Dyes and Pigments **21** (1993) 227–234

Synthesis and Characterization of Unsymmetrical Squaraines: A New Class of Cyanine Dyes

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(Received 3 November 1992; accepted 10 December 1992)

ABSTRACT

A new class of unsymmetrical cyanine dyes and their precursors has been synthesized and characterized with the aid of ^{1}*H-NMR, IR- and mass spectroscopy. The dyes exhibit high melting points, poor solubility in organic solvents and absorption maxima in the range 640–670 nm with high extinction coefficients.*

1 INTRODUCTION

The synthesis of symmetrical squaraines was first reported about 25 years ago.[1] Structural modification of squaraines has been an active area of research since the compounds were found to be useful for xerographic applications and optical recording.[2] This class of cyanine dyes exhibits a sharp absorption with high extinction coefficients in solution in the red and near IR region (600–750 nm), without the disadvantage of photochemical instability.[3] Although a wide range of squaraines has been synthesized, the majority belong to the class of symmetrical cyanine dyes. We now report the synthesis and spectral properties of unsymmetrical substituted squaraines, which cannot be obtained via a direct reaction of squaric acid with methylene bases.

Symmetrical squaraines are normally synthesized by condensation of squaric acid, or its derivatives, with electron-rich aromatic, heteroaromatic or olefinic compounds in a one-step reaction.[1,3] Unsymmetrical squaraines on the other hand are obtained through condensation of a mono-substituted

Dyes and Pigments 0143-7208/93/$06·00

squaric acid with a methylene base and were synthesized the first time by Treibs and Jakob from 3-hydroxy-4-(2-pyrrolyl)-cyclobutendione and different nucleophiles.[4] The mechanism of the squaraine formation has been investigated thoroughly.[5] Law and Bailey[5,6] used squaric acid and *N*,*N*-dimethylaniline as model reactants and 1-butanol/toluene as solvents and proposed an *n*-butylsquarate as the reactive intermediate in this synthesis. This butyl-squarate undergoes a substitution reaction with a nucleophile (methylene base, substituted aniline, other heterocyclic compounds), to the mono-substituted squaric acids, which further react by condensation with another nucleophile to the final squaraine product.

2 RESULTS AND DISCUSSION

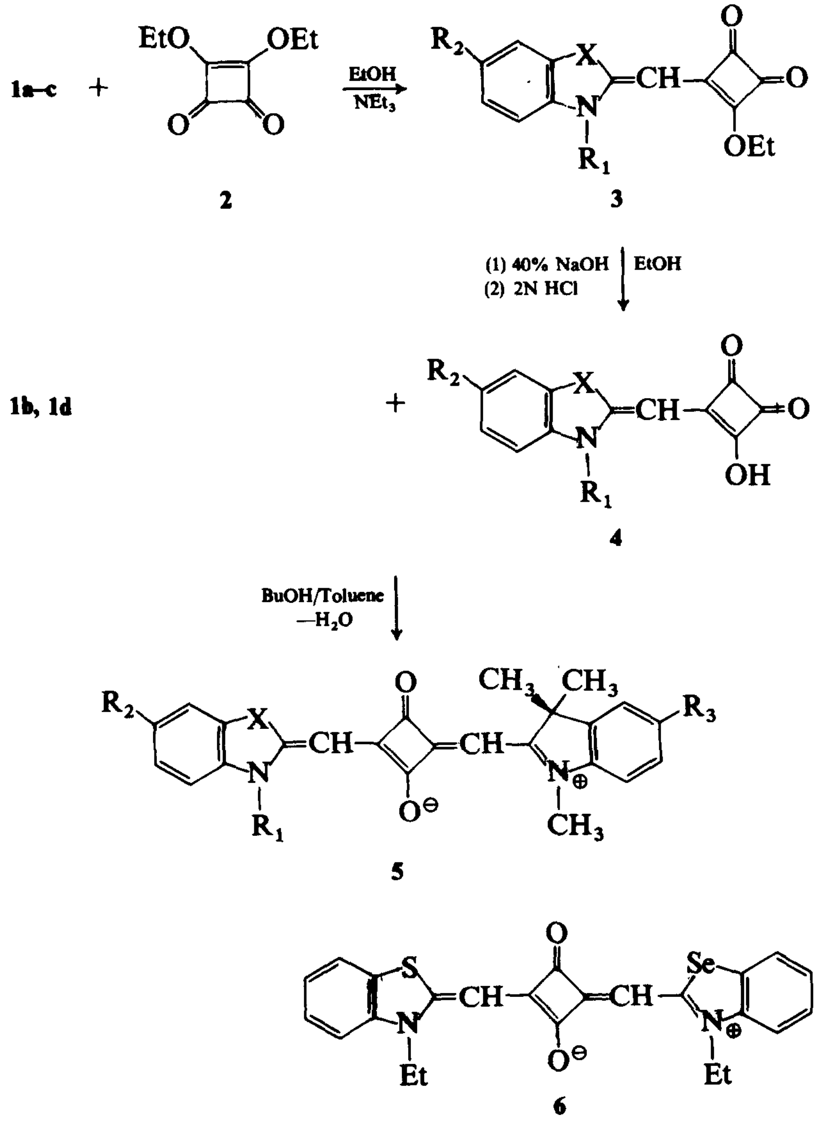
2.1 Synthesis of squaraine-precursors 4 and unsymmetrical squaraines 5 and 6 (see Scheme 1)

