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Preparation and Characterization of Porphyrin–Acridine Conjugates as Bifunctional Antitumour Agents

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Abstract

The porphyrin–acridine conjugates (22) and (23) were prepared by condensation of porphyrin (17) with the 9-aminoacridine derivative (6) or (15), respectively. The conjugate drugs were isolated by size-exclusion chromatography in yields of up to 35% and further purified by semipreparative h.p.l.c. to 98% purity. Characterization of the conjugates was effected by ^{1}H n.m.r. and u.v./vis. spectroscopy, f.a.b. mass spectrometry and u.v./vis. diode array h.p.l.c. Attempts to condense acridine (6) or (15) to porphyrin (16), (18) or (19) resulted in the isolation of the porphyrin–acridine conjugates (20), (21), (24) and (25) in low yields ($\leq$25%), but the products could not be obtained in a pure state. However, their presence was identified by several physical measurements.

Introduction

The incorporation of two different drugs into a single compound may lead to a 'conjugate' with characteristics contributed from both precursors. We have been interested in developing novel antitumour agents by constructing bifunctional drugs which take advantage of the tumour localizing and photosensitizing properties of porphyrins[1] and the inherent cytotoxicity of acridine molecules.[2] Hence, the porphyrin–acridine conjugates (20)–(25) represent a class of compounds which may effect tumour cell kill under photoirradiation conditions as well as being intrinsically cytotoxic. Also, the tumour selectivity of the porphyrin may be used as a means of localizing the acridine in tumour tissue *in vivo*. Preliminary results have indicated that conjugates (22) and (23) have cytotoxic activity against the C6 glioma and MCF-7 tumour cell line comparable to that of conventional cytotoxic agents, and *in vivo* show localization in tumour tissue of mice bearing the human colon carcinoma COBAp xenograft.[3]

We report here the synthesis and characterization of compounds (20)–(25) which incorporate two or four acridine chromophores per porphyrin molecule. Two different acridine derivatives based on 9-aminoacridine and 9-amino-*N*-[2-(dimethylamino)ethyl]acridine-4-carboxamide were prepared for amide coupling

[1] Dougherty, T. J., *Photochem. Photobiol.*, 1993, **58**, 895.
[2] Finlay, G. J., Marshall, E. S., Matthews, J. H. L., Paull, K. D., and Baguley, B. C., *Cancer Chemother. Pharmacol.* 1993, **31**, 401.
[3] Karagianis, G., Reiss, J. A., Zunino, F., and Phillips, D. R., unpublished data.

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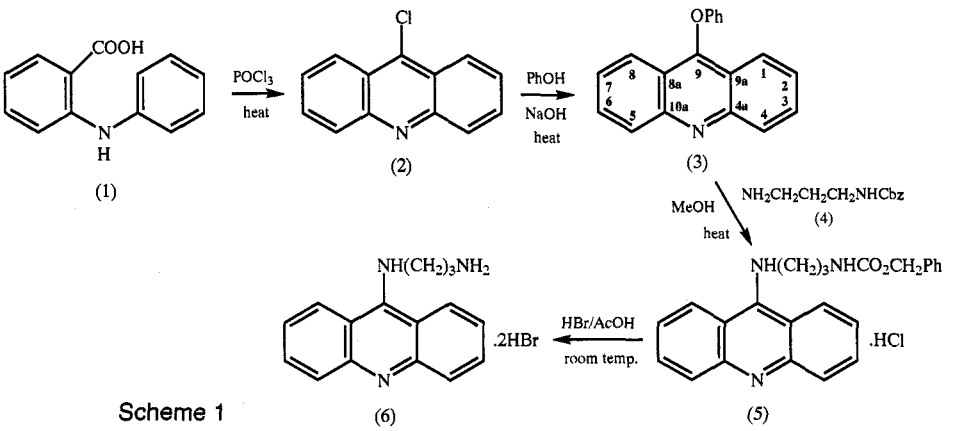
to porphyrins. The 9-aminoacridine ligand was used because of its ease of accessibility and characterization, whereas the 9-aminoacridine-4-carboxamide derivative was chosen on the basis of its high degree of antitumour activity.[4]

Synthesis of Acridine Ligands for Amide Coupling to Porphyrins

The synthetic schemes used to prepare the acridine derivatives 9-(3-aminopropylamino)acridine (6) and 9-(3-aminopropylamino)-*N*-[2-(dimethylamino)ethyl]acridine-4-carboxamide (15) for amide coupling to porphyrins are outlined in Scheme 1 and Scheme 2, respectively. In both acridine ligands, an aminopropylamino substituent at position 9 was used as the spacer and link between the chromophores of the desired porphyrin–acridine conjugates.

