Bridged Cyanine Dyes. Part 1. 1-(*N*-Methyl-4-pyridinio)-3-(*N*-methylpyridylene)cyclopenta-1,4-dienes

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1,3-Bis(*N*-methyl-4-pyridinio)propane is condensed with a series of α-diketones to form deep red monocyanine dyes **8**. In strongly acidic solutions *C*-protonation occurs at the central carbon atom. A similar condensation with α-ketoesters yields zwitterionic cyanines **12** with extinction coefficients exceeding 10^5.

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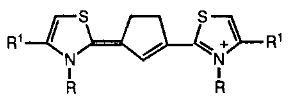
Since the chromophoric character of the cyanine (polymethine) structure was first recognized in 1926 by Konig [1], many deeply colored cyanine dyes have been synthesized. Many cyanine dyes and especially heterocyclic cyanines hold an important position in the chemistry of dyes and pigments. The nature of the terminal heterocyclic ring incorporated into cyanine dyes markedly affects the color as does changing length or substituents in the polymethine chain as described in the pioneering theoretical works of Brooker [2].

The great majority of the cyanines previously prepared contain two heterocycles linked by a simple polymethine chain containing an odd number of carbon atoms [3]. Bridged cyanine dyes in which a trimethine chain forms part of a five-membered cyclopentadiene or indene ring system were first recorded in 1933 [4]. The first examples were prepared from alkylthioquaternary salts of quinoline, pyridine, indole, benzimidazole and other heterocyclic ring systems. Heating diquarternary salts of 1,4-di(2-thiazolyl)butene with ethyl orthoformate gave the blue cyclopentene cyanine **1**, which was too unstable to be isolated [5]. Stable benzothiazole cyanines with various ring linkages (**2**, n = 0-6) have been synthesized [3]. The bridged cyanine dye **3** containing terminal pyridine rings was obtained on heating 2-methylthiopyridine methotoluene-*p*-sulfonate with indene [4,6]. In the cyanine **4**, four of the C-atoms of a benzene ring form part of the methine chain joining the N-atoms [7-8]. Bridged cyanine dyes with one or two substituents in a five or six-membered ring system are also known, but almost all such substituents have been simple alkyl groups, *i.e.*, methyl and ethyl [9]. No previous method has been available for the preparation of bridged cyanine dyes with a variety of substituents in a cyclopentadiene ring link.

We now report a simple synthetic method for such bridged cyanines which should be easily applicable to other systems. 1,3-Bis(*N*-methyl-4-pyridinio)propane **6** [available by the bisquaternization of 1,3-di(4-pyridyl)propane **5**] condenses with diverse α-diketones **7** to yield a



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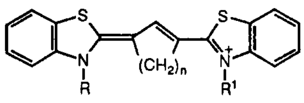

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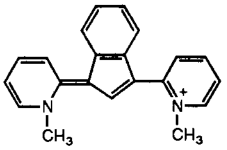

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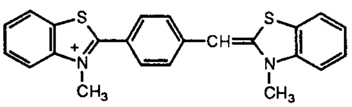

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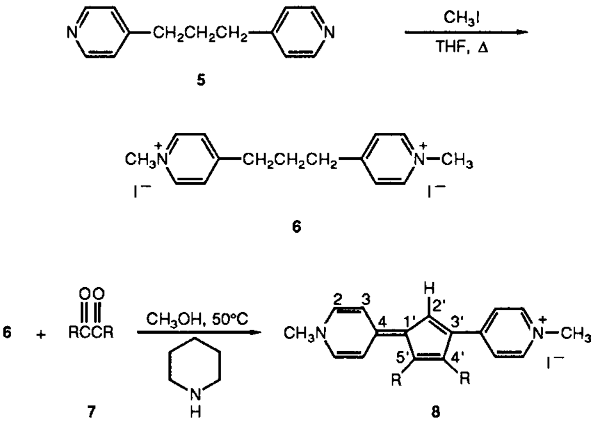
Scheme 1



a, R = Ph
b, R = CH_3
c, R = $-CH_2CH_2-$
d, R = 2-Py
e, R = 2-Fu
f, R = *m*-Cl-C_6H_4-