It is known[4] that reactions of squaric esters with methylene bases lead to monosubstituted esters **3**. Similar reactions have already been described previously.[7] Compound **1a** and **1c** (quarternized salts of methylene bases) and **1b** (free methylene base) (Scheme 2) were reacted with diethyl squarate to give the monosubstituted squaric esters **3**. Hydrolysis of these esters by 40% NaOH and subsequent protonation of the sodium salts with 2 N hydrochloric acid afforded the monosubstituted squaric acids **4**, the key intermediates in the unsymmetrical squaraine syntheses (yields, MPs and mass spectral data are shown in Table 1 and IR- and ^{1}H-NMR data in Table 2).

The condensation of **4** with methylene bases such as **1b** and **1d** gave the

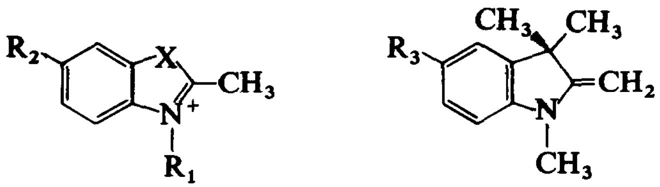
TABLE 1
Characterization Data for the Squaraine-Precursors **3** and **4**

Compound	*R_1*	*R_2*	*X*	*Yield (%)*	*MP (°C)*	*M^+* (*m/z*)	*M^+* *Rel. int. (%)*
3a	Et	H	S	41	185–87	301	100
3b	Me	Cl	$C(Me)_2$	43	200–02	331	17
3c	Et	H	Se	64	210–12	348	39
4a	Et	H	S	89	246–48	273	45
4b	Me	Cl	$C(Me)_2$	73	217–19	303	18
4c	Et	H	Se	99	252–54	—	—



Scheme 1

unsymmetrical squaraines **5**, and the reaction of **4c** with **1a** yielded compound **6** (see Scheme 1 and Table 3). The condensations were carried out in an *n*-butanol/toluene mixture. The water of the reaction was removed as an azeotrope with toluene using a Dean–Stark trap. The reaction mixture was then concentrated by rotary evaporation, the residue diluted with diethyl ether and the precipitate collected. Further purification of the dyes was achieved by column chromatography using $CHCl_3$/*i*-propanol or $CHCl_3$/ethyl acetate mixtures as eluents.



