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The preparation is described of two novel classes of bridged cyanines: zwitterionic bis-4-pyridyl and cationic bis-dimethylanilino and bis-methylcarbazolyl derivatives **5** and **11**. In these compounds an uneven number of carbon atoms of the methine chain forms part of a five- or six-membered ring. The visible absorption is discussed.

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We have recently disclosed synthetic methods for bridged cyanines containing substituents attached to a cyclopentadiene ring by condensation of 1,3-bis(*N*-methyl-4-pyridyl)- [1a] or 1,3-bis(*N*-methyl-2-benzothiazoyl)propane diiodide [1b] with α -diketones, quinones and compounds containing two adjacent active chlorine atoms. This present paper describes two further classes of bridged cyanines, zwitterionic derivatives **5** and diaryl compounds **11**; in both, the methine chain forms part of a five- or six-membered ring.

Zwitterionic Bridged Cyanines.

Aldol condensations of 4-pyridinecarboxaldehyde with cyclopentanone and cyclohexanone in aqueous alkali gave 2,2'-bis(4-pyridylmethylidene)cycloketones **1a,b** as yellow

crystals [2]. Methylation of the cycloketones **1a,b** with methyl iodide in methanol afforded the 2,2'-bis(*N*-methylpyridinio-4-methylidene)cycloketone bisiodides **2a,b** as brown solids. Reduction of ketones **1a,b** with sodium borohydride in methanol produced the corresponding secondary alcohols **3a,b**, which were then bisquaternized with methyl iodide to give 2,2'-bis(*N*-methylpyridinio-4-methylidene)cycloalkanols **4a,b**. Finally, treatment of these bisquaternized alcohols **4** with strong base gave the expected deep red zwitterionic bridged cyanines **5**. The reaction sequence is as shown in Scheme 1.

Similar reactions conducted with 2-pyridinecarboxaldehyde (Scheme 1) gave the compounds **1-4c** and **d**. Unfortunately, in this series the final zwitterionic bridged cyanines **5c,d** were too hygroscopic for easy isolation.

The properties of intermediates **1-4** and of the zwitterionic bridged cyanines **5a,b** are summarized in Table 1. All these compounds, most of which are new, were characterized by their ^1H (Table 2) and ^{13}C nmr (Table 3), by their ir spectra (Table 2), and by microanalysis (Table 1).

In the ^1H nmr spectra, the signals of CH= groups attached to a cyclopentanone or cyclohexanone ring appear at low field but are usually not overlapped by the pyridyl protons ($\delta > 7.0$ ppm except for alcohol **3**). The α -H signals of the CHOH group in **3-4** are very clear as singlets at 5.1-5.6 ppm. The signals for CHOH in the ^{13}C nmr at δ 70-80 ppm are also characteristic. The high-field shift of the N-CH₃ ^1H signals in **5a** (4.00 ppm) and in **5b** (3.95 ppm) compared with those for the diiodides (around 4.5 ppm) is consistent with the zwitterionic cyanine type structure. In the infrared spectra, the two expected characteristic bands were found for ν C=O and ν C=CH at around 1690 and 1620 cm^{-1} for ketones **1** and **2**. Secondary alcohols **3** and **4** showed ν OH and ν C=CH around 3400 and 1620 cm^{-1} . The ^{13}C nmr spectra of these compounds are also consistent with the expected structure.

Compounds **5a** and **5b** contain pyridyl cyanine chromophores which are conjugated through cyclopentene or cyclohexene enolates and thus are deeply colored (red). The visible absorption spectra were recorded in ethanol

