recrystallized from ethanol, the precipitate gave brown needles, m.p. and mixed m.p. 268-269°.

Found: C, 32.35; H, 3.7% $C_{30}H_{42}I_5N_5$ requires

C, 32.5; H, 3.8%.

Hydrolysis of the penta-ethiodide.

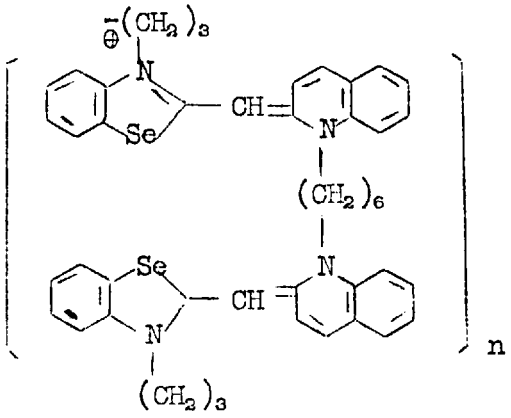
The penta-ethiodide (0.509 g.) was dissolved in methanol (2 ml.) and concentrated hydrochloric acid (10 ml.) was added and the solution was boiled for 10 min. When the solution was cooled in ice no precipitate formed, so the solution was evaporated to 3 ml. On cooling, colourless needles separated (0.010 g.), m.p. and mixed m.p. 77-79° (N-ethylphthalimide, m.p. 77°). The filtrate was evaporated to dryness and the reddish precipitate was taken up in boiling water (10 ml.) to which a saturated picric acid solution (5 ml.) was added. The yellow precipitate (0.19 g.), m.p. 188-189°, was recrystallized from isopropanol to give yellow needles, m.p. 193-194°.

Found: C, 46.4; H, 4.2% $C_{14}H_{15}N_5O_7$ requires C, 46.1; H, 4.1%.

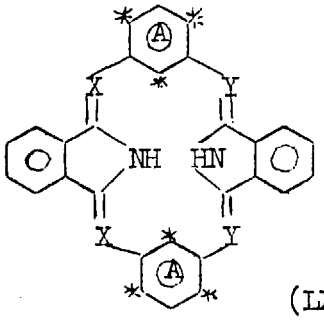
Chapter 6. Macrocyclic Cyanines.

A deviation from Beer's law has been observed for 2,2'-cyanine solution in water and this phenomenon was attributed to aggregation of the cyanine dye molecules.[42] Further support for this explanation came from osmotic pressure and conductivity measurements.[43] It was later found that trimethincyanines exist in unimolecular, dimolecular, and higher aggregation states by the study of their absorption spectra, and for different degrees of aggregation different absorption maxima and sensitizing maxima were observed.[44][45] The aggregate form sensitizes at a longer wavelength.[46]

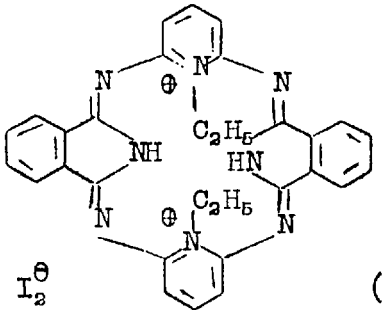
Polymeric cyanines have also been prepared. Active-methyl-substituted bisquaternary salts in which the two cyclic nitrogen atoms were linked by a hydrocarbon radical were used for condensations with other bifunctional compounds to generate polymeric cyanines as shown by the example (LXIV). This polymeric cyanine was claimed to have the ability to extend the sensitivity of silver halide photographic emulsions. Such cyanine dyes were also claimed to give much stronger absorption by the silver halide grains and to prevent the wandering of dyes to adjacent layers.[47]



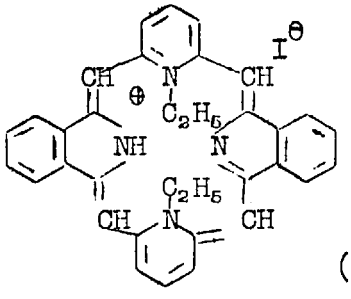
(LXIV)



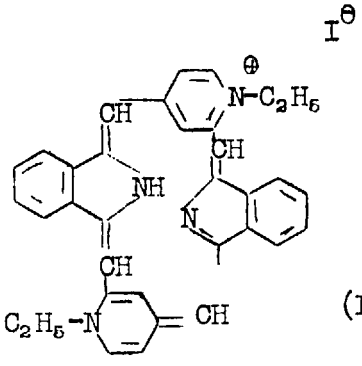
(LXV)



(LXVI)



(LXVII)



(LXVIII)

In view of the above findings, it might be possible to employ a macrocyclic cyanine cation analogous to the porphyrins and phthalocyanines. Since porphyrins and phthalocyanines are known to aggregate rather well under suitable conditions,[48] it would seem that if macrocyclic cyanines of this type were prepared successfully, their physical properties would afford a further test of the aggregation theory.

From the intermediates available in this work, cross-conjugated macrocycles of the general type (LXV)[49] could readily be made where X and Y = N and/or =CH-. For such compounds to be convertible into cyanines (via quaternization and elimination of the elements of hydrogen halide), it is necessary for the rings A to be aromatic nitrogen-heterocycles and it is essential that a hetero-nitrogen atom should be at one or more of the marked positions (*) in each ring. Hence 2,4- or 2,6-disubstituted pyridines or pyrimidines would be suitable intermediates for their preparation.

To begin with, quaternization of the established 2,6-pyridine macrocycle was re-examined. A previous attempt[50] to quaternize this compound by heating with methyl iodide at 100° in a sealed tube was unsuccessful. So further attempts were made by heating the macrocycle in

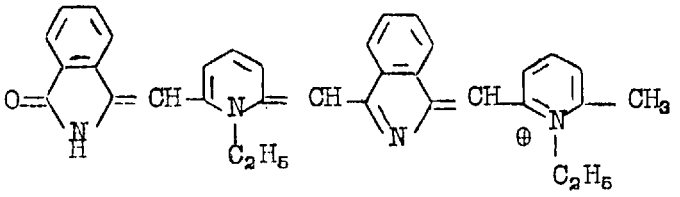
a polar solvent, nitroethane, with ethyl iodide. A brown-coloured alcohol-soluble product was obtained, but purification of this has still to be accomplished. It appears that the quaternization may be feasible, in spite of the obvious steric hindrance. It might be, of course, that quaternization is occurring on the aza links of the large ring, and not on the pyridine nitrogens, as indeed occurs with the benzene and naphthalene macrocycles.(51)

As an alternative approach, the reaction of 2,6-diaminopyridine ethiodide with di-iminoisoindoline in boiling butanol was tried. This afforded a red, water-soluble precipitate, elementary analysis of which indicated that the product had the composition $C_{20}H_{19}IN_6$. This is not intelligible on the basis of the reactants and its constitution remains uncertain. When nitroethane was used as a solvent, a product was obtained which had the correct composition for the macrocyclic bisquaternary salt (LXVI) but a proof of this structure has yet to be obtained.