1a $R_1 = Et; R_2 = H; X = S$ **1b** $R_3 = Cl$
1c $R_1 = Et; R_2 = H; X = Se$ **1d** $R_3 = H$

Scheme 2

2.2 Structure elucidation of the squaraine precursors 3 and 4

The structure elucidation of the precursors **3** and **4** was achieved mainly with the aid of IR- and ^{1}H-NMR as well as mass spectroscopy data (see Tables 1 and 2). The IR-spectra of compounds **3** and **4** show characteristic carbonyl absorptions at 1765–1775 cm^{-1} as well as 1690–1720 cm^{-1} in the case of **3** and 1660–1680 in the case of **4**, indicating the cyclobuten-dione moiety in the molecules. In addition, the IR-spectra of **4** show a broad OH-band at around 3700–3100 cm^{-1}. The signals in the ^{1}H-NMR spectra of **3** and **4** are in accord with the conformation of these compounds and Table 2 lists the pertinent proton assignment.

TABLE 2
Spectroscopic Properties of Squaraine Precursors 3 and 4

Compound	*IR* (*cm*$^{-1}$)	^{1}*H-NMR* [*CDCl*$_3$ (*3*), *D*$_6$-*DMSO* (*4*), *ppm from TMS*]
3a	2 937 (w), 1 765 (m), 1 702 (s)	1·40 (t, 3H), 1·52 (t, 3H), 4·07 (q, 2H), 4·85 (q, 2H), 5·48 (s, 1H), 7·08 (d, 1H), 7·17 (t, 1H), 7·35 (t, 1H), 7·51 (d, 1H)
3b	2 978 (w), 1 769 (s), 1 717 (s)	1·57 (t, 3H), 3·38 (s, 3H), 4·95 (q, 2H), 5·38 (s, 1H), 6·81 (d, 1H), 7·26 (s, 1H), 7·29 (d, 1H)
3c	2 988 (w), 1 769 (s), 1 694 (s)	1·40 (t, 3H), 1·52 (t, 3H), 4·07 (q, 2H), 4·84 (q, 2H), 5·69 (s, 1H), 7·05 (d, 1H), 7·13 (t, 1H), 7·35 (t, 1H), 7·55 (d, 1H)
4a	3 700–3 180 (w), 2 978 (w), 1 773 (s), 1 660 (s)	1·25 (t, 3H), 4·12 (q, 2H), 5·66 (s, 1H), 7·18 (t, 1H), 7·39 (m, 2H), 7·77 (d, 1H)
4b	3 650–3 190 (w), 2 932 (w), 1 775 (s), 1 682 (s)	1·54 (s, 6H), 3·30 (s, 3H), 5·60 (s, 1H), 7·09 (d, 1H), 7·26 (d, 1H), 7·47 (s, 1H)
4c	3 700–3 080 (m), 2 978 (w), 1 769 (s), 1 657 (s)	1·24 (t, 3H), 4·10 (q, 2H), 6·08 (s, 1H), 7·09 (t, 1H), 7·32 (m, 2H), 7·81 (d, 1H)

TABLE 3
Characterization data for Squaraines **5** and **6**

Compound	R_1	R_2	R_3	*X*	*Yield* (%)	*MP* (°C)	M^+	
							(*m/z*)	*Rel. int.* (%)
5a	Et	H	H	S	77	312–14	427	100
5b	Me	Cl	Cl	$CMe)_2$	82	>360	493	71
5c	Et	H	H	Se	88	278–80	474	98
5d	Et	H	Cl	S	68	244–46	463	100
5e	Me	Cl	H	$C(Me)_2$	66	310–12	458	100
5f	Et	H	Cl	Se	94	250–52	510	55
6	—	—	—	—	36	311–13	479	100

2.3 Properties of squaraines 5

The squaraines **5** are metallic shining, high melting compounds, with a low solubility in most organic solvents. The IR-spectra of these squaraines do not show any evidence of carbonyl absorption in the region 1800–1650 cm^{-1}, but exhibit strong absorption bands in the region of 1580–1605 cm^{-1}, indicating a strong bonding-delocalization within the four-membered ring system (see Table 4).

