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Preparation of 3-Substituted 6,7-Dimethoxyquinoxalin-2(1*H*)-ones and Studies of Their Potential as Fluoroionophores

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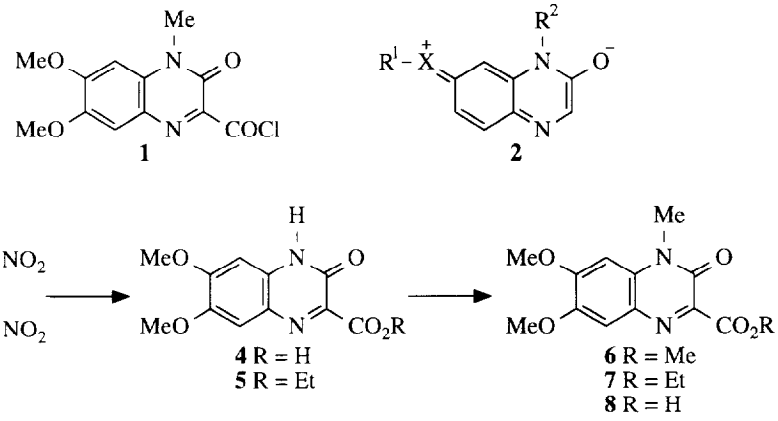
Dedicated to Prof. Hans Suschitzky on the occasion of his 80th birthday

Abstract: Improved routes to the quinoxalinone acid chloride **1** and the 3-methylquinoxalinone **21** are described. These intermediates are used to obtain the fluoroionophores **15**-**19** and **27**-**29**, respectively. The effects of the complexation of metal ions by the fluoroionophores is discussed. A red pigment **26** is obtained from **21**.

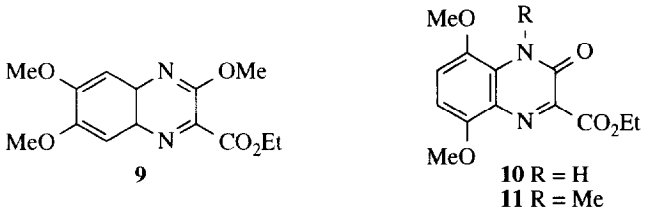
Fluoroionophores are compounds which change their fluorescence properties on complexation with an ion, usually a metal or ammonium ion. The fluoroionophore molecule contains both a fluorophore and a crown ether (or an azacrown group) which are either linked by one or two bonds or connected through a spacer group. Selectivity for an ion may be achieved by careful design of the complexing unit and of the total molecular architecture. The topic has been reviewed.[1] The commonly employed fluorophores include coumarins, stilbenes, azo dyes, benzo- and naphtho-anthracenes and anthraquinones. Recently, the acid chloride **1** has been described as a fluorescent reagent for the derivatization of alcohols[2] and amines,[3] but the use of the 2(1*H*)-quinoxalinone nucleus as the fluorophore in fluoroionophores has been little explored and we report here the results of our investigation of this potential application.

A high degree of fluorescence in 1-substituted 2(1*H*)-quinoxalinones is obtained when the 7-substituent is electron donating and can thus stabilize the excited state, to a first approximation represented by **2**. We decided to extend the use of the quinoxalinone nucleus as a fluorophore by incorporation of the moiety into potential fluoroionophores. The literature,[2] three-step, preparation of the acid **4** (Scheme 1) from *o*-dimethoxybenzene was followed, except that the hydrogenation of 1,2-dimethoxy-4,5-dinitrobenzene **3** was achieved most satisfactorily using a palladium catalyst. The troublesome step in the synthesis is the *N*- and *O*-methylation with diazomethane where only a 14% yield of **6** was obtained.[2] At about this time in our work, an improved preparation of **1** was reported.[4] In this procedure, the ethyl ester **5**, was methylated with dimethyl sulfate in the presence of potassium carbonate and acetone. The nOe evidence[4] showed the product (45% yield) was the required *N*-methylated derivative **7**. However, in our hands, this procedure[4] gave both **7** (39%) and the *O*-methyl isomer **9** (11%), and methylation of **5** with diazomethane gave almost equal amounts of **7** and **9**. The *O*-methylation of **5** is probably promoted by electron release from the 7-methoxyl group and it is interesting that methylation of 3-methylquinoxalin-2(1*H*)-one by the dimethyl sulfate procedure gave only the *N*-methylated product[5] and the same process with **10**[6] yielded the *N*-methyl derivative **11** as the sole product. Of further interest, and as expected, *N*-methyl-6,7-dimethoxy-

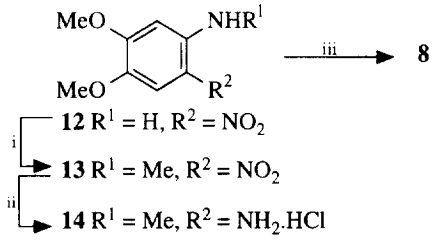
quinoxalinone **7** showed a higher fluorescence quantum yield than the 5,8-dimethoxy isomer **11**, and the *O*-methyl isomer **9** of **7** was not fluorescent.



Scheme 1

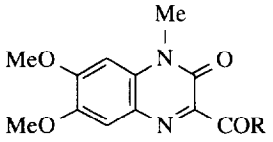


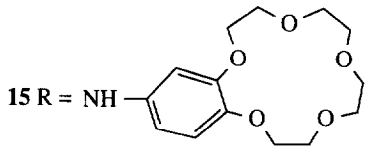
Faced with these unsatisfactory routes to **8** we devised an unambiguous, high yielding synthesis by performing the *N*-methylation step before forming the quinoxalinone nucleus. Monomethylation of the *N*-anion from **12**[7] at 0-5°C with methyl iodide produced **13** (96%) (Scheme 2), catalytic hydrogenation gave the diamine **14** (84%) and cyclization with ketomalonic acid yielded **8** (81%). Thus, acid chloride **1** was now readily available and was used to prepare the monoamide linked fluorophores **15-18**, the bisamide **19**, and the podand **20**.