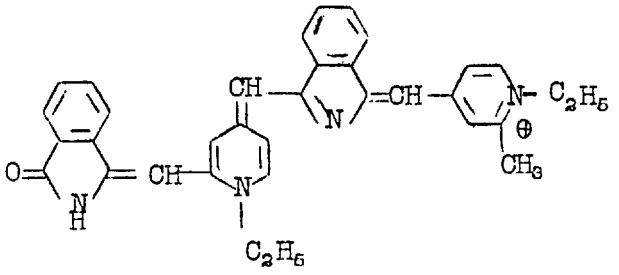
A possible similar extension of the reaction of active-methyl-substituted-quaternary-ammonium-salts with 1,3-di-iminoisoindoline was also examined. This could perhaps lead to the synthesis of macrocyclic cyanines which have methin links and which would have some relation to the porphyrins. It was hoped that such macrocyclic

cyanines might be comparatively soluble and that they would chelate metals. This further phase of work has only just been touched upon.

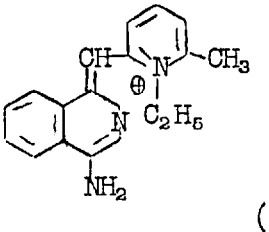
Some attempts to form macrocyclic bisquaternary salts were made by condensing 2,6- and 2,4-lutidine ethiodide with 1,3-di-iminoisoindoline in boiling butanol, pyridine, and in nitroethane. In butanol, prolonged heating (3 days) gave sparingly-alcohol-soluble compounds which showed light absorption maxima at 640 and 660 mμ (from the 2,6- and 2,4-lutidine reactions respectively). The analyses suggested that the two products were hydrates of the expected macrocyclic cyanines (LXVII) and (LXVIII), or alternatively that the products were linear four-unit compounds (LXIX), (LXX). However, a decision has not yet been reached. In pyridine as reaction medium, there were no signs of the formation of macrocyclic cyanines. The products formed were identified as the corresponding hemicyanines (LXXI) and (XVII), dinuclear pentamethinazacyanines (XLVII) and (XLVIII) and a merocyanine (XXVIII). In nitroethane, the reaction product has an interesting light absorption spectrum. Elementary analysis suggests that the product might be the macrocyclic bisquaternary salt, and the similarity of its spectrum with that of the supposed macrocyclic bisquaternary salt from 2,6-diamino-



(LXIX)



(LXX)



(LXXI)

pyridine (LXVI) furnishes some support. However, this work has not been completed for lack of time.

A few attempts were made to cyclise the hemicyanines (LXXI) and (XVII) to macrocycles by heating in nitroethane. The same brown coloured products were obtained as from the reactions of the lutidine ethiodides with di-iminoisoindoline in nitroethane: this was demonstrated by the similarity of the respective absorption spectra.

Yet another approach to cross-conjugated macrocycles which would result in compounds with mixed methin and aza links seemed feasible. It was considered that bisquaternary-salts, which have extranuclear methyl groups, should have some reactivity. If so, they should condense with 1,3-di-iminoisoindoline or another bifunctional compound such as a dialdehyde to form a macrocycle which had two methin and two aza links. A preliminary experiment showed that when the bisquaternary salt (LXII) was heated with 1,3-di-iminoisoindoline, ammonia was evolved and an intense red-coloured solution resulted. Isolation of the product has not been achieved, however.

Experimental Section.

2,6-Lutidine ethiodide (2.6 g.) and 1,3-diiminoisoindoline (3.0 g.) were heated in butanol (50 ml.). The solution changed to a dark green colour in 20 min. and ammonia was evolved. The solution was kept refluxing for 40 hr., after which the black-coloured precipitate was filtered off. (Chromatography of the filtrate gave a green and a red band. The green band was eluted with pyridine but the red-coloured band, which changed brown, was not eluted.) The black precipitate was soluble in acetone, chloroform, acetonitrile and only slightly soluble in pyridine forming a yellowish-green solution. Extractive crystallization of this product gave a black precipitate, m.p. 120-122° (gas evolution and blackening). This precipitate was extractively recrystallized further from butanol (3 times, 28 hr. each) giving a black precipitate, m.p. 212-214° (1.8 g.). Its light absorption (λ_{max} 640 mμ) is quite different from that of the corresponding hemicyanine (λ_{max} 415 mμ), dinuclear cyanine with a terminal AMIDE group, AND THE monazapentamethincyanine (λ_{max} 618 mμ).

Found: C, 62.0; H, 4.6; I, 17.3; N, 8.4; O, 4.8%

wt. loss @ 150°, 2.7%

$C_{34}H_{31}IN_4O.H_2O$ requires

C, 62.2; H, 5.1; I, 19.3; N, 8.5; O, 4.9%

wt. loss for hydrate, 2.7%.

When this compound was dried at 150° for 4 hr., the following elementary analysis was obtained.

Found: C, 63.6; H, 4.7; I, 19.4; N, 9.3%

$C_{34}H_{31}IN_4O$ requires

C, 63.95; H, 4.9; I, 19.9; N, 8.8%.

On further heating (8 hr. at 150°) in vacuum there was no loss in weight.

Condensation in Pyridine

2,6-Lutidine ethiodide (2.6 g.) and 1,3-diiminoisoindoline (1.4 g.) were heated together in pyridine (10 ml.) for 17 hr. during which ammonia was evolved. On cooling, the solution gave a bronzy precipitate (3.0 g.), m.p. 200-208°. This was redissolved in methanol (200 ml.) and chromatographed on alumina. Development with isopropanol afforded separation into a yellow, a blue, a green and an orange band (relative widths 1:4:10:6) which were separately eluted. The green solution (λ_{max} 415 mμ)

was identified as containing the hemicyanine (XIII), the blue solution (λ_{max} 618 mμ) contained the dinuclear monazapentamethincyanine iodide (XLV), and the orange coloured solution (λ_{max} 400, 470 mμ) the merocyanine (XXXVIII).

Condensation in propanol.

1,3-Di-iminoisoindoline (2.9 g.) and 2,6-lutidine ethiodide (5.2 g.) were heated together in propanol (500 ml.) for 24 hr. Ammonia was evolved. Although after 24 hr. ammonia was still being evolved, the green solution was evaporated to 50 ml. and the solution chromatographed on an alumina column. A blue, a green and an orange eluate were obtained by elution with acetone-10% ethanol. The blue solution (λ_{max} 618 mμ) was identified as containing the dinuclear monazapentamethincyanine iodide (XLV), the green solution (λ_{max} 415 mμ) contained the hemicyanine (XIII), and the orange solution (λ_{max} 400, 470 mμ) the merocyanine (XXVIII).

Condensation in nitroethane.

2,6-Lutidine ethiodide (2.6 g.) and 1,3-di-iminoisoindoline (1.45 g.) were heated in nitroethane (250 ml.) for 17 hr. during which ammonia was evolved and

the solution changed from a colourless to a green (2 hr) and then to a brown colour (10 hrs. heating). The solution, after being cooled in ice, was evaporated to dryness under reduced pressure and the residue was taken up in chloroform (200 ml.). This solution was chromatographed on an alumina column: the solution changed to a green colour on the column. The eluted solution was evaporated to dryness and the precipitate was redissolved in methanol. The solution gave a strong absorption at 580 and 630 mμ. but unfortunately no crystalline compound could be isolated.

Condensation of 2,4-lutidine ethiodide and 1,3-di-iminoisoindoline.

a. Condensation in butanol.

1,3-Di-iminoisoindoline (3.0 g.) and 2,4-lutidine ethiodide (2.7 g.) were heated together in butanol (50 ml.) for 28 hr. during which ammonia was evolved. On cooling the solution, a bluish-black precipitate formed (4.0 g.), m.p. $> 370^{\circ}$. The solution was extractively crystallized from butanol to yield a black solid, m.p. $213-214^{\circ}$. This absorbs strongly at 660 and 372 mμ and has another absorption of medium intensity at 258 mμ.