Structure elucidation was again accomplished mainly with the aid of ^1H-NMR and mass spectroscopy. The unsymmetrical substitution in the squaraines **5a**, **5c–5f** and **6** can be demonstrated by the splitting of the methine-proton signals. So the ^1H-NMR spectra of the unsymmetrical squaraines show two signals around 6 ppm for the methine-protons of the cyanine bridge, whereas the same appear as a singlet with a chemical shift of 5·96 ppm in the symmetrical indo-squaraine **5b**. The observed splitting of the six methyl-protons of **5a** (1·71 ppm, SH and 1·78 ppm, 3H) and **5f** (1·62 ppm, 3H and 1·76 ppm, 3H) into doublets is probably related to a twisting of the indolenine moiety out of the plane from the central carboxylic building block.[3] In a planar molecule these two methyl groups would have the same magnetic environment and should therefore appear as a singlet.

The squaraines **5** and **6** exhibit intense absorption in the visible region in solution. In chloroform their absorption maxima as well as their extinction coefficients depend on the nature of their heterocyclic bases. The fluorescence properties (quantum yields, emission wavelengths and fluorescence-lifetimes) of these squaraines will be reported in a separate paper.

TABLE 4
Spectroscopic Properties of Squaraines **5** and **6**

Compound	*IR* (*cm*$^{-1}$)	λ_{max} (*nm*) *log* ε (*CHCl*$_3$)	^{1}*H-NMR* (*CDCl*$_3$, *ppm from TMS*)
5a	2 926 (w), 1 591 (s), 1 511 (s)	649 (5·20)	1·45 (t, 3H), 1·71 (s, 3H), 1·78 (s, 3H), 3·46 (s, 2H), 4·23 (q, 2H), 5·77 (s, 1H), 6·03 (s, 1H), 6·92 (d, 1H), 7·08 (t, 1H), 7·21–7·35 (m, 4H), 7·42 (t, 1H), 7·58 (d, 1H)
5b	2 968 (w), 1 597 (s)	647 (5·46)	1·74 (s, 12H), 3·58 (s, 6H), 5·96 (s, 2H), 6·97 (d, 2H), 7·32 (m, 4H)
5c	2 947 (w), 1 595 (s), 1 577 (s)	657 (5·03)	1·45 (t, 3H), 1·77 (s, 6H), 3·46 (s, 3H), 4·23 (q, 2H), 5·76 (s, 1H), 6·19 (s, 1H), 6·94 (d, 1H), 7·09 (t, 1H), 7·31 (t, 1H), 7·32 (d, 1H), 7·39 (d, 1H), 7·41 (t, 1H) 7·62 (d, 1H)
5d	2 926 (w), 1 589 (s), 1 572 (s)	649 (5·08)	1·47 (t, 3H), 1·77 (s, 6H), 3·41 (s, 3H), 4·25 (q, 2H), 5·73 (s, 1H), 6·08 (s, 1H), 6·80 (d, 1H), 7·22–7·27 (m, 3H), 7·34 (d, 1H), 7·45 (t, 1H), 7·64 (d, 1H)
5e	2 962 (w), 1 602 (s), 1 504 (s)	637 (5·42)	1·77 (s, 12H), 3·48 (s, 3H), 3·61 (s, 3H), 5·88 (s, 1H), 5·94 (s, 1H), 6·87 (d, 1H), 7·03 (d, 1H), 7·17 (t, 1H), 7·27 (d, 1H), 7·28 (s, 1H), 7·33 (t, 1H), 7·36 (d, 1H)
5f	2 924 (w), 1 593 (s)	655 (5·07)	1·45 (t, 3H), 1·62 (s, 3H), 1·76 (s, 3H), 3·40 (s, 3H), 4·25 (q, 2H), 5·72 (s, 1H), 6·21 (s, 1H), 6·81 (d, 1H), 7·22–7·24 (m, 4H), 7·43 (t, 1H), 7·64 (d, 1H)
6	2 971 (w), 1 590 (s), 1 578 (s)	677 (5·03)	1·41 (dt, 6H), 4·16 (q, 4H), 5·8 (s, 1H), 6·05 (s, 1H), 7·11–7·13 (m, 4H), 7·35 (m, 2H), 7·53 (t, 2H)