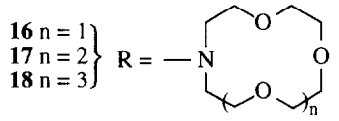
Reagents: (i) DMF, NaH, 0-5°C, MeI, 96% (ii) EtOH, Pd/C, H_2, r.t., 84%
(iii) 2-ketomalonic acid, 0.5 M HCl, 81%

Scheme 2



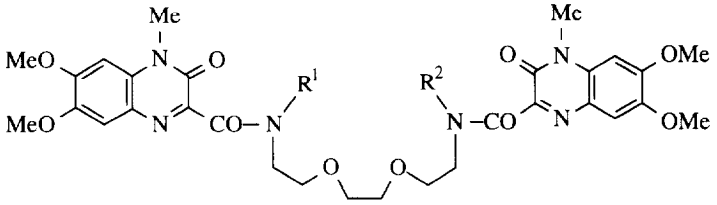


15 R = NH



16 n = 1
17 n = 2
18 n = 3

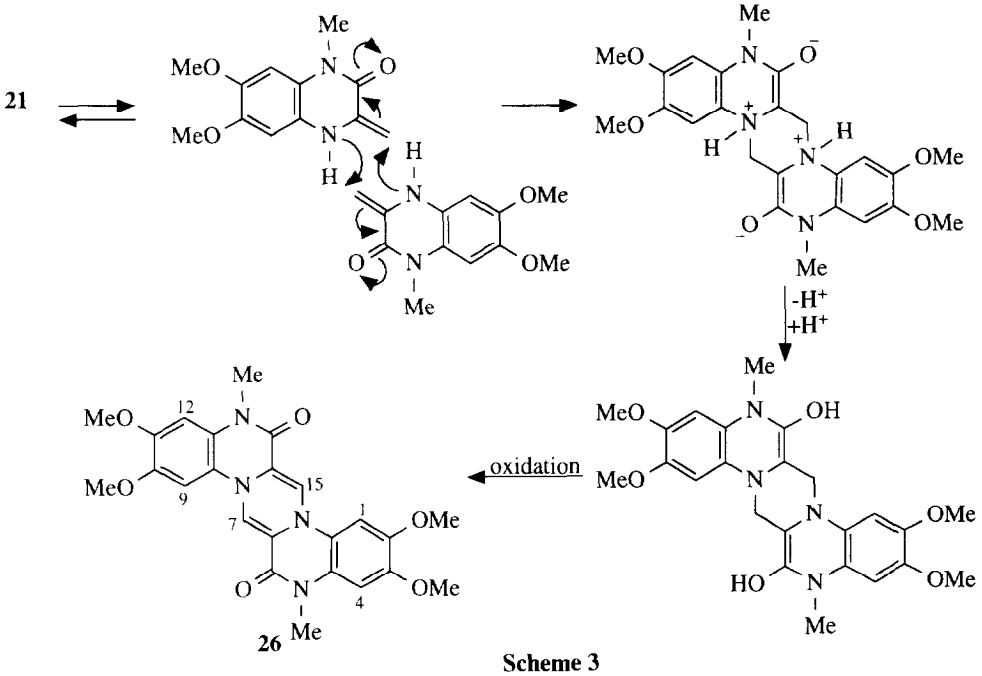
R =



19 $R^1R^2 = (CH_2)_2O(CH_2)_2O(CH_2)_2$
20 $R^1 = R^2 = H$

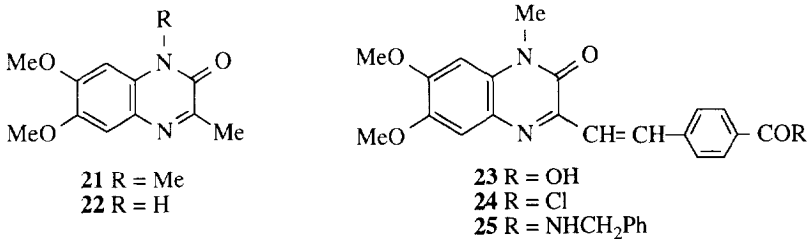
The reaction of pyruvic acid with the diamine **14** gave the 1,3-dimethylquinoxalinone **21**. This compound has been obtained previously[8] in low yield together with the *O*-methyl isomer by methylation of **22**. Condensation of the reactive *C*-methyl group of **21** with *p*-carboxybenzaldehyde in the presence of acetic anhydride gave the required, highly fluorescent **23** and an unexpected, insoluble red product.

This red solid was formed as the only product when **21** was heated alone in acetic anhydride and had very low solubility in commonly used organic solvents. The solid was purified by formation of an intensely blue solution in trifluoroacetic acid (presumably due to protonation) followed by precipitation of the red solid on the addition of water. The E.I. mass spectrum showed an M+2 peak at 466 daltons and a strong peak at 233 daltons. The ^1H n.m.r. spectrum (in trifluoroacetic acid) showed three two-proton singlets at δ 9.30, 7.51 and 7.30 ppm and three six-proton singlets at 4.31, 4.16 and 3.19 ppm. The simple proton spectrum and E.I. mass spectral data indicated a structure with some symmetry. The proposed structure **26** was based on the physical data, and the suggested mechanism for the formation of **26** is shown in Scheme 3. The accurate molecular mass determined by FAB mass spectrometry showed the compound to have the formula $C_{24}H_{24}N_4O_6$ in agreement with **26**. The cyclization step in the mechanism is shown as a concerted process for convenience but it may well occur as in two stages, though a compound corresponding to the product of the first step was not identified.