Condensation in pyridine.

2,4-Lutidine ethiodide (2.6 g.) and 1,3-di-iminoisoindoline (1.4 g.) were heated in boiling pyridine (10 ml.) for 7 hr. Ammonia was evolved at first, but finally this ceased. On cooling, a brownish crystalline precipitate (1.8 g.), m.p. 250-275° was obtained. Recrystallization from methanol gave brown needles, m.p. 238°. This was identified as the hemicyanine (XVII) having λ_{max} 432 mμ.

Condensation in propanol.

2,4-Lutidine ethiodide (2.6 g.) and 1,3-di-iminoisoindoline (1.4 g.) were heated in boiling propanol (50 ml.) for 24 hr. during which ammonia was evolved. The solution was cooled and a black-coloured precipitate (1.7 g.), m.p. 233-237° was collected. Recrystallization from methanol gave black needles, m.p. and mixed m.p. 238° which showed λ_{max} 432 mμ, identified as the hemicyanine (XVII).

Condensation in nitroethane.

1,3-Di-iminoisoindoline (1.4 g.) and 2,4-lutidine ethiodide (2.6 g.) were heated together in boiling

nitroethane for 24 hr. during which ammonia was evolved. The green colour which was formed in the first hour's refluxing changed into a brown colour overnight. On cooling, a black precipitate (1.5 g.) m.p. 400°, was obtained. Recrystallization from methanol gave a black precipitate, m.p. > 400° (0.2 g.).

Found: C, 52.8; H, 5.0; I, 29.8; N, 6.9%

$C_{36}H_{38}I_2N_4O_2$ requires

C, 53.2; H, 4.7; I, 31.2; N, 6.9%.

Its light absorption is as follows:

220 mμ, E = 27000; 253 mμ, E = 19000; 311 mμ, E = 14000; 345 mμ, E = 19000; 374 mμ, E = 25000; 450 mμ, E = 18000; 480 mμ, E = 17000; 527 mμ, E = 3000.

Condensation of 2,6-diaminopyridine ethiodide and 1,3-di-iminoisoindoline.

2,6-Diaminopyridine ethiodide (1.3 g.) and 1,3-di-iminoisoindoline (0.7 g.) were heated together in boiling butanol for 30 min. From the cold mixture an orange precipitate was filtered off (0.9 g.), m.p. 268-270° (with evolution of gas). Recrystallization from benzyl alcohol gave orange crystals, (0.4 g.) m.p. 268.5-269.5°.

Found: C, 51.3; H, 4.1; I, 26.6; N, 17.1%

$C_{20}H_{19}IN_6$ requires

C, 51.1; H, 4.1; I, 27.0; N, 17.9%.

When this compound was recrystallized from water it formed a dihydrate.

Found: C, 46.9; H, 4.1; I, 25.1; O, 6.3%

$C_{20}H_{19}IN_5.2H_2O$ requires

C, 47.4; H, 4.6; I, 25.1; O, 6.3%.

Condensation in nitroethane

1,3-Di-iminoisoindoline (0.7 g.) and 2,6-diaminopyridine ethiodide (1.3 g.) were heated together in nitroethane (50 ml.) for 24 hr. during which ammonia was evolved. On cooling the solution yielded an orange precipate, m.p. 274-275° (1.1 g.) Recrystallization from water gave orange-red needles, m.p. 274-275°.

Found: C, 44.2; H, 4.8; I, 31.7; N, 14.35; O, 5.1%

$C_{30}H_{26}I_2N_8.2H_2O$ requires

C, 44.6; H, 4.0; I, 31.5; N, 13.9; O, 6.0%.

Light absorption maxima at 250, 290, 350, 394, 485, 518 mμ.

Preparation of 2,4-dimethylquinoline methiodide.

2,4-Dimethylquinoline (3 g.) and ethyl iodide (5 ml.) were heated on the steam bath with methanol (10 ml.) for 17 hr. The residue was crystallized from methanol giving needles, m.p. 265-266°.

Found: C, 48.7; H, 4.8; I, 42.3; N, 4.8%

$C_{12}H_{14}IN$ requires

C, 58.2; H, 4.7; I, 42.4; N, 4.7%.

Condensation of 2,4-dimethylquinoline methiodide.

1,3-Di-iminoisoindoline (3.0 g.) and 2,4-dimethylquinoline methiodide (2.5 g.) were heated in butanol (100 ml.) for 40 hr. during which ammonia was evolved. A red solution appeared after 1 hr. and after 2 hrs. heating, a red precipitate was observed. On cooling, the red precipitate was collected (2.0 g.), m.p. 229-233°. Recrystallization from pyridine gave red needles, m.p. 253-254°.

Found: C, 58.2; H, 4.5; I, 19.9; N, 9.3; O, 5.9%

$C_{28}H_{22}IN_4O_2$ requires

C, 58.6; H, 3.9; I, 22.1; N, 9.8; O, 5.6%.

Preparation of 4-aminoquinaldine ethiodide.

4-Aminoquinaldine (4.7 g.) and ethyl iodide (4.7 g.) were heated together in a sealed tube at 100° for 10 hr. The precipitate was recrystallized from ethanol to give colourless needles (7.1 g.), m.p. 133-135°.

Found: C, 45.6; H, 5.0; I, 40.5; N, 9.1%

$C_{12}H_{15}IN_2$ requires

C, 45.8; H, 4.8; I, 40.4; N, 8.9%.

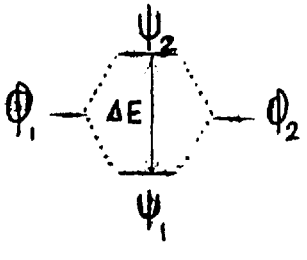
Chapter 7. Light absorption and photographic sensitivity of cyanine dyes containing the isoindole ring.

As reported in previous chapters, hemicyanines, amide cyanines, merocyanines, pentamethinazacyanines, pentamethindiazacyanines, pentamethintriazacyanines, and cyanines containing four heterocyalic units have been synthesized. They are all closely related and contain an isoindole ring as part of the chromophoric path. This new range of cyanine dyes offers an opportunity for testing the existing theories about colour. Some discussion of this is given after an outline of recent theory.

Colour and structure.