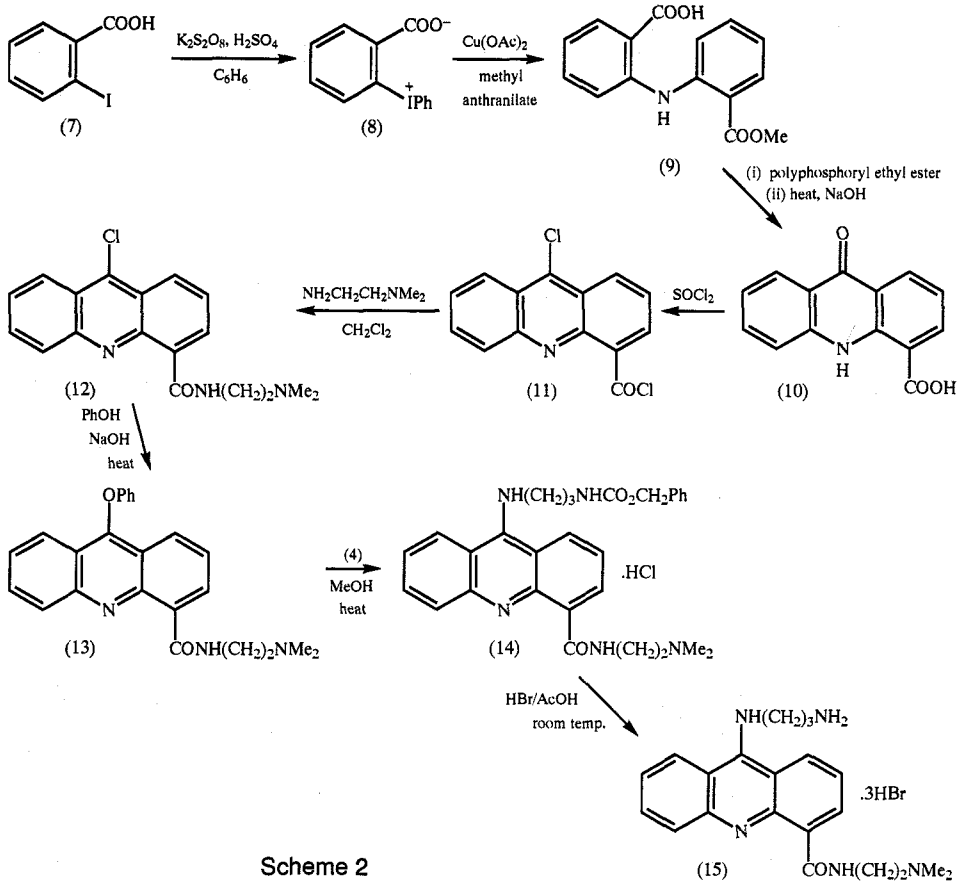


Scheme 1

9-(3-Aminopropylamino)acridine (6) was prepared through a five-step synthesis by using known procedures. 2-Phenylaminobenzoic acid (1) was formed by an Ullman-type reaction between 2-chlorobenzoic acid and aniline, with cupric oxide as the catalyst.[5] Ring closure of the acid (1) with phosphoryl chloride gave 9-chloroacridine (2) as green needles in quantitative yield.[6] Nucleophilic displacement of the chlorine of (2) by phenoxide gave 9-phenoxyacridine (3).[7] Commercially available propane-1,3-diamine was monoprotected at one of its amine groups with the benzyloxycarbonyl ($PhCH_2OCO$ or Cbz) group to give *N*-benzyloxycarbonylpropane-1,3-diamine (4) as a crude oil which was purified as the monohydrochloride salt.[8] Treatment of 9-phenoxyacridine (3) with (4) by refluxing in methanol gave the 9-[3-(benzyloxycarbonylamino)propylamino]acridine (5) as a bright yellow solid in quantitative yield. This compound was directly deprotected with hydrogen bromide in glacial acetic acid (45% w/v) to give 9-(3-aminopropylamino)acridine (6) as the dihydrobromide salt. The n.m.r. spectra (^1H and ^{13}C) showed the loss of the Cbz protecting group, while elemental analysis confirmed the conversion of (5) into the dihydrobromide salt.