Scheme 1

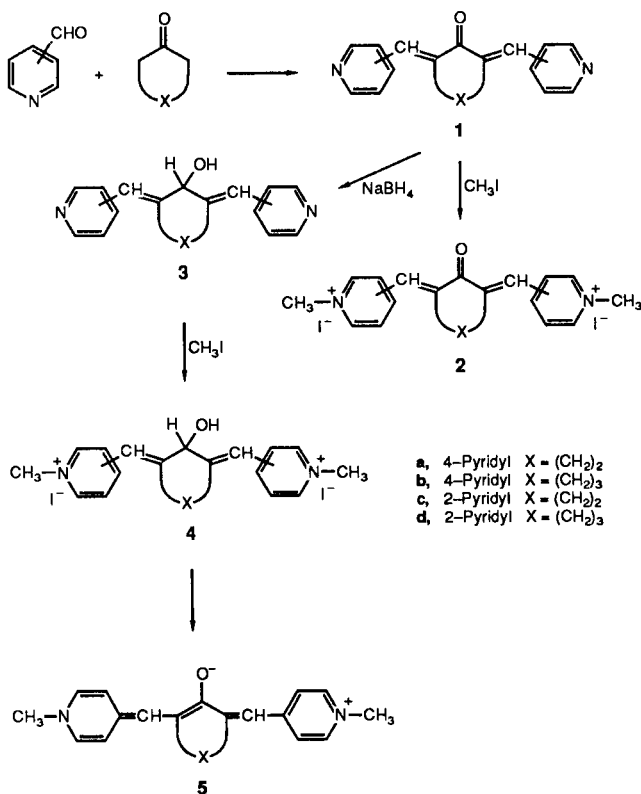


Table 1
Preparation of Intermediates **1-4** and Cyanines **5**

No.	Yield %	Crystal Color (solvent) [a]	mp (°C)	lit [2] m.p. (°C)	Calcd.			Formula	Found		
					C	H	N		C	H	N
1a	75	yellow (A)	237-238	238	77.74	5.40	10.68	C ₁₇ H ₁₄ N ₂ O	77.40	5.40	10.47
1b	82	yellow (A)	148-149	150	78.26	5.79	10.25	C ₁₈ H ₁₆ N ₂ O	78.14	5.90	10.03
1c	77	yellow (B)	195-196	197	77.74	5.40	10.68	C ₁₇ H ₁₄ N ₂ O	77.48	5.21	10.53
1d	81	yellow (B)	187-189	190	78.26	5.79	10.25	C ₁₈ H ₁₆ N ₂ O	78.47	5.59	10.61
2a	80	red	>250	---	41.77	3.66	5.13	C ₁₉ H ₂₀ N ₂ OI ₂	42.09	3.47	5.01
2b	68	brown	>250	---	42.94	3.93	5.00	C ₂₀ H ₂₂ N ₂ OI ₂	42.60	3.98	4.82
3a	78	white (C)	97-98	---	77.25	6.20	10.59	C ₁₇ H ₁₆ N ₂ O	77.01	6.42	10.20
3b	75	white (C)	138-139	---	77.67	6.51	10.06	C ₁₈ H ₁₈ N ₂ O	77.88	6.52	9.80
3c	79	white (C)	80-82	---	77.25	6.20	10.59	C ₁₇ H ₁₆ N ₂ O	77.22	6.47	10.40
3d	68	white (C)	134-135	---	77.67	6.51	10.06	C ₁₈ H ₁₈ N ₂ O	77.81	6.68	9.86
4a	67	brown (A)	144-145	---	40.31	4.27	4.90	C ₁₉ H ₂₂ N ₂ OI ₂ [b]	39.97	4.30	4.82
4b	77	brown (A)	218-219	---	42.72	4.27	4.98	C ₂₀ H ₂₄ N ₂ OI ₂	42.64	4.26	4.83
4c	58	brown (A)	280-282	---	41.60	4.06	5.13	C ₁₉ H ₂₂ N ₂ OI ₂	41.66	4.21	5.18
4d	55	brown (A)	255-257	---	42.72	4.27	4.98	C ₂₀ H ₂₄ N ₂ OI ₂	43.06	4.18	5.20
5a	66	red (A)	>250	---	77.53	7.13	9.50	C ₁₉ H ₂₀ N ₂ O	77.09	6.87	9.76
5b	51	red (A)	217-220	---	78.43	7.11	9.15	C ₂₀ H ₂₂ N ₂ O	78.70	6.85	9.38

[a] (A) ethanol, (B) acetone, (C) methanol. [b] Containing one mole of water of crystallization.

Table 2
Selected Proton NMR and IR Spectral Data of Intermediate **1-4** and **5** [a]