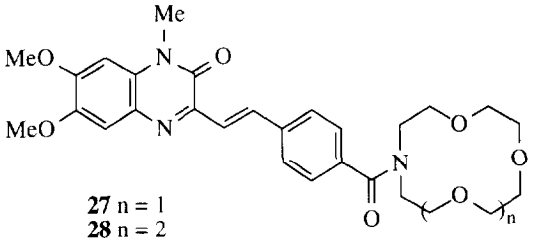
Scheme 3

The acid **23** was obtained smoothly when **21** and *p*-carboxybenzaldehyde were condensed in the presence of acid and piperidine with azeotropic removal of water. The solid acid chloride **24** was obtained by a standard method. Both the acid and the acid chloride showed intense yellow fluorescence and the acid chloride was used to obtain the fluoroionophores **25** and **27-29** by reaction with azacrowns. These compounds persistently gave low values for carbon on elemental analysis.



21 R = Me
22 R = H

23 R = OH
24 R = Cl
25 R = $NHCH_2Ph$



27 n = 1
28 n = 2
29 n = 3

We now turned our attention to fluorescence studies of the potential ionophores and the first result was disappointing: **15** was not fluorescent. This was surprising and interesting because the amides **16, 17** and **18** without the phenyl residue did exhibit fluorescence in solution in dichloromethane or methanol. The quantum yields are higher in the latter solvent and the fluorescence is at longer wavelength (by 14 to 20 nm) than in dichloromethane, presumably through greater stabilization of the $\Pi \rightarrow \Pi^*$ excited state in the solvent capable of forming hydrogen bonds. The size of the crown makes little difference to the fluorescence. Studies of mixtures containing a metal ion, the ionophore and dichloromethane showed the maximum increase in fluorescence quantum yield ϕ_f when the ionic size corresponded with the cavity size in the crown. Thus, Li^+ complexes with **16** gave $\phi_f = 0.24$ whereas other Group I and II metal ions gave $\phi_f = 0.1$ to 0.17. Correspondingly, **17** and **18** gave maximum ϕ_f values in the presence of Na^+ and K^+, respectively. The largest increase in quantum yield was found for the bisfluorophore **19** in the presence of potassium ions (Table 1). Models indicate that only the exocyclic amide oxygen atom is positioned above the crown helping to prevent the complexed metal ion from escaping. However, in the bisfluorophore the amide oxygen atoms are above and below the plane of the crown and may help to retain the metal ion within the cavity of the crown (Fig. 1).[9]

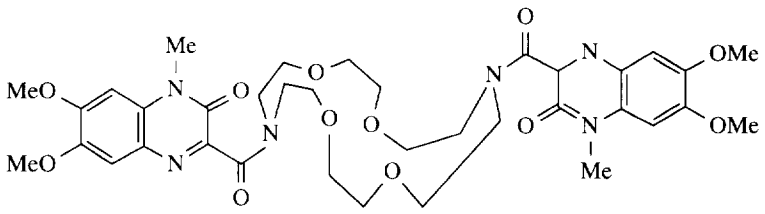


Figure 1

Shifts in the wavelength of maximum emission ($\lambda_{em.}$) upon complexation with a metal ion were small. Unexpectedly, the biggest shifts in $\lambda_{em.}$ were seen with **16** in the presence of magnesium, calcium and barium ions.

Solutions of **23** and **25** produced greenish-yellow fluorescence in daylight or under U.V. light whereas **8** and **16** were colourless in daylight but exhibited blue fluorescence under U.V. light. The quantum yields for **27**, **28** and **29** were in the range of 0.3-0.34 in methanol and 0.34-0.38 in dichloromethane (Table 1) but these showed little change on complexation with metal ions. It seems likely that the small positive charge created at the nitrogen atom of the crown upon complexation is too far removed from the fluorophore to affect the fluorescence. This idea is strengthened by the lack of correlation between ionic size and cavity size on the one hand with fluorescence quantum yield on the other hand for **27**, **28** and **29**, whereas, this correlation was marked for complexes of **16, 17** and **18**. The acid chloride **24** may be a better derivatizing agent for amines and alcohols than **1**.

Table 1 Spectral Data of the Azacrowns and their Complexes with Alkali and Alkaline Earth Ions in Dichloromethane

Compd.	16				17				18				19			
Metal ions	λ_{exc} (nm)	Conc.[a] (mol)	λ_{em} (nm)	Φ_f	λ_{exc} (nm)	Conc.[a] (mol)	λ_{em} (nm)	Φ_f	λ_{exc} (nm)	Conc.[a] (mol)	λ_{em} (nm)	Φ_f	λ_{exc} (nm)	Conc.[a] (mol)	λ_{em} (nm)	Φ_f
-	385	7.5×10^{-7}	454	0.06	385	7.5×10^{-7}	457	0.07	386	7.5×10^{-7}	455	0.07	386	4.5×10^{-7}	454	0.09
Li^+	392	5×10^{-5}	459	0.24	388	5×10^{-6}	457	0.18	387	5×10^{-5}	456	0.24	388	2×10^{-6}	455	0.25
Na^+	389	5×10^{-6}	456	0.17	388	5×10^{-5}	457	0.26	388	1×10^{-5}	458	0.31	389	1×10^{-4}	454	0.40
K^+	387	1×10^{-5}	456	0.10	390	5×10^{-5}	457	0.24	387	5×10^{-5}	458	0.33	389	5×10^{-5}	455	0.41
Mg^{++}	390	1×10^{-5}	467	0.13	390	1×10^{-5}	457	0.19	387	3×10^{-6}	457	0.26	390	1×10^{-6}	456	0.17
Ca^{++}	396	1×10^{-4}	473	0.13	388	1×10^{-5}	457	0.23	387	1×10^{-5}	456	0.27	390	1×10^{-5}	456	0.36
Ba^{++}	398	1×10^{-4}	464	0.14	390	5×10^{-5}	458	0.20	388	2×10^{-6}	457	0.25	389	5×10^{-6}	454	0.34