[4] Rewcastle, G. W., Atwell, G. J., Chambers, D., Baguley, B. C., and Denny, W. A., *J. Med. Chem.*, 1986, **29**, 472.
[5] Allen, C. F. H., and McKee, G. H. W., *Org. Synth.*, 1943, Collect. Vol. 2, 15.
[6] Albert, A., and Ritchie, B., *Org. Synth.*, 1955, Collect. Vol. 3, 53.
[7] Albert, A., 'The Acridines' 2nd Edn, p. 282 (Edward Arnold: London 1966).
[8] Denny, W. A., and Atwell, G. J., *Synthesis*, 1984, 1032.

Homonuclear decoupling experiments showed that the doublet at δ 8·62 and the triplet at δ 7·55 were due to coupling between the hydrogens at positions 4 and 3, respectively, thus confirming their assignment. Due to the symmetrical nature of 9-substituted acridine derivatives the chemical shifts of the acridine protons at positions 1, 2, 3 and 4 are equivalent to those at positions 8, 7, 6 and 5, respectively, and therefore only the former proton positions are quoted in this paper.



Scheme 2

9-(3-Aminopropylamino)-*N*-[2-(dimethylamino)ethyl]acridine-4-carboxamide (15) was prepared through a nine-step synthesis by using literature procedures. 2-Iodobenzoic acid (7) was prepared from diazotized anthranilic acid and potassium iodide.[9] Treatment of the acid (7) by a standard procedure involving oxidation with potassium persulfate in sulfuric acid and subsequent coupling with benzene produced the diphenyliodonium-2-carboxylate (8) intermediate.[10] The reaction of (8) with methyl anthranilate in the presence of copper(II) acetate gave 2-(2-methoxycarbonyl-phenylamino)benzoic acid (9) as pale green prisms upon

[9] Vogel, A., "Vogel's Textbook of Practical Organic Chemistry" 4th Edn, p. 697 (Longmans: London 1978).
[10] Scherrer, R. A., and Beatly, H. R., *J. Org. Chem.*, 1980, **45**, 2127.

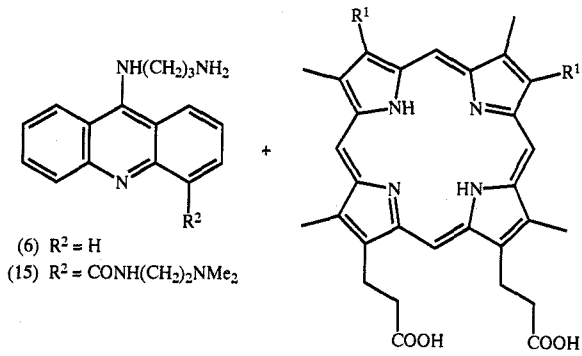
recrystallization from methanol.[11] Ring closure of the ester acid (9) was performed with polyphosphoryl ethyl ester[12] to give the methyl ester of 9-oxoacridan-4-carboxylic acid (10); the methyl ester was hydrolysed directly to the free acid by heating under reflux with sodium hydroxide solution.[11] Treatment of the acridone acid (10) with thionyl chloride gave crude 9-chloroacridine-4-carbonyl chloride (11) as a bright yellow solid.[13] Reaction of the acyl chloride (11) with the primary amine of *N,N*-dimethylethylenediamine in anhydrous dichloromethane gave 9-chloro-*N*-[2-(dimethylamino)ethyl]acridine-4-carboxamide (12) in quantitative yield.[13] Nucleophilic displacement of the chlorine in (12) by phenoxide gave crude 9-phenoxy-*N*-[2-(dimethylamino)ethyl]acridine-4-carboxamide (13). Due to the unsymmetrical nature of (13) the ^{13}C n.m.r. spectrum showed a signal for each of the 13 acridine carbons. The six acridine quaternary carbons (4, 4a, 8a, 9, 9a and 10a) were easily identified from the low intensity of their ^{13}C resonance signals. Furthermore, the ^{1}H n.m.r. spectrum showed the expected proton splitting pattern for the seven acridine protons, i.e. four doublets and three triplets in the aromatic region. Subsequent treatment of (13) with the monoprotected propane-1,3-diamine (4) gave 9-[3-(benzyloxycarbonylamino)-propylamino]-*N*-[2-(dimethylamino)ethyl]acridine-4-carboxamide (14) as a crude oil. Removal of the Cbz protecting group with hydrogen bromide in glacial acetic acid (45% w/v) gave 9-(3-aminopropylamino)-*N*-[2-(dimethylamino)ethyl]acridine-4-carboxamide (15) as the trihydrobromide salt. Characterization was effected by i.r. and n.m.r. spectroscopy, f.a.b. mass spectrometry and elemental analysis. The mass spectrum showed a strong protonated molecular ion at *m/z* 366 and a fragmentation pattern which was consistent with the desired structure.