No.	Py-H		¹ H NMR (δ, TMS)				IR (cm ⁻¹ Potassium bromide)		
			=CH (s)	CHOH (s)	CH ₂	N-CH ₃	ν C=O	=CH	ν OH
1a	8.93 (d)	8.35 (d)	7.92	---	3.54 (s)	---	1670	1630	---
1b	8.90 (d)	8.15 (d)	7.80	---	3.00 1.85	---	1675	1630	---
1c	7.90-8.50 (m)		7.70	---	3.50 (s)	---	1690	1610	---
1d	8.00-8.50 (m)		7.65	---	2.88 1.80	---	1700	1600	---
2a	9.30 (d)	8.60 (d)	7.80	---	3.40 (s)	4.55	1690	1640	---
2b	9.28 (d)	8.50 (d)	7.85	---	3.10 1.88	4.57	1695	1640	---
3a	8.64 (d)	7.25 (d)	6.70	5.15	3.10 (s)	---	---	1610	3500
3b	8.80 (d)	7.50 (d)	6.75	5.08	2.80 1.85	---	---	1600	3450
3c	7.00-7.95 (m)		6.65	5.12	2.98 (s)	---	---	1615	3350
3d	7.10-8.10 (m)		6.55	5.16	2.75 1.70	---	---	1600	3350
4a	9.15 (d)	8.35 (d)	7.70	5.60	3.40 (s)	4.40	---	1620	3500
4b	9.18 (d)	8.50 (d)	7.85	5.50	3.29 2.00	4.37	---	1625	3450
4c	7.60-9.00 (m)		7.45	5.40	3.40 (s)	4.54	---	1630	3450
4d	7.80-9.10 (m)		7.55	5.40	3.00 1.95	4.60	---	1635	3400
5a	8.85 (d)	8.15 (d)	7.55	---	3.20 (s)	4.00	---	1620	---
5b	8.95 (d)	8.20 (d)	7.60	---	3.20 1.95	3.95	---	1610	---

[a] Solvent used in nmr measurement: trifluoroacetic acid for **1**, deuteriochloroform for **3**, dimethyl sulfoxide-d₆ for **2**, **4** and **5**.

Table 3
Selected Carbon NMR Spectral Data of Compounds 1-4 (δ) [a]

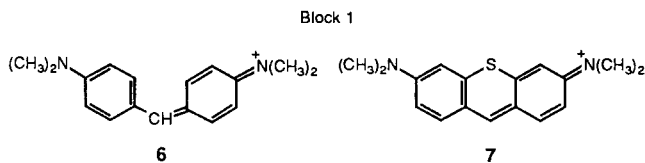
No.	CO	CHOH	CH ₂	NCH ₃	PY-C, CH= and C=							
1a	204.9	---	25.3	---	150.0	149.6	141.2	129.6	123.4			
1b	203.5	---	28.1	22.4	---	150.7	149.7	143.0	132.2	123.9		
1c	198.8	---	26.2	---	151.1	149.4	143.4	141.0	136.2	130.5	123.4	
1d	201.2	---	27.4	22.8	---	150.9	148.7	144.4	137.7	136.7	133.6	123.4
2a	204.1	---	26.1	46.2	153.1	150.6	142.2	129.7	124.0			
2b	204.7	---	28.5	23.0	45.7	152.9	149.9	142.7	130.2	124.8		
3a	---	76.7	26.5	---	150.2	149.6	144.2	122.8	118.3			
3b	---	75.4	26.7	22.3	---	149.4	148.9	144.8	123.4	118.5		
3c	---	77.3	26.8	---	149.1	146.9	146.7	135.2	133.2	123.2	118.3	
3d	---	78.2	27.2	23.3	---	149.6	147.0	146.0	136.2	133.3	123.1	118.7
4b	---	76.8	27.2	23.8	47.5	150.3	144.9	143.5	130.1	127.3		
4d	---	78.5	28.1	24.0	47.8	154.0	149.2	144.0	138.7	133.9	124.3	120.1

[a] Solvent: deuteriochloroform for 3a-3d, dimethyl sulfoxide-d₆ for others.

and in 1M hydrochloric acid. In ethanol, the maximum absorption peak appears at 484 nm for 5a and 486 nm for 5b, the extinction coefficients are 20000 and 21000, respectively. In 1M hydrochloric acid, they became yellow (absorption peak at ~410 nm), indicating that the cyanine structure was destroyed in acid.

Bridged Diaryl Cyanines.

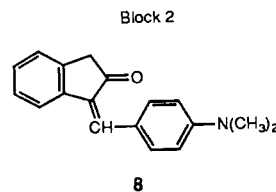
Diaryl- and triaryl-methane dyes can be classified as cyanines, e.g. the commercially available Michler's hydrol blue 6 and thiopyronine dye 7 [3]. In addition to the dimethylanilino system, *N*-methylpyrrole and *N*-methylindole units have been used to construct cyanines [4]. Such cyanine dyes are usually of the open chain type with one or three methine group between two aryl terminals. We now report diaryl methane dyes in which three methine groups form part of a cycloalkene ring, and 9-methylcarbazol-3-ylmethylidene was the heterocyclic terminal group.