Compd.	27				28				29			
Metal ions	λ_{exc} (nm)	Conc.[a] (mol)	λ_{em} (nm)	Φ_f	λ_{exc} (nm)	Conc.[a] (mol)	λ_{exc} (nm)	Φ_f	λ_{exc} (nm)	Conc.[a] (mol)	λ_{em} (nm)	Φ_f
-	431	4.5×10^{-7}	488	0.31	431	4.5×10^{-7}	490	0.31	431	4.5×10^{-7}	491	0.31
Li^+	431	1×10^{-3}	495	0.34	434	5×10^{-4}	502	0.40	433	1×10^{-4}	502	0.38
Na^+	432	1×10^{-3}	498	0.35	432	1×10^{-3}	502	0.41	432	5×10^{-4}	500	0.38
K^+	431	5×10^{-5}	491	0.36	433	1×10^{-4}	503	0.39	433	2×10^{-4}	499	0.38
Mg^{++}	431	1×10^{-3}	493	0.36	431	5×10^{-4}	493	0.40	432	1×10^{-4}	499	0.38
Ca^{++}	431	5×10^{-4}	497	0.37	434	5×10^{-3}	505	0.41	434	5×10^{-4}	500	0.43
Ba^{++}	431	5×10^{-5}	491	0.32	432	2×10^{-3}	501	0.37	433	5×10^{-4}	500	0.33

[a] Concentration of the Fluorophore

EXPERIMENTAL

Melting points were determined on an Electrothermal digital apparatus and are uncorrected. The IR spectra were produced on a Perkin-Elmer 1420 spectrometer and ^{1}H NMR spectra were obtained for solutions containing TMS as the internal standard on either a Varian CFT-20 or Jeol FX-200 spectrometer. Low resolution EI mass spectra were obtained on an AEI MS-902 instrument and the accurate mass measurements were provided by SERC Mass Spectrometry Service Centre, Swansea. Elemental analyses were determined by Medac Ltd., Brunel University. Analytical thin-layer chromatography was carried out on silica gel G/UV_{254} on precoated plastic sheets from Camlab. Column chromatography was performed on May and Baker silica gel (40-60 μm) with slight positive pressure. Petroleum spirit refers to petroleum ether of boiling range 40-60°C. Solvents for chromatography were distilled before use.

UV spectra were recorded usilng a Perkin-Elmer Lambda 9 UV/VIS/NIR spectrophotometer for solutions in quartz cells. Excitation and fluorescence emission spectra were obtained at room temperature (25°C) on a Perkin-Elmer LS 50B Luminescence spectrometer for solutions with an absorbance of 0.01 at the excitation wavelength. A solution of quinine sulfate in perchloric acid (0.1 mol/dm^{-3}) with an absorbance of 0.01 was used as the standard for quantum yield (ϕ_f) measurements and was taken to have ϕ_f = 0.59. The solutions of the metal ions were prepared by dissolving the metal perchlorate in a few drops of methanol and diluting to a known volume with dichloromethane.

Methylation of 5 with diazomethane to give 7 and 9

A cold stirred solution of the ester **5**[4] (0.5 g, 1.8 mmol) in dry methanol (100 ml) was treated with ethereal diazomethane solution (20 ml) in small portions. When the reaction was complete (t.l.c.), the solvent removed and the residue separated by column chromatography (silica gel, ethyl acetate-petroleum spirit, 1:1 *v/v*). The first compound eluted was crystallized from ethyl acetate-dichloromethane mixture to give **ethyl 2,6,7-trimethoxyquinoxaline-3-carboxylate** (**9**) (0.25 g, 47%), m.p. 131-132°C; $\nu_{max.}$ 1720 (CO), 1630 cm^{-1} (CO); δ ($CDCl_3$) 1.44 (3H, t, CH_2CH_3), 3.98 (3H, s, 6-OCH_3), 4.03 (3H, s, 7-OCH_3), 4.11 (3H, s, 2-OCH_3), 4.48 (2H, q, CH_2CH_3), 7.15 (1H, s, 8-H), 7.37 (1H, s, 5-H); m/z 293 (MH^+, 16%), 292 (M^+, 100%), 247 (M^+-C_2H_5, 17%), 219 (M^+-$COOC_2H_5$, 46%); Anal. Calcd. for $C_{14}H_{16}N_2O_5$: C, 57.53; H, 5.52; N, 9.58. Found: C, 57.64; H, 5.54; N, 9.60%.

The second component eluted was crystallized from methanol-dichloromethane mixture to yield the bright yellow **ethyl 6,7-dimethoxy-1-methyl-2(1*H*)-quinoxalinone-3-carboxylate** (**7**) (0.24 g, 45%), m.p. 258-260°C (lit., [4] 259-260°C); $\nu_{max.}$ 1730 (CO), 1650 cm^{-1} (CO-amide); δ ($CDCl_3$) 1.43 (3H, t, CH_2CH_3), 3.71 (3H, s, N-CH_3), 3.92 (3H, s, 6-OCH_3), 4.02 (3H, s, 7-OCH_3), 4.47 (2H, q, CH_2CH_3), 6.64 (1H, s, 8-H), 7.34 (1H, s, 5-H); m/z 293 (MH^+, 15%), 292 (M^+, 100%), 277 (M^+-CH_3, 11%), 247 (M^+-OC_2H_5, 15%), 219 (M^+-$COOC_2H_5$, 13%).

Ethyl 5,8-dimethoxy-2(1*H*)-quinoxalinone-3-carboxylate (11)

A mixture of **10**[6] (0.1 g, 0.36 mmol), anhydrous potassium carbonate (1 g) and acetone (50 ml) was stirred for 15 min. Dimethyl sulfate (2 ml) was then added dropwise, the reaction maintained at 40°C for 4 h and then boiled under reflux for 30 min. The reaction mixture was poured into water, the precipitate filtered

off and crystallized from ethanol to give the yellow ethyl 5,8-dimethoxy-2(1*H*)-quinoxalinone-3-carboxylate (**11**) (0.33g, 63%), m.p. 168-169°C; $\nu_{max.}$ 1750 (CO), 1650 cm^{-1} (CO-amide); δ ($CDCl_3$) 1.40 (3H, t, CH_2CH_3), 3.84 (3H, s, N-CH_3), 3.94 (6H, s, 5- and 8-OCH_3), 4.43 (2H, q, CH_2CH_3), 6.67 (1H, d, 6-H), 7.06 (1H, d, 7-H); m/z 293 (MH^+, 2%), 292 (M^+, 7%), 278 (M^+-CH_2, 100%), 263 (47), 235 (58), 218 (45); Anal. Calcd. for $C_{14}H_{16}N_2O_5$: C, 57.53; H, 5.52; N, 9.58. Found: C, 57.08; H, 5.43; N, 9.44%.