Synthesis and Purification of Porphyrin–Acridine Conjugates

The porphyrin–acridine conjugates (20)–(25) were prepared as illustrated in Scheme 3. Coupling was achieved by condensation of the carboxylic acid groups of the respective porphyrin with the primary amine group of the desired acridine mediated by benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP) in the presence of benzotriazol-1-ol hydrate (HOBt). Initially, the standard amide coupling reagents 1,1′-carbonyldiimidazole and dicyclohexylcarbodiimide in the presence of HOBt were tried but these reagents were found to cause little or no coupling between the porphyrin and acridine as indicated by t.l.c. and h.p.l.c. analysis of the reaction mixture. It must be noted that coupling of the acridine ligand (15) (2 equiv) to porphyrin (18) (1 equiv) may take place at either of the side chains containing a carboxylic acid group. However, mass spectral data support the formation of conjugate (24), with the acridine ligands attached to the propanoic acid side chains (refer to F.A.B. Mass Spectra and Experimental for further details).

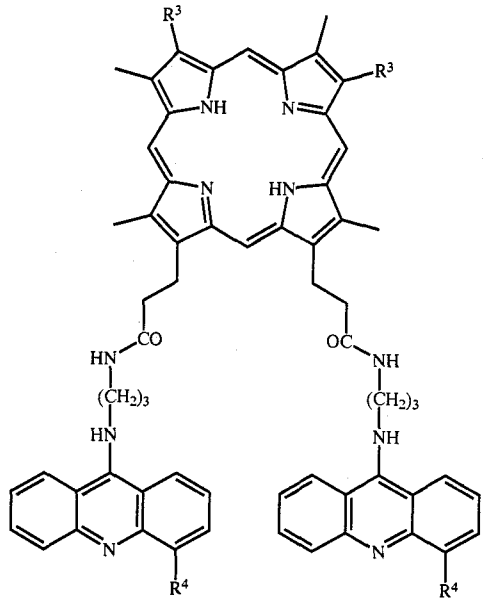
The formation of the porphyrin–acridine conjugates was followed by analytical gradient h.p.l.c. at detector wavelengths of 280 nm (showing acridine absorbance only) and 405 nm (showing porphyrin and acridine absorbances) simultaneously,

[11] Rewcastle, G. W., and Denny, W. A., *Synthesis*, 1985, 220.
[12] Pollmann, W., and Schramm, G., *Biochim. Biophys. Acta*, 1964, **80**, 1.
[13] Atwell, G. J., Cain, B. F., Baguley, B. C., Finlay, G. J., and Denny, W. A., *J. Med. Chem.*, 1984, **27**, 1481.