Aldol condensation of 9-methylcarbazole-3-aldehyde (see [5]) with cyclopentanone afforded 2,2'-bis(9-methyl-3-carbazoylmethylidene)cyclopentanone 9a (80%) as orange crystals. Reduction of ketone 9a with sodium borohydride in diglyme gave the corresponding secondary alcohol 10a as white needles, which with perchloric acid produced the blue dye 11a. Similar reactions were carried out with cyclohexanone to give the blue cyanine dye 11b. The reac-

tion sequence is shown in Scheme 2.

Reaction of 4-dimethylaminobenzaldehyde with cyclopentanone and cyclohexanone in alkaline aqueous solution produced the 2,2'-bis(4-dimethylaminobenzylidene)-cyclopentanone 9c or -cyclohexanone 9d. The preparation of 9d by condensation has already been reported, but in very low yield (4%) [6], the yield has now been improved to 90% by using strong basic conditions (two equivalents of sodium hydroxide). However, only the monocondensation product, 1-(4-dimethylaminobenzylidene)indan-2-one 8



was obtained from the reaction of 4-dimethylaminobenzaldehyde with indan-2-one under the same conditions. Reductions of 9c,d with sodium borohydride gave the alcohols 10c,d respectively, which with perchloric produced the purple hygroscopic dyes 11c,d.

The properties of the bridged cyanine dyes 11a-d and of the intermediates 9-10 are summarized in Table 4. The microanalyses, ¹H and ¹³C nmr, ir spectra and visible absorptions are listed in Tables 4 and 5. The CH= signals attached to cycloalkanone rings appear downfield and sometimes overlap those of the aromatic protons. These CH= signals were shifted about one ppm to higher field when the carbonyl group was reduced to secondary alcohol. The secondary alcohols are also characterized by a CHOH signals at 75-80 ppm in the ¹³C nmr. In the infrared spectra the two expected characteristic bands were

Table 4
Preparation of Intermediates (9-10) and Cyanines (11)

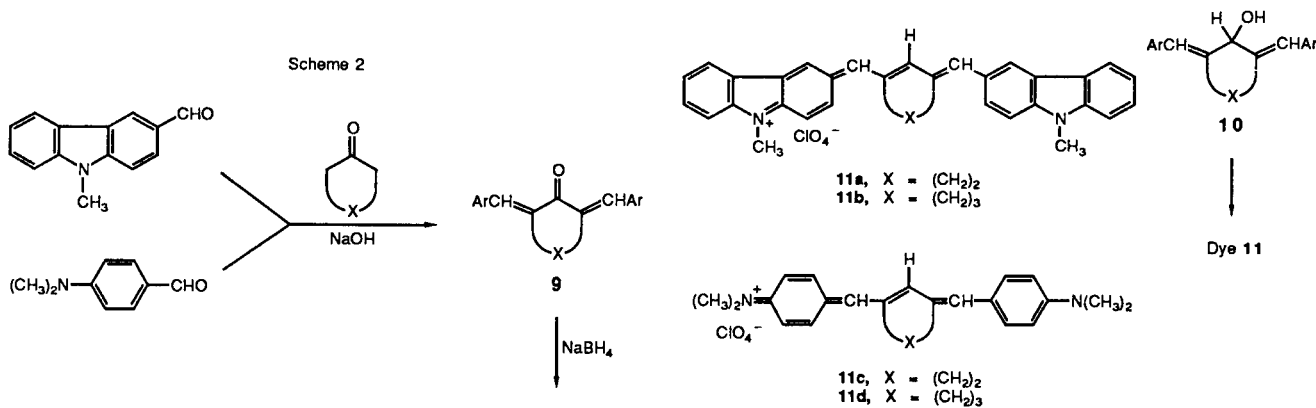
No.	Yield %	Crystal Form (solvent) [a]	UV/Vis [b] λ (ϵ)	mp ($^{\circ}\text{C}$)	Calcd.			Formula	Found		
					C	H	N		C	H	N
9a	80	orange (A)	425 (35000)	257-260	84.98	5.58	6.01	$\text{C}_{33}\text{H}_{26}\text{N}_2\text{O}$	84.62	5.69	5.90
9b	72	orange (A)	418 (29500)	>260	85.00	5.83	5.83	$\text{C}_{34}\text{H}_{28}\text{N}_2\text{O}$	84.68	5.92	5.49
9c	98	orange (B)	431 (37000)	>300 [c]	79.77	7.51	8.09	$\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}$	79.39	7.65	8.21
9d	80	orange (B)	428 (38500)	252-254	(lit [6] mp 250)						
10a	90	white (C)	---	178-180	84.62	5.98	5.98	$\text{C}_{33}\text{H}_{28}\text{N}_2\text{O}$	84.21	6.07	5.70
10b	75	white (C)	---		84.65	6.22	5.81	$\text{C}_{34}\text{H}_{30}\text{N}_2\text{O}$	84.30	6.34	5.61
10c	79	white (A)	---	110-112	79.21	8.05	8.05	$\text{C}_{23}\text{H}_{28}\text{N}_2\text{O}$	78.79	8.23	7.68
10d	70	white (A)	---	82-84	79.56	8.29	7.78	$\text{C}_{24}\text{H}_{30}\text{N}_2\text{O}$	79.52	8.55	7.40
11a	90	blue	588 (22000)	>270 (dec)	71.93	4.90	5.09	$\text{C}_{33}\text{H}_{27}\text{N}_2\text{O}_4\text{Cl}$	71.68	4.64	4.69
11b	75	blue	580 (21000)	>270 (dec)	72.28	5.14	4.96	$\text{C}_{34}\text{H}_{29}\text{N}_2\text{O}_4\text{Cl}$	71.89	5.25	4.61
11c		purple	538					hygroscopic			
11d		purple	540					hygroscopic			