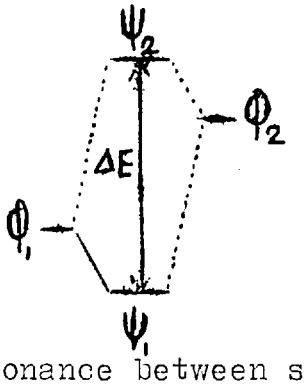
Dewar has pointed out that an understanding of the relation between colour and constitution was not possible until quantum theory had been developed.(52) The number of energy states possible for a molecule is not infinite but limited, and light will be absorbed if the quantum energy of the radiation is equal to the difference in energy between two of the possible states for the molecule (usually a ground state and one of the excited states). Direct consequence of a molecule being a resonance hybrid is a reduction in the minimum

excitation energy, and this reduction is greater the more similar the extreme canonical structures. If a molecule can be regarded as a hybrid of two equivalent structures (wave functions ϕ_1 and ϕ_2), then the quantum mechanical interaction of these gives rise to two possible linear combinations of the original wave-functions, $(\phi_1 + \phi_2)$ & $(\phi_1 - \phi_2)$, respectively. The energy difference between these states, the (quantum-mechanical) interaction splitting, gives the excitation energy. If, however, the two extreme canonical structures are not of the same energy, then the difference in energy between the two possible states ψ_1 and ψ_2 is given by the sum of the interaction splitting and the energy difference between the interacting (i.e. mesomeric) structures. The minimum excitation energy is thus raised and the light absorption will go to shorter wave-lengths. The energy relationships between ground and excited states can be represented approximately as follows:-



Resonance between structures of like energy

Fig. A

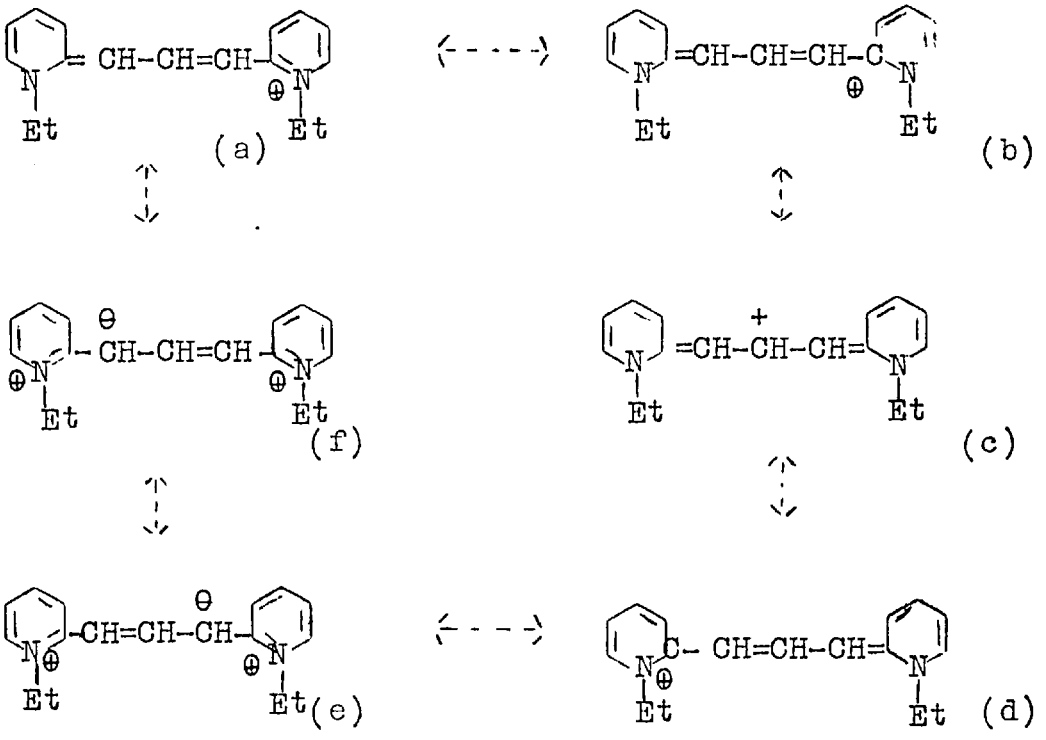


Resonance between structures of unlike energy.

Fig. B

Brooker's work[53] on the cyanine dyes has provided much experimental support. When the end groups ('nuclei') of a cyanine dye are dissimilar, the long-wavelength absorption is not the mean of the absorptions of the two related symmetrical dyes but there is a hypsochromic shift.

However, Pauling[54] and Moffitt[55] have shown that there is a flaw in the simple theory because pairs of extreme structures of the cyanine dye kind cannot 'interact' appreciably but only through a chain of structures in which the formal charges reside on intermediate carbon atoms. For example, besides the two equivalent low energy structures (a) and (d) for the following dye, account must also be taken of the intermediate higher energy structures such as (b) - (c), (e) and (f).



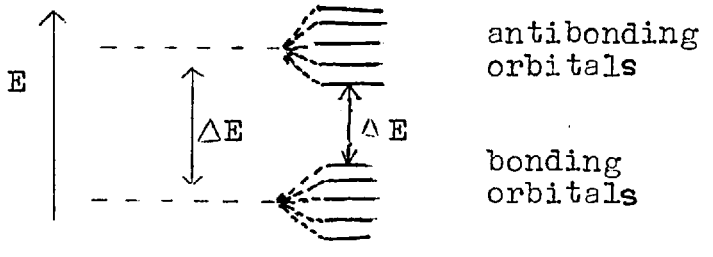


Fig C.

The mathematical treatment then becomes very tedious, but full calculations of this kind have been done.[56] As a result the conclusions drawn from the simple treatment have been justified and two further important results obtained. These are that for symmetrical dyes the wavelength of the first absorption band (longest wavelength band) should increase linearly with increasing chain length, but that for unsymmetrical dyes a limit is approached asymptotically. These effects are indeed observed.[57],[58]

A molecular orbital approach, in which the total electronic energy is taken as the sum of the energies of the individual electrons is easier to apply for quantitative calculations. The energy of excitation of a molecule is taken as the energy required to move a single electron from an orbital which it occupies in the ground state to one of higher energy. For prediction of the effects of structural changes upon light absorption, the mathematical technique of perturbation theory can be applied. This enables changes in molecular structure to be related directly to changes in wave function energy. First applications have been promising.[59]

In the molecular orbital approach, a conjugated hydrocarbon, for example, is first considered as a

collection of two-centre ethylenic π -molecular orbitals - as many as the number of double bonds. All of the π - orbitals have the same two energy levels, corresponding to the bonding and the antibonding state (see Fig. A), and the excitation energy will correspond to the energy difference between the two levels, for in the ground state all of the electrons will be in bonding molecular orbitals. If now the real structure is a mesomeric one, then there will be interaction between all of the molecular orbitals and the interaction splitting will give rise to two sets of orbitals as indicated approximately in Fig. C. The result is a diminution of the minimum excitation energy because the energy of some of the bonding orbitals is raised whilst that of some of the antibonding orbitals is lowered. The effect should increase the more orbitals there are to interact and so the light absorption should shift to longer wavelengths the longer the conjugated system. This result applies only for closed conjugated systems (aromatic hydrocarbons) or for mesomeric systems of the symmetrical cyanine dye type. In a linear polyene, or an asymmetrical cyanine, the resonance is not between equivalent bond structures and so there is some degree of alternation in bond order along the chain, and the ratio of the resonance integrals for any two successive bonds is no

longer unity. This leads to the prediction that the position of the first absorption band converges to a limit with increasing chain length. The theoretically derived equation fits the experimental values very well.

Other relations derived from the theory are also of particular interest in that they bear out experimental findings well. For dyes formally derived from odd alternant hydrocarbons * (i.e. alternant hydrocarbons with an odd number of conjugated atoms) the following rules have been obtained. (1) any positive substituent (+ I, + E) at an active position, or any negative substituent (- I, - E) at an 'inactive' position should have a large hypsochromic effect. (2) Any positive substituent at an 'inactive' position, or negative substituent at an 'active' position should have a smaller bathochromic effect. (3) Replacing carbon by nitrogen has the same effect as a + E substituent at the adjacent position.** (4) Any $\pm$ E substituent anywhere has a bathochromic effect. The terms 'active' and 'inactive' position are convenient labels for

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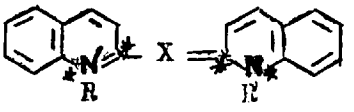
Footnotes: * Molecules in which every other atom can be 'starred' without two stars or two unmarked positions being adjacent. Thus naphthalene is an alternant hydrocarbon but not acenaphthylene.