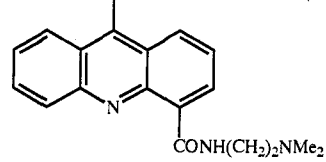


(6) $R^2 = H$
(15) $R^2 = CONH(CH_2)_2NMe_2$

(16) $R^1 = CH{=}CH_2$
(17) $R^1 = CH(Me)S(CH_2)_2NMe_2$
(18) $R^1 = CH(Me)SCH_2CH(NHAc)COOH$
(19) $R^1 = CH(Me)S(CH_2)_2COOH$



	R^3	R^4
(20)	$CH{=}CH_2$	H
(21)	$CH{=}CH_2$	$CONH(CH_2)_2NMe_2$
(22)	$CH(Me)S(CH_2)_2NMe_2$	H
(23)	$CH(Me)S(CH_2)_2NMe_2$	$CONH(CH_2)_2NMe_2$
(24)	$CH(Me)SCH_2CH(NHAc)COOH$	$CONH(CH_2)_2NMe_2$
(25)	$CH(Me)S(CH_2)_2CONH(CH_2)_3NH$	$CONH(CH_2)_2NMe_2$



Scheme 3

and traces were obtained with a dual-pen chart recorder (refer to Experimental for further details). This h.p.l.c. system enabled the unambiguous detection of the desired conjugate in the ultraviolet and visible absorbance regions. In all cases, the desired conjugate was formed within 1 h of reaction time. Conjugates (22)–(25) contain two chiral carbon centres; however, under these h.p.l.c. conditions the chromatogram profiles of conjugate (22) and (23) each showed one peak, i.e. all diastereoisomers co-eluted. For conjugate (24) all four diastereoisomers were resolved, and for (25) three isomers could be resolved.

The conjugates were isolated by size-exclusion gel chromatography by using Sephadex G-15 and an eluent of water/5% formic acid (pH 2) for conjugates (21) and (23)–(25), and Sephadex LH-20 and an eluent of methanol/5% formic acid (pH 2) for conjugates (20) and (22) (refer to Experimental for further details). As expected, the desired conjugate was present in the initial fractions collected. After workup the yields obtained were between 20 and 35%, and product purity ranged from 75 to 90%, with the exception of compound (24) which was obtained in 60% purity.

Further purification of conjugates (22) and (23) was achieved by semipreparative h.p.l.c. as outlined in the Experimental. Sample injections were limited to 10 mg. The purified conjugate collected was reduced by half its volume by rotary evaporation, and isolated as above. The purity of the isolated samples was *c.* 98% (established by using the analytical gradient h.p.l.c. conditions described in the Experimental). Purification of conjugates (20), (21), (24) and (25) by the above semipreparative h.p.l.c. procedure proved unsuccessful. Isolated samples of compounds (20) and (21) after semipreparative h.p.l.c. showed the presence of a decomposition product (*c.* 30% by analytical gradient h.p.l.c.), which may have been due to the hydrolysis of the two vinyl groups (to form the corresponding 1-hydroxyethyl groups) during the h.p.l.c. purification and/or workup procedures. The purity of compounds (24) and (25) could not be improved upon by using the above semipreparative h.p.l.c. method.

Characterization of the Porphyrin–Acridine Conjugates

The techniques suitable for characterization of these high molecular weight, photolabile and relatively complex compounds are limited. U.v./vis. spectroscopy is a very sensitive technique and it was used to show the presence of both of the chromophores in the conjugates. Likewise, u.v./vis. diode array h.p.l.c. was used to confirm the unambiguous formation and purity of several of the compounds. ^{1}H n.m.r. spectroscopy is sufficiently sensitive to give a spectrum from a small amount of sample (i.e. 1 mg), and was used to characterize those conjugates which were obtained in high purity. F.a.b. mass spectrometry proved invaluable for identifying these large porphyrin–acridine derivatives.

Ultraviolet/Visible Spectroscopy

U.v./vis. spectroscopy offered the quickest method of showing that both chromophores (porphyrin and acridine) had been incorporated into the isolated products. The absorbance maxima of these two chromophores have different wavelengths and are clearly separable. Table 1 presents the λ_{max} values and the absorption coefficients (ϵ) at these wavelengths for several of the porphyrin–bisacridine conjugates and their monomeric parent chromophores. An examination

of Table 1 reveals that the porphyrin and acridine chromophores were incorporated into the conjugates (presumably in a ratio of two acridines per porphyrin).