***N*-Methyl-2-nitro-4, 5-dimethoxyaniline (13)**

To a solution of 4-amino-5-nitroveratrol[7] (**12**) (2.11 g, 11 mmol) in dry DMF (40 ml) at 0-5°C was added sodium hydride (0.26 g, 11.3 mmol) and the mixture stirred for 10 min. Methyl iodide (3 ml) was added dropwise at 0-5°C over a period of 30 min. Stirring was continued for 1 h each at 0-5°C and then at room temperature. The reaction mixture was diluted with water (100 ml) and cooled. The precipitate was filtered off, washed with water and crystallized from ethanol to yield **13** (2.16 g, 96%), m.p. 145-146°C; $\nu_{max.}$ 3390 cm^{-1} (NH); δ ($CDCl_3$) 3.03 (3H, d, exchanged into a multiplet on addition of D_2O, N-CH_3), 3.84 (3H, s, 4-OCH_3), 3.95 (3H, s, 5-OCH_3), 6.12 (1H, s, 6-H), 7.57 (1H, s, 3-H), 8.47 (1H, br.s, exchanged with D_2O, NH); m/z 213 (MH^+, 11%), 212 (M^+, 100%), 197 (M^+-CH_3, 67%), 183 (30), 150 (23); Anal. Calcd. for $C_9H_{12}N_2O_4$: C, 50.94; H, 5.66; N, 13.20. Found: C, 51.09; H, 5.61; N, 12.98%.

2-(*N*-Methylamino)-4,5-dimethoxyaniline monohydrochloride (14)

To *N*-methyl-2-nitro-4,5-dimethoxyaniline (**13**) (2.16 g, 10 mmol) in ethanol (75 ml), palladium on carbon (10%) (0.5 g) was added and the reaction mixture hydrogenated for 4 h in a Parr hydrogenator at 60 lb/in^2. The catalyst was filtered off, the filtrate concentrated to 20 ml and conc. hydrochloric acid (5 ml) added. The grey-purple precipitate obtained was filtered off, washed with dichloromethane and crystallized from ethanol (1.87 g, 84%), m.p. 207-209°C (decomp.); $\nu_{max.}$ 3450 cm^{-1} (OH); δ [$(CD_3)_2SO$] 2.57 (3H, s, N-CH_3), 3.71 (2H, br.s, exchanged with D_2O, NH_2); m/z 182 (M^+, 69%), 167 (M^+-CH_3, 100%), 152 (M^+-$2CH_3$, 35%); Anal. Calcd. for $C_9H_{15}N_2O_2Cl.H_2O$: C, 45.76; H, 6.35; N, 11.83; Cl, 14.83. Found: C, 45.65; H, 6.28; N, 11.59; Cl, 14.48%.

General Preparation for the Quinoxalines 8 and 21

A mixture of the monohydrochloride **14** (13.5 mmol), pyruvic acid or 2-ketomalonic acid and hydrochloric acid (0.5 M, 130 ml) was heated for 2 to 3 h in a boiling water-bath. The reaction mixture was basified with aqueous sodium hydroxide (1 M), extracted with dichloromethane, the extracts washed with water, dried and evaporated *in vacuo* to obtain the crude product.

6,7-Dimethoxy-1-methyl-2(1*H*)-oxoquinoxaline-3-carboxylic acid (8) was crystallized from mixture of methanol and dichloromethane in 81% yield, m.p. 233-235°C (lit.,[4] m.p. 234-235°C).

6,7-Dimethoxy-1,3-dimethyl-2(1*H*)-oxoquinoxaline (21) was crystallized from ethyl acetate--dichloromethane mixture in 73% yield, m.p. 169-170°C (lit.,[8] 170-171°C).

Reaction of 6,7-dimethoxy-1,3-dimethyl-2-oxoquinoxaline (21) with *p*-carboxybenzaldehyde to obtain 23 and 26

A mixture of **21** (0.5 g, 2.13 mmol), *p*-carboxybenzaldehyde (0.33 g, 2.2 mmol) and acetic anhydride (30 ml) was refluxed for 3 h. The reaction mixture developed a yellow fluorescence and a red precipitate was formed which was filtered off. The filtrate was diluted with water (100 ml), neutralized with sodium carbonate solution and extracted with dichloromethane (3x100 ml). The extract was dried (anhydrous sodium sulfate), evaporated *in vacuo* and the yellow residue was purified by repeated dissolution in NaOH solution (1 M) and precipitation by the addition of dil. HCl. The solid was then crystallized from methanol-dichloromethane mixture to yield orange **6,7-dimethoxy-1-methyl-3-(*p*-carboxyphenylvinyl)-2(1*H*)-quinoxalinone (23)** (0.12 g, 42%), m.p. 301-302°C; $\nu_{max.}$ 3480 (OH), 1645 cm^{-1} (CO); δ[$(CD_3)_2SO$] 3.70 (3H, s, N-CH_3), 3.87 (3H, s, 6-OCH_3), 3.97 (3H, s, 7-OCH_3), 7.01 (1H, s, 8-H), 7.32 (1H, s, 5-H), 7.70 (1H, d, *J* 16 Hz, CH=C*H*), 7.77 (2H, d, *J* 8.3 Hz, 2- and 6-H), 7.96 (d, 2H, *J* 8.3 Hz, 3- and 5-H), 8.00 (1H, d, *J* 16 Hz, heteroaryl-C*H*=CH); m/z 367 (MH^+, 24%), 366 (M^+, 100%), 351 (M^+-CH_3, 37%), 322 (M^+-CO_2, 6%), 219 (M^+-*p*-carboxystyryl, 29%), 149 (73); Anal. Calcd. for $C_{20}H_{18}N_2O_5$: C, 65.57; H, 4.95; N, 7.65. Found: C, 65.33; H, 5.23; N, 7.50%.