** This rule is reworded here to avoid an ambiguity.

atomic positions in the dye molecule, an 'active' position being one where the formal charge can be placed by writing principal resonance forms.

The effects of nitrogen atoms within conjugated chains.

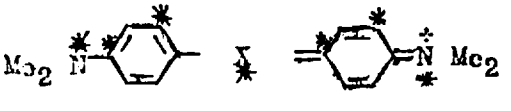
The preceeding, theoretically derived rules indicate that substitution of nitrogen -N= for a methin link in a cyanine dye could have two possible effects depending on the position in the chain. Examples quoted by Dewar(60) illustrate this well. Thus for the dye



(where X = CH, λ_{max} = 523 mμ)

in which the 'active' positions are those starred, replacement of the central methin link by nitrogen (X = N) produces a strong hypsochromic shift (to λ_{max} = 424 mμ). The effect is the same as that of a + E substituent attached to an active position - Rule (1).

For the dye (LXXII)

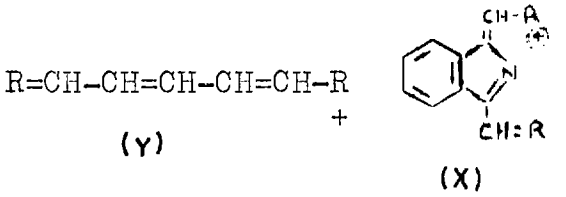


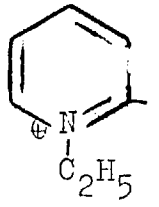
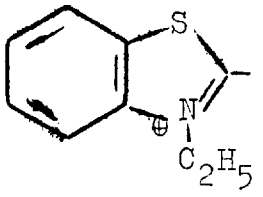
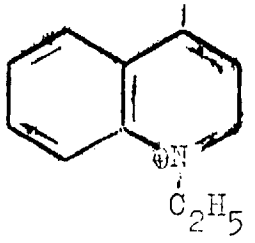
(LXXII)

the replacement of a methin link (X = CH; λ_{max}=610 mμ) by nitrogen (X = N) produces a bathochromic shift (to λ_{max} = 740 mμ). Here the result is equivalent to the attachment of a + E substituent at an inactive position - Rule (2).

In the following Table data for our monazacyanine dyes (in which the aza link is provided by the nitrogen atom of the isoindolenine ring) are listed together with the first absorption maxima of known corresponding methin cyanines.

Table VI Long-wavelength absorption maxima in mμ for pentamethinazacyanines and the corresponding known pentamethincyanines.



	Nucleus, R	Structure (y)	Structure (x)	Difference
(A)		648	615	33
(B)		648	621	27
(C)		810	735	75

Each of our dyes shows a small hypsochromic shift. By Rule (3) the isoindolenine nitrogen atom is effectively to be regarded as a + E substituent attached at an 'active' position. This leads from Rule (1) to the prediction of a strong hypsochromic shift. The phenylene bridging group is a $\pm$ E substituent and by Rule (4) it is expected to produce a bathochromic effect. The nett result should be a medium hypsochromic shift. The fact that the observed shift is only small possibly requires an additional explanation. This can be given in terms of steric hindrance to coplanarity for our dyes, which may also serve to account for the relative difference between our 4-quinoline dye and the 2-pyridine and -benzothiazole examples.

Theory [52] indicates that non-coplanarity can have two consequences. In general it results in a bathochromic effect. It also tends to increase alternation in bond order along the chain, which as already pointed out, results in a hypsochromic effect. This second effect will be more important, the more there is bond-alternation initially. So in unsymmetrical cyanines hypsochromic shifts in the first absorption band will result from steric hindrance to coplanarity whilst bathochromic effects will appear for symmetrical dyes.

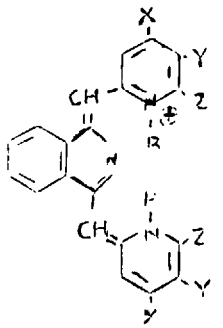
The symmetrical dye (LXXIII) absorbs at 470 mμ. The change in substitution as in (LXXIV) renders the molecule non-planar and it then absorbs 40 mμ to longer wavelength at 510 mμ.(60)

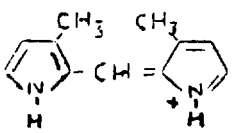
The unsymmetrical dye (LXXV) absorbs at 500 mμ. Here, the introduction of hindrance to coplanarity as in the derivative (LXXVI) results in a hypsochromic shift to 493 mμ.(60)

Our dyes, listed in the second column of the foregoing Table (VI), are symmetrical and so bathochromic shifts are expected to result from any lack of coplanarity, provided this is not so marked as to inhibit resonance altogether. Scale drawings (see Figs. 16 & 18) indicate that there is some hindrance in the 4-quinoline dye (x, C) but that this is less than in either the 2-pyridine dye (x, A) or the 2-benzothiazole dye (x, B).(These two are much alike). None of the reference cyanines (y) shows any lack of coplanarity. Hence the 4-quinoline dye (x, C) should show the least bathochromic shift due to lack of coplanarity, as is indeed the case.

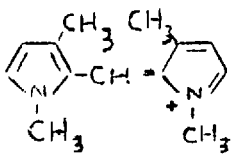
Bis-quaternary salts.

An interesting point arises from the light absorption data for the bis-quaternary salts prepared from

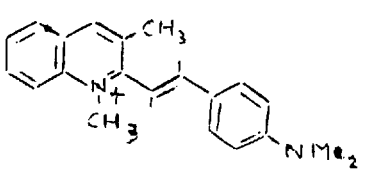




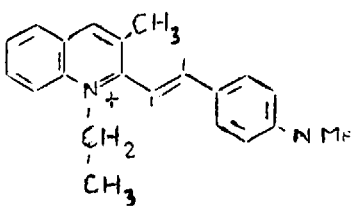
(LXXIII)



(LXXIV)

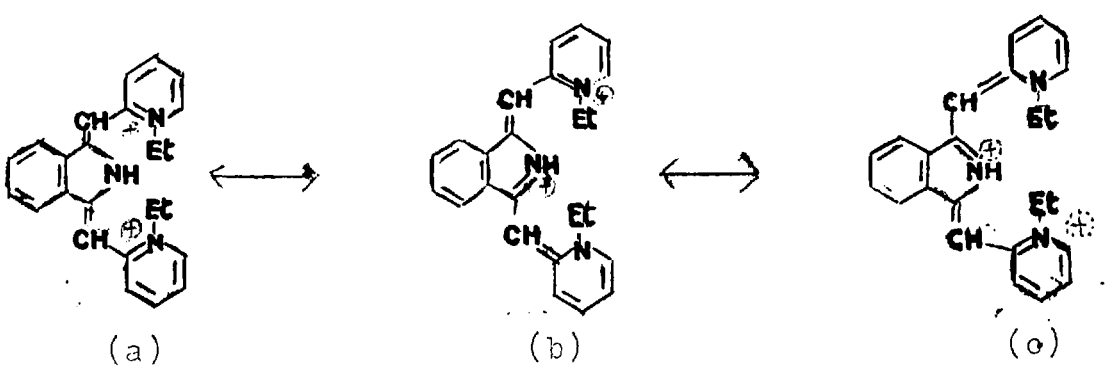


(LXXV)



(LXXVI)

the 3-unit compounds. Each of these bis-quaternary salts shows a first absorption band in the same position as for the corresponding cyanine, but of reduced intensity, and a second, intense band at about 150 mμ to shorter wavelengths. It appears then as if principal resonance forms must be closely related to the two extreme, equivalent canonical forms for the cyanine. Such resonance forms for the bis-quaternary salt can indeed be written as (b) ⟷ (c).