[a] (A): ethanol, (B): acetone, (C): methanol. [b] The visible spectra was measured in ethanol. [c] No mp is given in ref [8].

Table 5
Selected Spectral Data of Compounds 9, 10 and 11 [a]

No.	CH=	$^1\text{H NMR}$ (δ , TMS)			CHOH	$^{13}\text{C NMR}$ (δ)			IR (Bromoforn)		
		CHOH	CH_2	N- CH_3		CH $_2$	N- CH_3	ν C=O	ν =CH	ν OH	
9a	7.75	---	3.10	3.65	---	---	---	---	1690	1590	---
9b	7.65	---	3.00 1.95	3.75	---	---	---	---	1690	1590	---
9c	7.95	---	3.25	3.70	---	---	---	---	1670	1600	---
9d	8.00	---	3.10 2.05	3.60	---	---	---	---	1660	1606	---
10a	6.80	5.25	2.75	3.85	79.4	28.8	48.5	---	1610	3350	
10b	6.85	5.30	2.70 1.95	3.82	78.9	26.7 22.4	48.0	---	1615	3400	
10c	6.85	5.30	2.82	3.60	77.2	28.4	45.1	---	1605	3400	
10d	6.90	5.35	2.75 2.00	3.55	77.9	27.0 22.8	44.8	---	1610	3400	
11a			not soluble					---	1600	---	
11b			not soluble					---	1610	---	

[a] Solvent: trifluoroacetic acid for 9, deuteriochloroform for 10.



found for ν C=O at around 1690, and for ν C=C around 1600 cm^{-1} for **9**, and a band for ν OH at 3400 cm^{-1} in **10**. On treatment with acid, alcohols **10** lose hydroxide ion to form the cyanine dyes **11**. The high extinction coefficients of **11** in ethanol (>20000) with λ max around 580 nm, indicated the strong cyanine chromophore. The two aromatic rings with N-CH₃ are mono-positively charged and are conjugated with each other through an uneven number of carbon atoms in the cyclopentene and cyclohexene rings.

EXPERIMENTAL

The ¹H nmr and ¹³C nmr spectra were taken on Varian EM 360L (60 MHz) and JEOL JNM FX 100 (25 MHz) spectrometers, respectively. The solvents used for nmr measurements are indicated as relevant in text and Tables. Ir spectra were obtained on a Perkin Elmer 283 spectrometer. The visible spectra were recorded on a Perkin-Elmer 330 spectrophotometer. Melting points were determined on a Thomas-Hoover capillary melting point apparatus without correction.

The following compounds were prepared by the literature method quoted: 9-methylcarbazole, mp 87-88° (lit [7] mp 87°); 9-methylcarbazole-3-aldehyde, mp 74-75°, (lit [5] mp 74°).

2,2'-Bis(4-pyridylmethylidene)cyclopentanone **1a**.

A mixture of 4-pyridinecarbaldehyde (0.10 mole) and cyclopentanone (0.05 mole) in 200 ml water was stirred and cooled to 5°, 10 ml of 20% sodium hydroxide solution was added and the stirring was continued for 10 hours at 25°. The solution was neutralized with diluted hydrochloric acid and the solid formed was collected by filtration. Recrystallization from ethanol gave yellow needles (Table 1).