Scheme 2

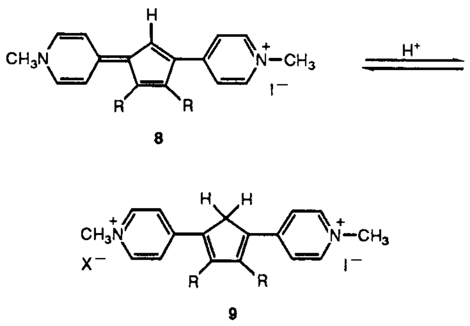


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Table I

Characterization of Cyanine Dyes **8**

No.	R	Yield %	crystal form	mp °C	Calcd.			analysis formula	Found		
					C	H	N		C	H	N
8a	C_6H_5	42	red microcrystals [a]	314-316	63.33	4.95	5.12	$C_{29}H_{29}IN_2O$	62.89	4.97	4.84
8b	CH_3	47	red microcrystals [a]	276-278	56.43	5.20	6.93	$C_{19}H_{23}IN_2O$	56.13	5.16	6.68
8c	$-CH_2CH_2-$	54	gold plates [b]	266-267	56.25	5.58	6.25	$C_{21}H_{25}IN_2O$	56.21	5.54	6.07
8d	2-Pyridyl	43	red prism [b]	302-304	59.12	4.56	10.21	$C_{27}H_{25}IN_4O$	59.36	4.76	9.89
8e	2-furyl	55	brown prism [b]	275-278	57.03	4.36	5.32	$C_{25}H_{21}IN_2O$	57.21	4.11	5.10
8f	3-ClC_6H_4	58	brown prism [b]	223-226	56.56	4.06	4.55	$C_{29}H_{27}Cl_2IN_2O$	56.21	4.00	4.25

[a] Recrystallization from ethanol. [b] from methanol.

Table II

^1H NMR Spectra of Cyanine Dyes **8**

No.	R	Pyridinium Ring		Cyclopent 1H (s)	NCH_3 6H (s)	H_2O 2H (s)	Other peaks
		α-4H (d)	β-4H (d)				
8a	C_6H_5	8.30	[a]	7.78	4.07	3.40	7.75-7.40 (m, 14H, Ph and PyH)
8b	CH_3	8.25	7.80	7.65	3.98	3.40	2.25 (s, 6H, CH_3)
8c	$-CH_2CH_2-$	8.20	7.80	7.85	3.98	3.36	2.85 (t, 4H, CH_2) 1.85 (t, 4H, CH_2)
8d	2-Pyridyl	8.60	8.22	[a]	3.98	3.40	7.62 (m, 2H, Py-H)
8e	2-Furyl	8.60	7.22	[a]	4.03	3.38	7.74 (bs, 3H) 6.59 (t, 2H) 6.38 (d, 2H)
8f	3-ClC_6H_4	8.22	[a]	7.70	4.00	3.38	8.33 (s, 2H, ArH) 7.02-7.40 (m, 10H)

[a] Overlapped along with the peaks for the "R" groups.

Table III

^{13}C NMR Spectra of Cyanine Dyes **8**

No.	R	^{13}C Chemical shift							R group
		C2	C3	C4	C1′	C2′	C5′	CH_3	
8a	C_6H_5	151.6	118.9	125.8	120.3	141.8	121.9	44.8	139.0, 131.4, 130.5, 127.7
8b	CH_3	150.6	118.1	124.2	120.2	141.6	123.2	44.4	13.9
8c	$-CH_2CH_2-$	150.1	117.9	127.1	120.2	141.5	122.2	44.4	26.8, 23.2
8d	2-Pyridyl	151.8	119.6	125.3	120.6	141.6	121.9	44.8	157.5, 148.8, 135.6, 131.5, 120.9
8e	2-Furyl	151.6	119.1	122.1	120.6	141.5	119.4	45.0	150.4, 142.3, 111.3, 108.9
8f	3-ClC_6H_4	151.6	119.1	125.8	120.4	142.0	121.3	44.8	140.9, 132.4, 129.9, 129.8, 129.2, 116.6

novel class of cyanine dyes **8**. The new derivatives **8a**-**8f** were characterized analytically (Table I), and by their ^1H (Table II) and ^{13}C nmr (Table III) spectra.

Compounds **8a**-**8f** all contain one mole of water of crystallization as indicated by elemental analysis; the presence of water is also indicated by proton nmr spectral peaks at δ 3.36-3.40 ppm. A characteristic 1H singlet near δ 7.70-7.80 in the ^1H nmr is assigned to the five-membered ring CH of the cyclopentadiene (fulvene) system; the =CH– signal of open-chain pyridocyanines occurs at about 5-6 ppm [10]. The high-field shift of the N–CH_3 signals in **8a**-**8f** compared with the starting diiodide **6** is consistent with the cyanine-type structure. The other peaks in the proton nmr spectra are readily assigned (Table II). The ^{13}C nmr spectra (Table III) also agree well with the assigned cyanine structure: the nature of the substituents R has little effect on the ^{13}C chemical shifts of the parent bridged cyanine dye system.