(a) (b) (c)

The similarity in long-wavelength absorption to that of the related true cyanine (x, A) is therefore to be expected.

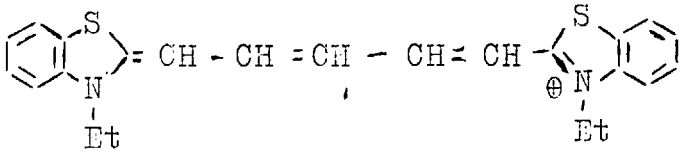
Further, it appears that superimposed on the resonance so far considered is cationic resonance between the nitrogen atoms in rings A and B. This can be written as (a) ⟷ (b) plus (c) ⟷ (a) and it is suggested that the 'interaction' of these shorter cyanine-like chromophores could give rise to the second intense band observed for the bis-quaternary salts.

Benzothiazole series.

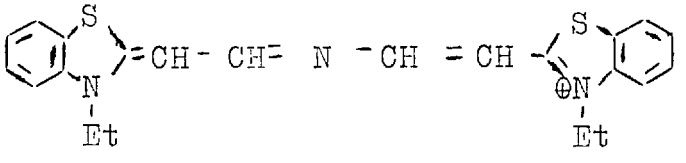
In the benzothiazole series we succeeded in obtaining all representatives of the aza-cyanines which our synthetical methods would allow. These compounds and their first absorption maxima are listed in Table (VII), together with the previously known pentamethincyanine (LXXVII) and symmetrical monazacyanine (LXXVIII) for comparison. [The 6-methyl group in these dyes causes only a very small bathochromic shift as shown by the data for compounds (LXXXII) and (LXXXIII)]. The bathochromic shift observed on going from (LXXVIII) to (LXXXIX) indicates the magnitude of the bathochromic effect (67 mμ) resulting from the ± E bridging phenylene group (Rule (4), above). It is almost two-thirds of the magnitude of the hypsochromic effect of the central aza link which by itself is 94 mu (LXXVII to LXXVIII). The introduction of a further aza link as in (LXXX), however, produces a further hypsochromic shift of only 61 mμ, whilst a third aza link, as in (LXXXI) gives rise to the comparatively small hypsochromic increment of 25 mμ. In each case a hypsochromic shift is expected, from Rules (3) and (1), above but the rapid falling-off in the effect is unexpected. The final dye (LXXXI) is symmetrical, in that respect resembling (LXXIX), and a theoretical hypsochromic shift for each

additional nitrogen in (LXXXI) can be taken as half the difference between (LXXIX) and (LXXXI), which is 86/2 = 43 mμ. The dye (LXXX) is unsymmetrical and so the absorption would not be expected to fall mid-way between the values for (LXXIX) and (LXXXI) but should be shifted hypsochromically, as observed.

In conclusion, it should be mentioned that a selection of the new cyanine dyes described in this thesis has been tested for photographic sensitizing action. With the exception of Compound (LII) which showed a alight sensitizing effect in chlorobromide emulsion at 600-670 mμ, none of the compounds proved of interest in this connection: they were strong desensitizers.

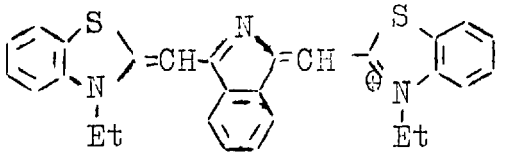
Compound	1st maxima in mμ
	648

(LXXVII)



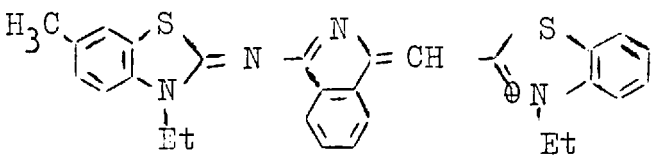
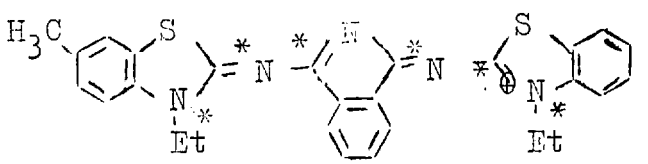
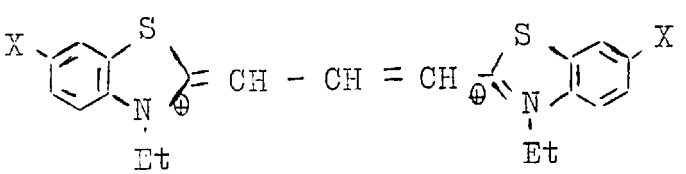
554

(LXXVIII)



621

(LXXIX)

Compound	1st maxima in mu
 (LXXX)	560
 (LXXXI)	535
 (LXXXII), (62) X = H	557
(LXXXIII), X = CH_3	563