The red solid was purified by dissolution in trifluoroacetic acid and precipation by addition of water. The solid was washed thoroughly with water, methanol and finally with acetone to give bright red micro crystal of **2,3,10,11-tetramethoxy-5,13-dimethylpyrazino[1,2-a;4,5-a′]diquinoxaline-6,14(5*H*,13*H*)-dione (26)** (0.155 g, 47%), m.p. >350°C; $\nu_{max.}$ 1650 cm^{-1} (CO); δ (CF_3COOH) 4.16 (6H, s, 5- and 13-NCH_3), 4.19 (6H, s, 2- and 10-CH_3), 4.30 (6H, s, 3- and 11-OCH_3), 7.30 (2H, s, 4- and 12-H), 7.51 (2H, s, 1- and 9-H), 9.30 (2H, s, 7- and 15-H); m/z 466 (M^++2, 100%), 452 (11), 440 (11), 380 (19), 365 (14); Anal. Calcd. for $C_{24}H_{24}N_4O_6$: C, 62.06; H, 5.21; N, 12.06. Found: C, 60.79; H, 5.14; N, 11.70%. (Found (FAB; NOBA): MH^+, 465.1774. $C_{24}H_{25}N_4O_6$ requires MH, 465.1743).

2,3,10,11-Tetramethoxy-5,13-dimethoxypyrazino[1,2-a;4,5-a′]diquinoxaline-6,14(5*H*,13*H*-dione (26)

A mixture of 6,7-dimethoxy-1,3-dimethyl-2-oxoquinoxaline (**21**) (0.1 g, 0.4 mmol) and acetic anhydride was refluxed for 3 h. The red solid was filtered off and purified as described (0.06 g, 56%).

6,7-Dimethoxy-1-methyl-3-(*p*-carboxyphenylvinyl)-2(1*H*)-quinoxalinone (23)

To a solution of **21** (0.5 g, 2.13 mmol) and *p*-carboxybenzaldehyde (0.33 g, 2.2 mmol) in dry toluene (50 ml) was added glacial acetic acid (0.8 ml) and piperidine (1 ml) and the mixture refluxed in a flask fitted with a Dean and Stark apparatus for 24 h. The solid was filtered off, washed with a little cold water and crystallized from a mixture of methanol and dichloromethane to give **23** (0.58 g, 74%), m.p. 301-302°C; the physical data was the same as described above.

General Procedure for the Preparation of the Acid Chlorides 1 and 24

To freshly distilled thionyl chloride (20 ml), the appropriate acid (3 mmol) was added and the mixture refluxed for 20 min to 1 h. The precipitate formed on addition of petroleum spirit was crystallized from benzene-petroleum spirit mixture to give the orange yellow acid chloride in 91-93% yield.

6,7-Dimethoxy-1-methyl-2(1*H*)-quinoxalinone-3-carbonyl chloride (**1**). m.p. 258-261°C (decomp.) (lit.,[2] 261°C).

6,7-Dimethoxy-1-methyl-3-vinylphenyl-2(1*H*)-quinoxalinone-4-carbonyl chloride (**24**). m.p. 278-280°C; $\nu_{max.}$ 1740 (CO), 1655 cm^{-1} (CO); δ [$(CD_3)_2SO$] 3.71 (3H, s, 1-NCH_3), 3.79 (3H, s, 7-OCH_3), 3.87 (3H, s, 6-OCH_3), 7.01 (1H, s, 8-H), 7.39 (1H, s, 5-H), 7.70 (1H, d, *J* 16 Hz, CH=C*H*), 7.78 (2H, d, *J* 8.3 Hz, 2- and 6-H), 7.97 (2H, d, *J* 8.3 Hz, 3- and 5-H), 8.00 (1H, d *J* 16 Hz, heteroaryl-C*H*=CH); m/z 386 (M^+, 13% for ^{37}Cl), 384 (M^+, 36% for ^{35}Cl), 369 (M^+-CH_3, 9%), 349 (M^+-^{35}Cl, 7%); Anal. Calcd. for $C_{20}H_{17}N_2O_4Cl$: C, 62.42; H, 4.45; N, 7.28; Cl, 9.21. Found: C, 62.16; H, 4.30; N, 7.17; Cl, 8.93%.

General Procedure for the Preparation of Crown Ether 15, Azacrowns 16, 17, 18, 27, 28, 29 and the Amide 25

A mixture of the appropriate amine (0.5 mmol) and sodium hydride (0.52 mmol) in dry benzene (30 ml) was stirred for 15 min followed by the addition of the appropriate acid chloride **1** or **24** (0.51 mmol). The reaction mixture was refluxed for 3 to 6 h, washed thoroughly with dil. hydrochloric acid (0.1 M) and finally with water. The dried solution was evaporated *in vacuo* to yield the crude product.

***N*-(6,7-Dimethoxy-1-methyl-2(1*H*)-quinoxalinone-3-carbonyl)-4-aminobenzo-15-crown-5** (**15**) was purified by column chromatography (silica gel, ethyl acetate-dichloromethane, 20:1 *v/v*) and crystallized from ethyl acetate-dichloromethane mixture to give the amide **15** (0.17g, 64%), m.p. 181-182°C; $\nu_{max.}$ 3440 (NH), 1675 cm^{-1} (CO); δ ($CDCl_3$) 3.76 (8H, s, 8-, 9-, 11- and 12-CH_2), 3.84 (3H, s, N-CH_3), 3.91 (4H, t, 6- and 14-CH_2), 3.98 (3H, s, 6-OCH_3), 4.07 (3H, s, 7-OCH_3), 4.17 (4H, t, 5- and 15-CH_2), 4.73 (1H, s, exchanged with D_2O, NH), 6.73 (1H, s, 8-H), 6.87 (1H, d, *J* 8 Hz, 3-Ar-H), 7.20 (1H, dd, *J* 8.8, 2.4 Hz, 5-Ar-H), 7.63 (1H, s, 5-H), 7.66 (1H, d, *J* 2.5 Hz, 6-Ar-H); m/z 530 (MH^+, 27%), 529 (M^+, 100%), 309 (11), 283 (21), 247 (17); Anal. Calcd. for $C_{25}H_{31}N_3O_9$: C, 58.02; H, 6.04; N, 8.12. Found: C, 57.65; H, 5.87; N, 7.62%.