3 EXPERIMENTAL

3.1 General

Melting points were determined using a Thomas Hoover capillary melting point apparatus and are uncorrected. IR-spectra were recorded on an Analect Instruments FT-IR (MAP-66) using KBr pellets. Proton-NMR spectra were taken with a General Electrics QE-300 spectrometer and absorption spectra were determined on Perkin Elmer Lambda 6 UV/Vis spectrometer. Mass spectra of compounds **5a–f**, **6**, **3a** and **4a** were recorded on a Kratos Concept 1 H high resolution mass spectrometer. Ionization: liquid secondary ion mass spectrometry (LSIMS) using a Cs^+ ion gun with an incident energy of 35 keV. The samples were applied in a mixture of $CHCl_3:MeOH = 4:1$ using thioglycerol as matrix. The mass spectra of samples **3b**, **3c** and **4b** were taken on an Extrel Simulscan quadrupol mass spectrometer, 70 eV, El. The samples were applied in MeOH and measured as solids.

3.2 Synthesis of substituted squaraine derivatives 3 and 4

3.2.1 Monosubstituted ethylsquarates 3

A portion (15 mmol) of the methylene base **1b** or the quaternized salts (iodides) **1a** or **1c** were added to a stirred, hot solution of 10 mmol ethylsquarate and 2 ml of triethylamine in 15 ml ethanol. The solution was kept at 70–80°C for 5 min, cooled to RT and the yellow to red colored precipitates filtered, washed with ether and dried. In the case of **4b** no further purification was required; **4a** and **4c** were purified by column chromatography using silica gel (100–200 mesh) with $CHCl_3$/EtOAc 9:1 as eluent. Yields and MPs are shown in Table 1.

3.2.2 Monosubstituted squaric acids 4

A portion (5 mmol) of **3** was suspended in boiling ethanol. On adding 0·6 ml of 40% NaOH the precipitate dissolved and the solution was kept at boiling for 5 min and then cooled to RT. After addition of 6–7 ml 2 N HCl, the solution was concentrated by rotary evaporation and the resulting precipitates collected and used in the squaraine synthesis without further purification (for yields and MPs see Table 1).

3.2.3 Squaraine synthesis

A portion (1 mmol) of the squaric acid **4a–c** and 1 mmol of methylene base **1a**, **1b** or **1d** were heated under reflux in a mixture of 20 ml toluene and 20 ml 1-butanol. Water was removed azeotropically using a Dean–Stark trap. After 16 h, the reaction mixture was cooled to room temperature and the solvents removed by rotary evaporation. The residue was treated with ether and the product filtered. Further purification was achieved by column chromatography using silicagel (100–200 mesh) as adsorbent and chloroform–2-propanol mixtures as eluents.

ACKNOWLEDGEMENTS

This work was supported by a grant from the National Institutes of Health (RR 08119). Mass spectral measurements were carried out at the Middle Atlantic Mass Spectrometry Facility at The Johns Hopkins University, an NSF Shared Instrumentation Facility.

REFERENCES

1. Sprenger, H. E. & Ziegenbein, W., *Angew. Chem. Int. Ed. Engl.*, **5** (1966) 894.
2. Emmelius, M. Pawlowski, G. & Vollmann, H. W., *Angew. Chem.*, **101** (1989) 1475.
3. Keil, D. & Hartmann, H., *Dyes and Pigments*, **17** (1991) 19.
4. Treibs, A. & Jakob, K., *Liebigs Ann. Chem.*, **712** (1968) 123.
5. Law, K. & Bailey, F. C., *Can. J. Chem.*, **64** (1986) 1608.
6. Law, K. & Bailey, F. C., *Dyes and Pigments*, **9** (1988) 85–107.
7. Kampfer, H. & Verbille, K. E., US Patent 3,617,270, 1969.