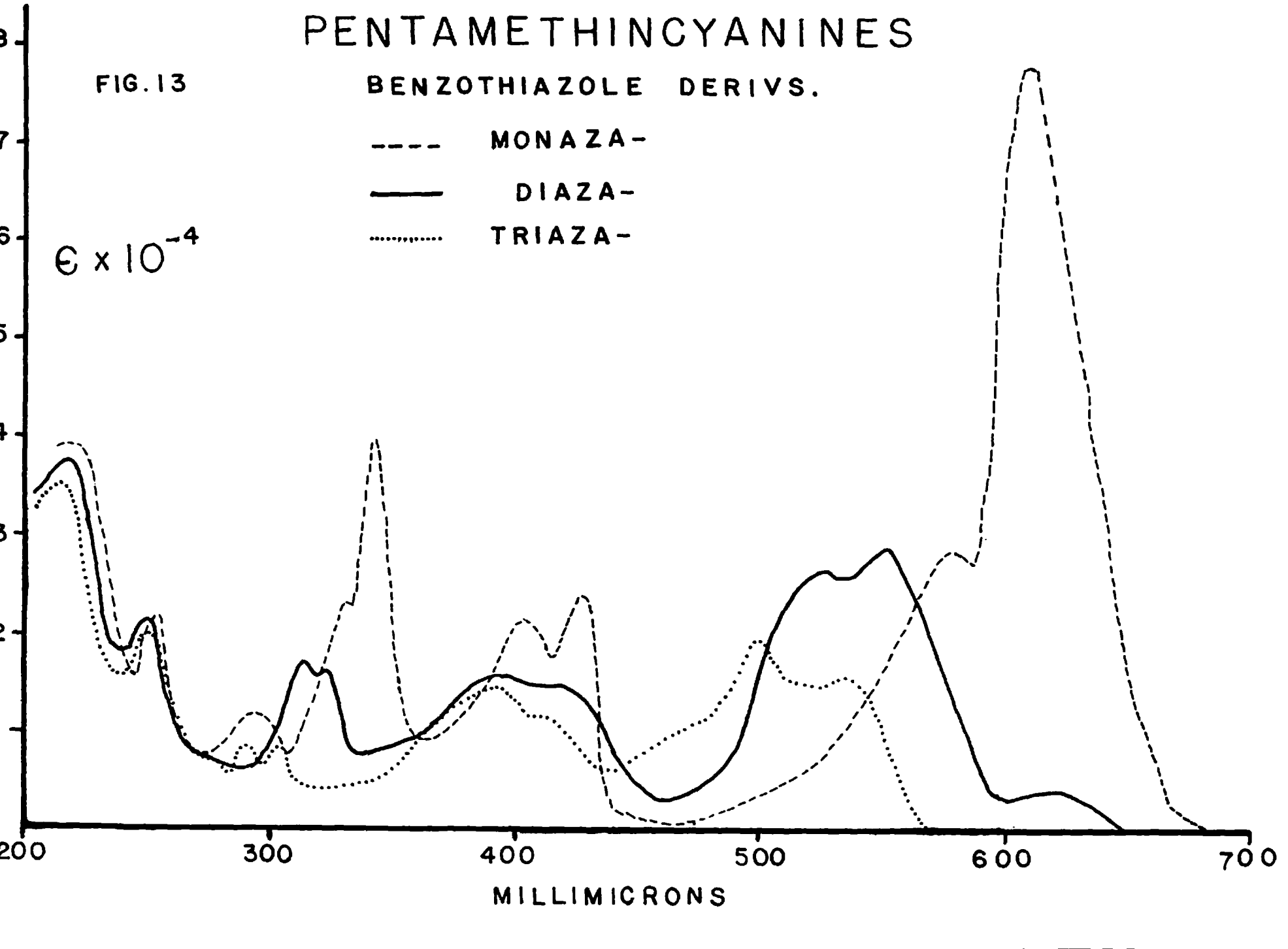
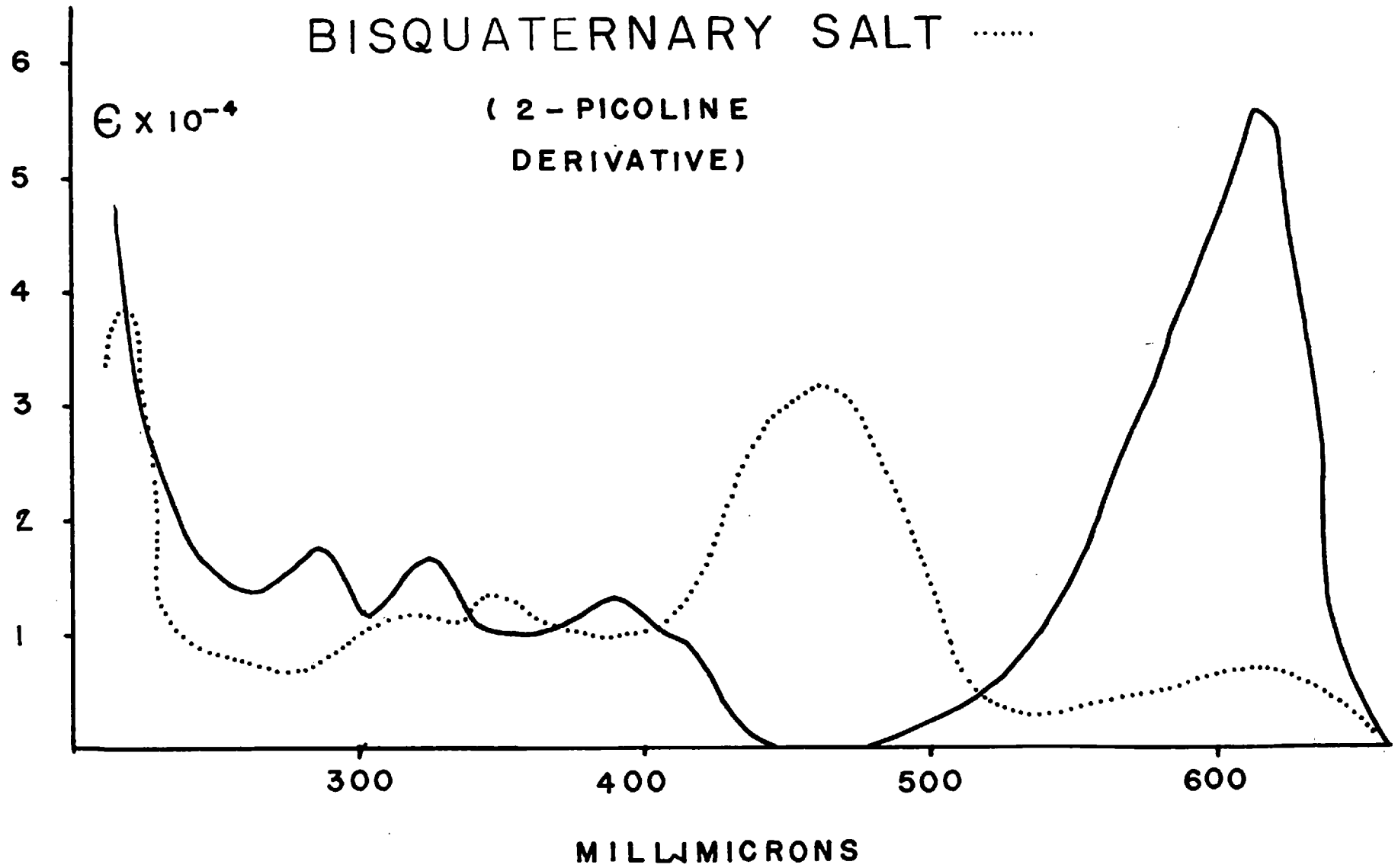
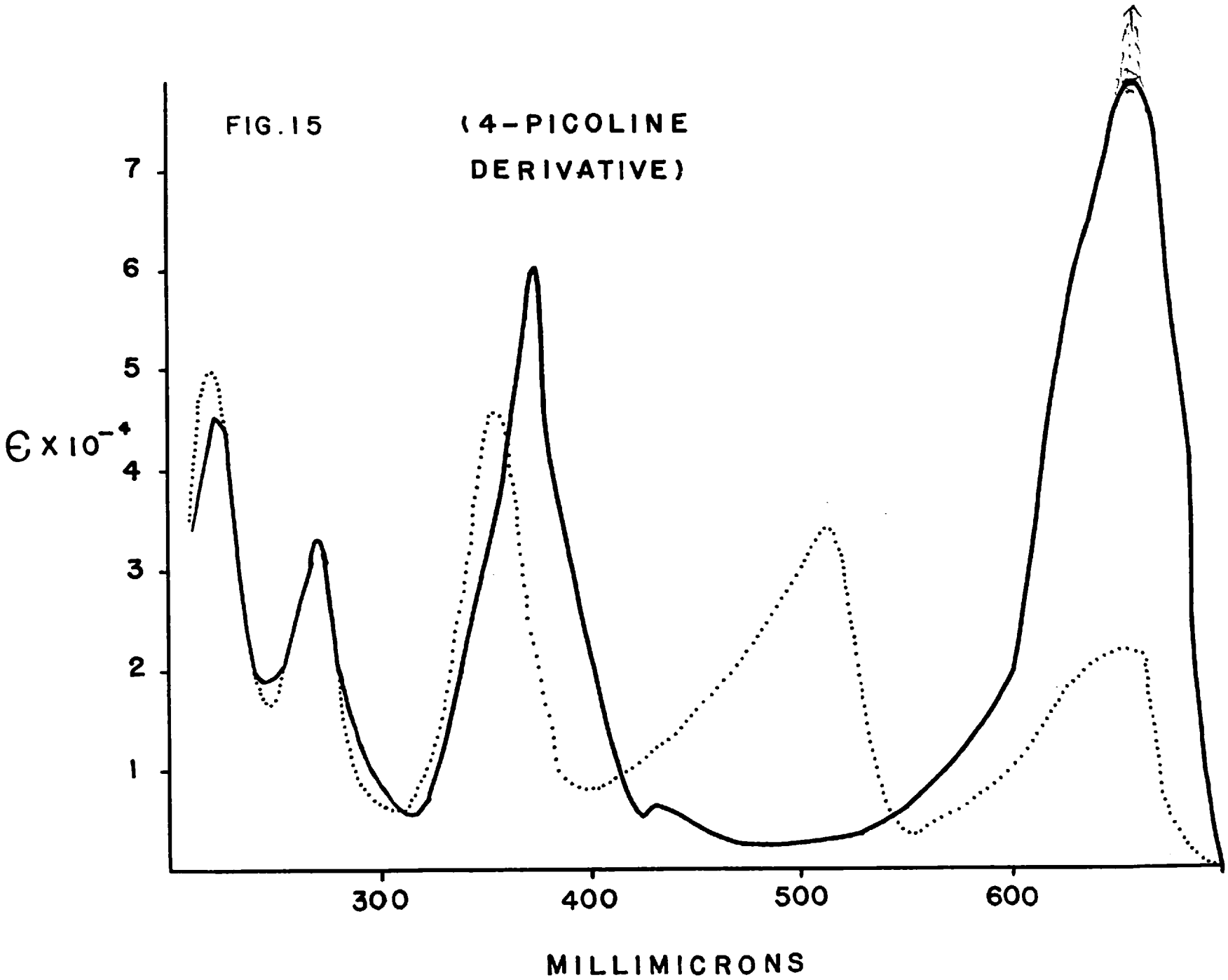