3-(1,4,7-Trioxa-10-azacyclododecane-10-carbonyl)-6,7-dimethoxy-1-methylquinoxaline-2(1*H*)-one (**16**) was purified by preparative layer chromatography (ethyl acetate-dichloromethane, 9:1 *v/v*), followed by crystallization from the mixture of ethyl acetate-dichloromethane to yield the light yellow amide **16** (0.17 g, 82%), m.p. 124-125°C; $\nu_{max.}$ 1655 (CO), 1635 cm^{-1} (CO); δ ($CDCl_3$) 3.67 (16H, m, 8xCH_2), 3.83 (3H, s, N-CH_3), 3.91 (3H, s, 6-OCH_3), 4.00 (3H, s, 7-OCH_3), 6.66 (1H, s, 8-H), 7.24 (1H, s, 5-H); m/z 422 (MH^+, 9%), 421 (M^+, 35%), 247 (24), 219 (28), 191 (27), 57 (100); Anal. Calcd. for $C_{20}H_{27}N_3O_7$: C, 57.00; H, 6.46; N, 9.97. Found: C, 56.85; H, 6.43; N, 9.91%.

3-(1,4,7,10-Tetraoxa-13-azacyclopentadecane-13-carbonyl)-6,7-dimethoxy-1-methyl-2-(1*H*)-quinoxalinone (**17**) was purified by preparative layer chromatography (ethyl acetate-methanol, 9:1 *v/v*) and crystallized from a mixture of ethyl acetate and methanol (69%), m.p. 174-175°C; $\nu_{max.}$ 1650 (CO), 1635 cm^{-1} (CO); δ ($CDCl_3$) 3.59 (20H, m, 10xCH_2), 3.81 (3H, s, N-CH_3), 3.91 (3H, s, 6-OCH_3), 4.01 (3H, s, 7-OCH_3), 6.61 (1H, s, 8-H), 7.25 (1H, s, 5-H); m/z 466 (MH^+, 33%), 465 (M^+, 100%), 450 (M^+-CH_3, 3%),

435 (4), 247 (10); Anal. Calcd. for $C_{22}H_{31}N_3O_8$: C, 56.76; H, 6.71; N, 9.03. Found: C, 56.66; H, 6.72; N, 8.93%.

3-(1,4,7,10-Pentaoxa-16-azacyclooctadecane-16-carbonyl)-6,7-dimethoxy-1-methyl-2(1*H*)-quinoxalinone (**18**) was purified by preparative layer chromatography (ethyl acetate-methanol, 9:1 *v/v)* followed by crystallization from ethyl acetate-methanol mixture (0.16 g, 63%), m.p. 151-152°C; $\nu_{max.}$ 1640 (CO), 1615 cm^{-1} (CO); δ ($CDCl_3$) 3.59 (24H, m, 12XCH_2), 3.83 (3H, s, N-CH_3), 3.91 (3H, s, 6-OCH_3), 4.00 (3H, s, 7-OCH_3), 6.66 (1H, s, 8-H), 7.25 (1H, s, 5-H); m/z 509 (M^+, 100%), 276 (30), 262 (54), 247 (48), 235 (55), 219 (50), 191 (36); Anal. Calcd. for $C_{24}H_{35}N_3O_9$: C, 56.57; H, 6.92; N, 8.25. Found: C, 56.43; H, 6.99; N, 8.14%.

6,7-Dimethoxy-1-methyl-3-[4-(*N*-benzylcarboxamido)]phenylvinyl-2(1*H*)-quinoxalinone (**25**) was obtained in 81% yield, m.p. 255-256°C; $\nu_{max.}$ 3300 (NH), 1655 (CO), 1635 cm^{-1} (CO); δ ($CDCl_3$) 3.75 (3H, s, N-CH_3), 3.98 (3H, s, 6-OCH_3), 4.04 (3H, s, 7-OCH_3), 4.66 (2H, d, *J* 5.5 Hz, CH_2), 6.42 (1H, t, exchanged with D_2O, NH), 6.70 (1H, s, 8-H), 7.32 (1H, s, 5-H), 7.33 (5H, m, Ph-H), 7.72 (2H, d, *J* 8.6 Hz, 2- and 6-H), 7.76 (1H, d, *J* 16.5 Hz, CH=C*H*), 7.81 (2H, d, *J* 8.6 Hz, 3- and 5-H), 8.04 (1H, d, *J* 16.4 Hz, heteroaryl-C*H*=CH); m/z 456 (MH^+, 30%), 455 (M^+, 100%), 440 (M^+-CH_3, 15%); Anal. Calcd. for $C_{27}H_{25}N_3O_4$: C, 71.19; H, 5.53; N, 9.22. Found: C, 70.22; H, 5.41; N, 9.21%.

3-(2-[4-{1,4,7-Trioxa-10-azacyclododecane-10-carbonyl}phenyl]vinyl)-6,7-dimethoxy-1-methyl-2-(1*H*)-quinoxalinone (**27**) was obtained in 68% yield, m.p. 214-215°C; $\nu_{max.}$ 1655 (CO), 1630 cm^{-1} (CO); δ ($CDCl_3$) 3.76 (3H, s, N-CH_3), 3.67 (16H, m, 8xCH_2), 3.99 (3H, s, 6-OCH_3), 4.04 (3H, s, 7-OCH_3), 6.70 (1H, s, 8-H), 7.33 (1H, s, 5-H), 7.54 (2H, d, *J* 7.8 Hz, 2- and 6-H), 7.67 (d, 2H, *J* 8.3 Hz, 3- and 5-H), 7.74 (1H, d, *J* 16.2 Hz, CH=C*H*), 8.3 (1H, d, *J* 16.2 Hz, heteroaryl-C*H*=CH); m/z 524 (MH^+, 12%), 523 (M^+, 27%), 278 (18), 220 (15), 149 (20), 57 (100); Anal. Calcd. for $C_{28}H_{33}N_3O_7$: C, 64.23; H, 6.35; N, 8.02. Found: C, 63.03; H, 6.41; N, 7.78%. (Found: (FAB; NOBA): M^+, 523.232. $C_{28}H_{33}N_3O_7$ requires M, 523.231).