Table 1. The λ_{max} and ϵ values for porphyrin–acridine conjugates and their parent monomers at 10^{-5} M concentration[A]

Compound	λ_{max} (nm) and ϵ (dm^3 mol^{-1} cm^{-1})								
(6)[B]	222	266	392	410	432				
	31600	70800	9300	13200	11000				
(6)[C]	221	265	390	410	431				
	20000	56400	6400	9900	8200				
(15)[C]		265		418	437				
		55600		12500	12200				
(16)[B]				410		506	542	580	630
				40700		10000	8900	7800	5000
(17)[D]			381			505	540	566	618
			52400			3300	2300	2000	900
(20)[B]	221	258	401			506	540	576	630
	55000	66000	95500			11200	10000	7600	5400
(22)[C]	221	264	396			507	542	574	625
	38000	86500	78800			8000	4800	4000	1800
(23)[C]		265	401			506	540	572	623
		72000	91700			7100	4200	3900	1900

[A] Compound purities were ≥90%. [B] Compound in MeOH. [C] Compound in 0·01 PIPES. [D] Compound in 0·1 PIPES.

Porphyrins do not absorb at the absorption maxima wavelengths of the acridines in the u.v. region, but acridines absorb at the porphyrin Soret band region (i.e. $\lambda_{max} \approx 400$ nm), and hence this region in the spectra of the conjugates is enhanced (Table 1). However, the absorption coefficients for the spectra of the porphyrin–bisacridine conjugates do not correspond to those expected for two acridines per porphyrin molecule. In the u.v. region the absorption coefficients are smaller than the sum of the ϵ values for two acridines, whereas in the visible region they are higher than the sum of the ϵ values for the respective porphyrin and two acridines. This difference in ϵ is due to the intramolecular stacking of the linked chromophores (hence ϵ is reduced in the u.v. region), with a concomitant decrease in aggregation (i.e. intermolecular stacking) between the porphyrin rings (hence ϵ is enhanced in the visible region). It is well known that porphyrin absorption spectra are concentration and medium dependent due to aggregation effects.[14] A decrease in porphyrin aggregation is typically accompanied by a shift of the Soret band maxima to longer wavelengths. This behaviour was observed in the spectra of compounds (22) and (23), i.e. the Soret band maxima increased by 15–20 nm upon the formation of the conjugates in comparison with the precursor porphyrin (17) (Table 1). Therefore, the addition of the two acridine ligands to the porphyrin has reduced the intermolecular stacking between the porphyrin rings, thus enhancing the absorption coefficients of the porphyrin chromophore.

[14] White, W. I., in 'The Porphyrins' (Ed. D. Dolphin) Vol. 5, p. 303 (Academic: New York 1978).

Control experiments of mixtures in a 1:2 ratio of the unlinked porphyrin and acridine components of the conjugates (22) and (23), showed spectrophotometric profiles similar to the individual pure components. Hence, the spectrophotometric changes observed in the spectra of the conjugates are more likely attributable to intermolecular stacking and aggregation effects, rather than to intramolecular electronic perturbations.

Compounds (22) and (23) were further analysed by u.v./vis. diode array h.p.l.c. under the solvent conditions described in the Experimental. The h.p.l.c. trace of each conjugate showed a single peak, and analysis of the u.v./vis. profile of the area under the peak (at three different peak time points) confirmed the presence of both chromophores and the unambiguous purity of the conjugate.

^{1}H N.M.R. Spectra

N.m.r. spectroscopy was a less than ideal technique for the characterization of the conjugates because of their large molecular size and the inherent problems encountered with porphyrin n.m.r. spectra due to ring current and aggregation effects. This was particular evident in the proton n.m.r. spectra of the conjugates where a full assignment was not possible due to the occurrence of several broad and unresolved signals. However, a partial structural assignment of several of the compounds was obtained from proton n.m.r. spectra. The ^{1}H n.m.r. spectra of compounds (20), (22) and (23) showed the expected proton signals from both the acridines and porphyrin chromophore, and the integrals for each spectrum were consistent with each structure having two acridines and one porphyrin moiety.