As shown in Table IV, dyes **8a**-**8f** have extremely high extinction coefficients and are deep red in ethanol and in dimethyl sulfoxide solution. The effect of variation of the substituents R in the cyclopentene ring on the uv/vis ab-

Table IV

UV/Visible and IR Spectra of Cyanine Dyes **8**

No.	Visible Spectra λ (ε) Ethanol	1*M* NaOH	1*M* HCl	IR (Bromoform) cm^{-1}
8a	518 (95500)	480 (57500)	400 (13800)	2940, 1628, 1500, 1460, 960, 840
8b	536 (89100)	498 (38000)	405 (13500)	1625, 1500, 1460, 1090
8c	535 (79400)	491 (35500)	410 (14100)	1625, 1500, 1460, 1075, 930
8d	498 (61700)	470 (38000)	426 (28100)	2910, 1660, 1580, 1520, 1465, 1240, 950, 820
8e	502 (74100)	474 (50100)	409 (14500)	2920, 1630, 1510, 1220
8f	508 (89100)	474 (24600)	398 (16600)	2940, 1625, 1590, 1510, 960, 790

sorption is relatively small, since the two pyridine rings are conjugated with each other through an uneven number of carbon atoms. The bridged cyanine parent structure thus possesses a very strong chromophore; however, in strongly acidic solution, a dramatic hypsochromic shift (the color was changed to yellow), and also a very strong hypochromic effect is found. The bridged cyanine dyes are evidently protonated at the central ring to form dications **9** with resulting loss of the cyanine conjugation.

Feldman and co-workers calculated the p*K*a values of some simple open-chain cyanines from the *p*H dependence of their spectra [11]. The behaviour of our bridged cyanine dyes is similar, typical absorption spectra showing the *p*H dependence of cyanine dye **8a** are shown in Figure 1. The absorption at λ 488 nm due to the cyanine **8a** in weakly acidic solution is the same as that in basic solution (see Table IV). At *p*H < 4, a new peak at λ 398 nm appears for the dication **9a**; it is the only peak in strongly acidic solution (*p*H < 2).

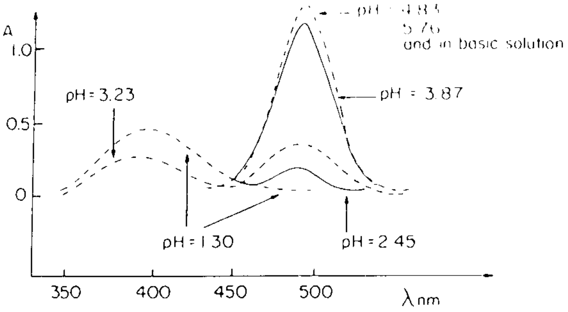


Figure 1. *p*H dependence of absorption of cyanine dye **8a** in aqueous solution.

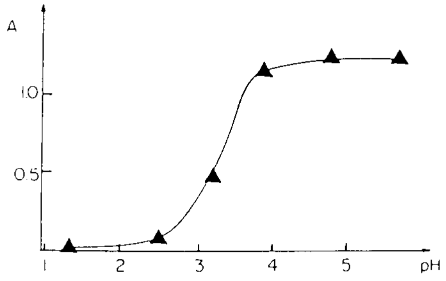
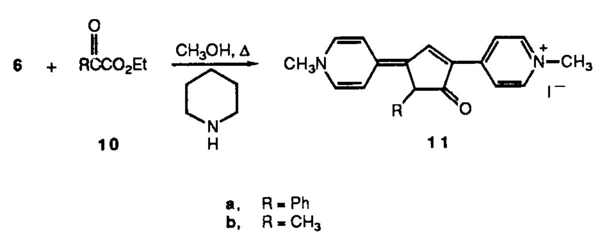


Figure 2. *p*H dependence of absorption intensity of cynanine dye **8a** at λ max 488 nm.

The p*K*a of the cyanine dye **8a** was evaluated as 3.50 from the *p*H dependence of dye spectra at λ 488 nm (Figure II). Since substitutents have small effect on the uv/vis absorption and nmr spectra, the p*K*a's of other bridged cyanine dyes **8b-8f** should be close.

The protonation of dyes **8a-8f** affects their ^1H nmr spectra. In trifloroacetic acid the entire spectrum was shifted to lower field 0.3-0.6 ppm; also the CH singlet corresponding to the fulvene ring proton of **8a-8f** is replaced by a two proton singlet at δ 4.5-4.6 ppm for the methylene groups of the dications **9**.

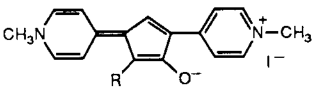
Scheme 3



Propane compound **6** reacts with α-ketoesters **10a,10b** to yield a different type of cyanine dyes **11a,11b**, as shown by ^1H and ^{13}C nmr spectra and by analysis. For **11a**, a 1H singlet at δ 4.32 is due to the ring methine between the carbonyl and the phenyl. In **11b**, this methine is replaced by a quartet at δ 3.55 because coupling occurs with the methyl group. The ^{13}C nmr spectra clearly indicate the carbonyl groups by peaks at δ 199.7 for **11a** and 203.3 for **11b**. The ir spectra show carbonyl absorption at 1635 cm^{-1} for **11a** and at 1680 cm^{-1} for **11b**.