3-(2-[4-{1,4,7,10-Tetraoxa-13-azacyclopentadecane-13-carbonyl}phenyl]vinyl)-6,7-dimethoxy-1-methyl-2(1*H*)-quinoxalinone (**28**) was obtained in 61% yield, m.p. 194-195°C; $\nu_{max.}$ 1645 cm^{-1} (CO); δ ($CDCl_3$) 3.64 (20H, m, 10xCH_2), 3.77 (3H, s, N-CH_3), 3.95 (3H, s, 6-OCH_3), 4.00 (3H, s 7-OCH_3), 6.66 (1H, s, 8-H), 7.27 (1H, s, 5-H), 7.37 (2H, d, *J* 8.2Hz, 2- and 6-H), 7.62 (2H, d, *J* 8.3 Hz, 3- and 5-H), 7.65 (1H, d, *J* 16 Hz, CH=C*H*), 8.01 (1H, d, *J* 16.3 Hz, heteroaryl-C*H*=CH); m/z 568 (MH^+, 46%), 567 (M^+, 100%), 552 (M^+-CH_3, 4%), 339 (15); Anal. Calcd. for $C_{30}H_{37}N_3O_8.H_2O$: C, 61.53; H, 6.66; N, 7.17. Found: C, 61.78; H, 6.58; N, 6.93%. (Found: (FAB; NOBA): MH^+, 568.2655. $C_{30}H_{38}N_3O_8$ requires MH, 568.2659).

3-(2-[4{1,4,7,10,13-Pentaoxa-17-azacyclooctandecane-16-carbonyl}phenyl]vinyl)-6,7-dimethoxy-1-methyl-2(1*H*)-quinoxalinone (**29**) was obtained in 63% yield, m.p. 169-170°C; $\nu_{max.}$ 1655 (CO), 1625 cm^{-1}(CO); δ ($CDCl_3$) 3.69 (24H, m, 12xCH_2), 3.76 (3H, s, N-CH_3), 3.99 (3H, s, 6-OCH_3), 4.04 (3H, s, 7-OCH_3), 6.71 (1H, s, 8-H), 7.33 (1H, s, 5-H), 7.43 (2H, d, *J* 8.3 Hz, 2- and 6-H), 7.67 (2H, d, *J* 8.8 Hz, 3-

and 5-H), 7.74 (1H, d, *J* 16 Hz, CH=C*H*), 8.03 (1H, d, *J* 16.6 Hz, heteroaryl-C*H*=CH); m/z 612 (MH^+, 46%), 611 (M^+, 96%), 563 (12), 510 (16), 509 (53), 349 (30); Anal. Calcd. for $C_{32}H_{41}N_3O_9$: C, 62.83; H, 6.76; N, 6.87. Found: C, 61.74; H, 6.76; N, 6.72%. (Found (FAB; NOBA): MH^+, 612.2915. $C_{32}H_{42}N_3O_9$ requires 612.2921).

General Procedure for the Preparation of Bisamide 19 and Podand 20

The reaction was carried out as described as for **15** except that sodium hydride and the acid chloride were used in 2 molar equivalents.

***N,N'*-Bis(6,7-dimethoxy-1-methyl-2(1*H*)-oxoquinoxaline-3-carbonyl)-1,4,10,13-tetraoxa-6,16-diazacyclooctadecane** (**19**) was purified by preparative layer chromatography followed by crystallization from a mixture of ethyl acetate and dichloromethane (79%), m.p. 153-154°C; $\nu_{max.}$ 1660 (CO), 1640 cm^{-1} (CO); δ ($CDCl_3$) 3.70 (24H, m, 12xCH_2), 3.69 (6H, s, 2xNCH_3), 3.92 (6H, s, 2x7-OCH_3), 4.02 (6H, s, 2x6-OCH_3), 6.67 (2H, s, 2x5-H), 7.26 (2H, s, 2x8-H); m/z 754 (M^+, 13%); Anal. Calcd. for $C_{36}H_{46}N_6O_{12}$: C, 57.29; H, 6.14; N, 11.13. Found: C, 55.96; H, 6.15; N, 10.76%. (Found (FAB; NOBA): MH^+, 755.3255. $C_{36}H_{47}N_6O_{12}$ requires 755.3255).

***N,N'*-Bis(6,7-dimethoxy-1-methyl-2(1*H*)-oxoquinoxaline-3-carbonyl)-1,8-diamino-3,6-dioxaoctane** (**20**) was crystallized from methanol-dichloromethane mixture as a bright yellow solid (64%), m.p. 240-241°C; $\nu_{max.}$ 3290 (NH), 1675 (CO), 1640 cm^{-1} (CO); δ ($CDCl_3$) 3.68 (6H, s, 2xNCH_3), 3.77 (12H, m, 6xCH_2), 3.81 (6H, s, 2x7-OCH_3), 4.01 (6H, s, 2x6-OCH_3), 6.59 (2H, s, 2x5-H), 7.10 (2H, s, 2x8-H), 10.08 (2H, s, exchanged with D_2O, 2xNH); m/z 640 (M^+, 42%), 490 (19), 420 (53), 264 (33), 247 (54), 220 (100); Anal. Calcd. for $C_{30}H_{36}N_6O_{16}$: C, 56.24; H, 5.66; N, 13.12. Found: C, 56.24; H, 5.66; N, 13.12%.

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