Other 2,2'-bispyridylmethylidenecycloketones were prepared in the same way (Table 1). In the case of 4-dimethylaminobenzaldehyde, two equivalents of sodium hydroxide were required (Table 4 and 5).

2,2'-Bis(9-methyl-3-carbazolylmethylidene)cyclopentanone **9a**.

To a mixture of 9-methylcarbazole-3-aldehyde (40 mmoles) and cyclopentanone (20 mmoles) in 50% aqueous dimethyl sulfoxide, 10 ml of 20% sodium hydroxide was added. The mixture was stirred at 100° for 5 hours. After cooling and neutralizing, the resulting solid was filtrated, washed with water and recrystallized from ethanol to give an orange solid (for details see Table 4).

2,2'-Bis(9-methyl-3-carbazolylmethylidene)cyclohexanone **9b** was prepared in the same manner.

1-(4-Dimethylaminobenzylidene)indan-2-one **8**.

Preparation as above, recrystallized from ethanol, yield 76%, red microcrystals, mp 118-120°; ¹H nmr (deuteriochloroform): 6.9-8.3 (m, 8H, Ar-H), 6.75 (s, 1H, CH=), 3.30 (s, 2H, CH₂), 2.98 (s, 6H, NMe₂); uv/vis (ethanol): λ 452 nm (16100).

Anal. Calcd. for C₁₈H₁₇NO: C, 82.13; H, 6.46; N, 5.32. Found: C, 81.76; H, 6.27; N, 5.15.

2,2'-Bis(4-pyridylmethylidene)cyclopentanol **3a**.

To ketone **1a** (20 mmoles) in 100 ml methanol, sodium borohydride (10 mmoles) was added slowly with stirring. The stirring was continued for 1 hour and followed by hydrolysis. The solid was separated by filtration and washed with water. Recrystallized from methanol gave white needles (Tables 1, 2 and 3).

Other secondary alcohols were prepared in the same procedure except for the carbazolylmethylidenes, which were accomplished by heating the corresponding ketones in diglyme with sodium borohydride.

2,2'-Bis(N-methyl-4-pyridylmethylidene)cyclopentanol **4a**, General Procedure of Bisquaternization.

2,2'-Bis(4-pyridylmethylidene)cyclopentanol was stirred with excess methyl iodide in methanol at 25° for 2 days. The solid formed was collected by filtration and recrystallized from ethanol to give **4** (Table 1 to 5).

Zwitterionic Cyanine Dyes **5**.

Compound **4** was dissolved in aqueous sodium hydroxide solution and heated at 65° with stirring for 20 hours. After cooling, the resulting solid was filtrated and washed with water to give dye **5** (for details see Table 1).

Diaryl Cyanine Dyes **11**.

2,2'-Bis(9-methylcarbazolylmethylidene)cycloalkanol was stirred with perchloric acid (70%) at 25° for 1 hour, the solution turn to dark blue. The resulting blue solid was collected by filtration and washed with ethanol (for details see Table 4).

Acknowledgements.

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REFERENCES AND NOTES

- [1a] Part 1. A. R. Katritzky, W.-Q. Fan and Q.-L. Li, *J. Heterocyclic Chem.* **25**, 1311 (1988); [b] Part 2. A. R. Katritzky, D.-S. Liang and W.-Q. Fan, *J. Heterocyclic Chem.*, **25**, 1315 (1988).
- [2] N. P. Buu-Hoi and N. D. Xuong, *Compt. Rend.*, 251, 2725 (1960).
- [3] D. R. Waring in "Comprehensive Heterocyclic Chemistry", A. R. Katritzky, C. W. Rees and O. Meth-Cohn, eds, Pergamon Press, 1984, p 346.
- [4] L. G. S. Brooker and R. H. Sprague, *J. Am. Chem. Soc.*, **67**, 1869, (1945).
- [5] N. P. Buu-Hoi and N. Hoan, *J. Am. Chem. Soc.*, **73**, 98 (1951).
- [6] P. J. Smith, J. R. Dimmock and W. A. Turner, *Can. J. Chem.*, **51**, 1458 (1973).
- [7] C. Graebe and B. Adlerskron, *Ann. Chem.*, **202**, 23 (1880).
- [8] N. P. Buu-Hoi, N. D. Xuong and N. V. Bac, *Compt. Rend.*, **258**, 1343 (1964).