The bridged cyanine dyes **11a,11b** were a deep red color in ethanol with extinction coefficients exceeding 10^5: λ max 560 (105000) for **11a** and 562 (107000) for **11b**. The insensitivity of the visible spectra to substitution (phenyl and methyl) is similar to the behaviour of the cyanine dyes

8. Compounds **11** in strong acid are almost colorless, demonstrating that protonation destroys the cyanine conjugation. In basic solution, although the wavelength maxima of **11** were not changed very much, the absorption intensity decreases dramatically, perhaps because **11** lose a proton to form the zwitterions **12**.



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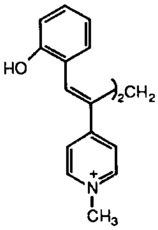

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The only previous application of **6** to the formation of cyanine dyes was in low yield (7%) synthesis of bis[α-(2-hydroxyphenyl)-1-(*N*-methyl-4-pyridinio)]vinylmethene **13**, used as a "double-barrelled" solvatochromic compound to study the relationship of absorption energy and solvent polarity [12].

EXPERIMENTAL

The ^{1}H nmr spectra were taken on a EM-360L (60 MHz) and ^{13}C nmr on a JEOL-FX-100 (25.0 MHz) spectrometer. The ir spectra were recorded with a Perkin-Elmer 283B instrument. Visible spectra were measured on a Perkin-Elmer 330 spectrophotometer. Melting points were determined on Thomas-Hoover capillary melting point apparatus without correction. Microanalysis was conducted in this department under Dr. R. W. King. Furil and *m*-chlorobenzil were prepared from furaldehyde and *m*-chlorobenzaldehyde according to the literature method [13].

1,3-Bis(*N*-methyl-4-pyridinio)propane Diiodide **6**.

It was prepared from 1,3-di(4-pyridyl)propane **5** and excess of methyl iodide in tetrahydrofuran, yield 79%, mp 143-145° (lit [12] mp 141-144°).

Preparation of Cyanine Dyes **8**.

A mixture of 0.05 mole of **6**, 0.05 mole of the appropriate α-diketone, and 0.11 mole of piperidine in methanol (20 ml) was stirred at 50° for 4-6 hours. The deeply colored solid was filtered and washed with ethanol. Crude products were recrystallized from methanol or ethanol to give well formed crystals (see Table I).

Preparation of Cyanine Dyes **11**.

Dyes **11** were synthesized by the same method as described above using the appropriate α-ketoester.

1-(*N*-Methylpyridin-4-ylene)-3-(*N*-methylpyridinio-4-yl)-5-phenylcyclopent-2-ene-4-one **11a** was obtained as a green powder (methanol), yield 41%, mp 286-287°; ir (bromoform): 2920, 1635, 1500, 1410, 1230, and 825 cm^{-1}; ^{1}H nmr (deuterated dimethyl sulfoxide): δ 9.28 (s, 1H, cyclopentene-H), 7.9-8.5 (m, 6H, PyH), 7.05-7.60 (m, 7H, ArH), 4.32 (s, 1H, CH), 3.98 (s, 6H, N-CH_3), 3.34 (s, H_2O); ^{13}C nmr (deuterated dimethyl sulfoxide): δ 199.7 (C=O), 149.3, 146.8, 146.5, 141.5, 138.0, 128.5, 127.7, 126.9, 126.4, 120.8, 117.2, 115.8, 113.3, 57.8 (CH), 44.7 (N-CH_3), 44.5 (N-CH_3).

Anal. Calcd. for $C_{23}H_{22}IN_2O_2$: C, 56.91; H, 4.69; N, 5.76. Found: C, 57.07; H, 4.48; N, 5.60.

The corresponding 5-methyl compound **11b** formed gold plates (methanol), yield 30%; mp 223-225°; ir (bromoform): 1680, 1655, 1550, 1340 cm^{-1}; ^{1}H nmr (deuterated dimethyl sulfoxide): δ 9.02 (s, 1H, cyclopentene-H), 7.50-8.45 (m, 8H, Py-H), 4.01 (s, 6H, N-CH_3), 3.15-3.55 (m, C*H*CH_3 and H_2O), 1.25 (d, 3H, CH_3); ^{13}C nmr (deuterated dimethyl sulfoxide): δ 203.3 (C=O), 147.0, 146.8, 146.1, 126.9, 126.7, 123.0, 117.2, 115.6, 112.1, 45.9 (CH), 44.5 (N-CH_3), 15.6 (C-CH_3).

Anal. Calcd. for $C_{18}H_{20}IN_2O_2$: C, 51.14; H, 4.95; N, 6.60. Found: C, 51.53; H, 4.75; N, 6.52.

Acknowledgements.

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