PENTAMETHINCYANINES
FIG. 13
BENZOTHIAZOLE DERIVS.
---- MONAZA-
—— DIAZA-
..... TRIAZA-
ε x 10^-4
200
300
400
500
600
700
MILLIMICRONS

FIG. 14

PENTAMETHINMONAZACYANINES — AND ITS BISQUATERNARY SALT .....




FIG. 15
(4-PICOLINE
DERIVATIVE)
ε X 10⁻⁴
7
6
5
4
3
2
1
300
400
500
600
MILLIMICRONS

PENTAMETINAZACYANINES - STERIC EFFECT

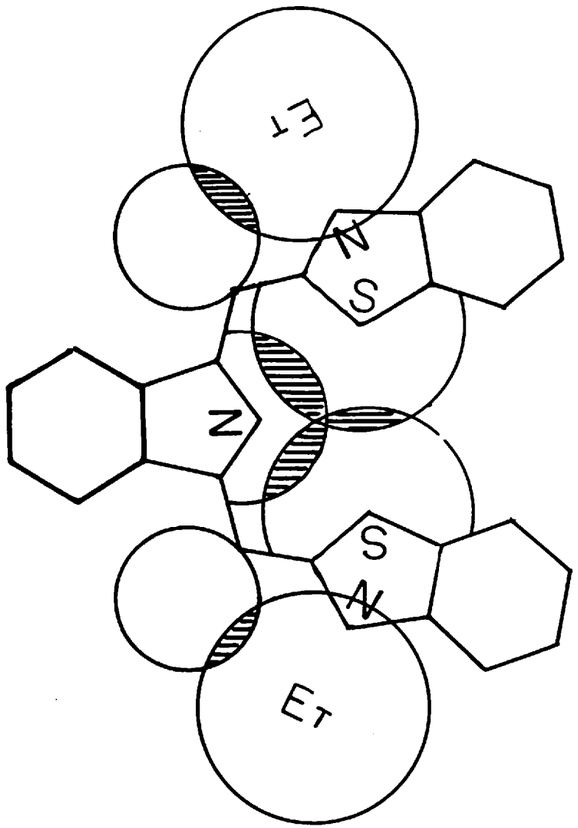


FIG. 16

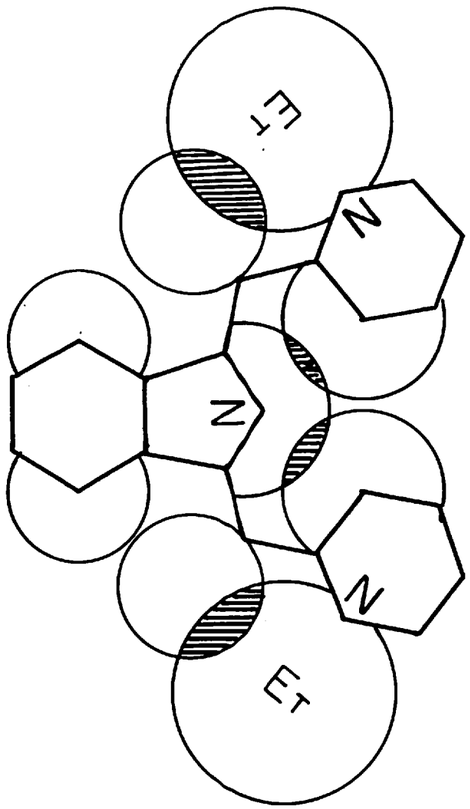


FIG. 17

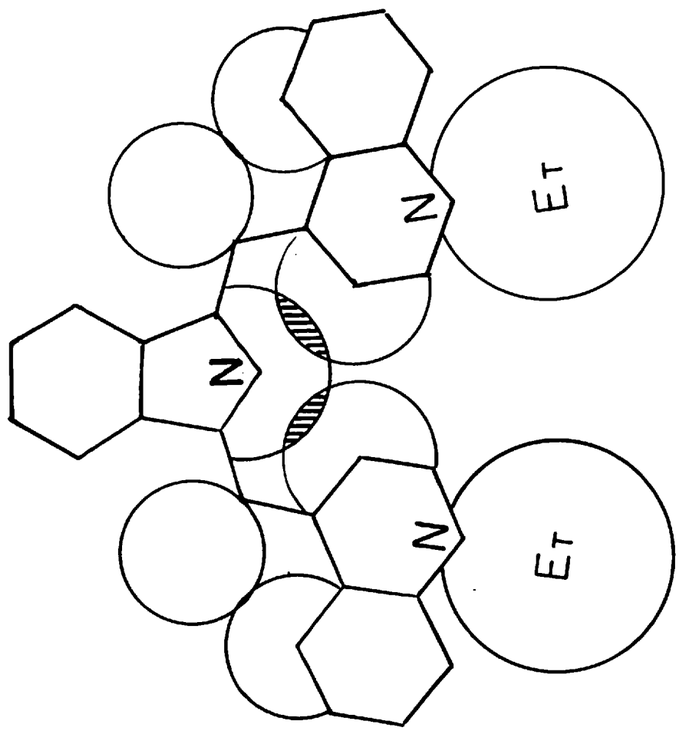


FIG. 18

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