F.A.B. Mass Spectra

Although f.a.b. mass spectrometry provides reliable values for the molecular weights of compounds, it only gives limited information on their structure. The significant ions observed in the f.a.b. mass spectra of the porphyrin–acridine derivatives (20)–(25) are presented in Table 2. For these compounds the molecular ions (M^+) were prominent, with the exception for compound (25) in which the protonated molecular ion was significant. Compounds (22) and (23) showed a similar fragmentation pattern which involved the loss of one thioether chain (ions m/z 1135 and 1363, respectively), both thioether chains (ions m/z 1031 and 1259, respectively) and both acridine ligands, along with several methyl groups (ions m/z 753 and 735, respectively). The fragmentation ion m/z 445 was common in

Table 2. Significant ions observed in the f.a.b. mass spectra of the porphyrin–acridine conjugates (20)–(25)

Compound	Significant ions (m/z values)							
	MH^+	M^+	*a*	*b*	*c*	*d*	*e*	*f*
(20)		1029	752	445				
(21)[A]		1257	937					
(22)		1239	1135	1031	753	445		
(23)		1467	1363	1259	1175	735	445	
(24)[B]		1583	1439	1302				
(25)[B]	2164		1900	1872	1817	1711	1366	1072

[A] Spectrum below m/z 800 not recorded. [B] Spectrum below m/z 1000 not recorded.

the spectra of (20), (22) and (23) and corresponds to the loss of the substituents at positions 3, 7, 8, 12, 13 and 17 on the porphyrin ring and the loss of both acridine ligands. Compound (24) showed a fragmentation pattern which involved the loss of both dimethylaminoethyl side chains on the acridine (ion m/z 1439) and one thioether chain, along with several methyl groups (ion m/z 1302), and is consistent with the site of attachment of the acridine linker at the propanoic acid side chains of the porphyrin. The probable fragmentation processes to account for the fragment ions observed are included in the Experimental.

Experimental

All experimental procedures involving porphyrins were performed in dim light and at room temperature. Melting points were determined by using a Büchi electric oil bath and are uncorrected. U.v./vis. absorption spectra were determined in quartz cuvettes on a Cary 118c spectrophotometer. I.r. spectra were recorded in Nujol with a Perkin–Elmer 237 grating or 1430 ratio recording infrared spectrophotometer. Elemental microanalyses were carried out by the Chemistry Department, University of Otago (New Zealand).

Preliminary ^{1}H n.m.r. spectra were recorded on a Perkin–Elmer R-32 spectrometer operating at 90 MHz. Routine n.m.r. spectra were recorded on a Jeol FX-200 Fourier-transform spectrometer operating at 199·50 MHz for ^{1}H and 50·1 MHz for ^{13}C. A 4000 Hz sweep width was used for ^{1}H n.m.r. spectra and 12004 Hz sweep width for ^{13}C n.m.r. spectra (16384 data points were used in both cases). ^{13}C n.m.r. spectra were normally processed with a 1·2 Hz exponential line-broadening. Higher frequency n.m.r. spectra were recorded on a Brüker AM 400 Fourier-transform spectrometer operating at 400·14 MHz for ^{1}H and 100·6 MHz for ^{13}C. A 7576 Hz sweep width was used for ^{1}H n.m.r. spectra and 23810 Hz sweep width for ^{13}C n.m.r. spectra (16384 data points were used in both cases). ^{1}H and ^{13}C n.m.r. spectra were normally processed with a 1·0 Hz exponential line-broadening. All chemical shifts (δ) are quoted in ppm downfield from tetramethylsilane. N.m.r. spectra were determined at a probe temperature of 20°C.

Size-exclusion gel chromatography was performed on Sephadex G-15 or Sephadex LH-20 (Pharmacia Fine Chemicals) by using an eluent of water/5% formic acid (pH 2) or methanol/5% formic acid (pH 2), respectively. A column size of 420 by 20 mm i.d. or 600 by 25 mm i.d. was used with a flow rate of 6 ml/h.

Gradient h.p.l.c. was performed on a Waters Millipore liquid chromatograph consisting of a U6K injector, an M-45 pump, a model 440 fixed-wavelength dual-absorbance detector operating at 280 and 405 nm, and an Isco 2360 solvent programmer. Gradient profiles were recorded using an Omniscribe dual-pen chart recorder (Houston Instruments) with a chart speed of 0·25 cm/min. The analytical column used was a Radial Z-pak C_{18} 10 μm cartridge (100 by 8 mm i.d.) compressed in a Z-module system, and for semipreparative work a 30 cm by 7·8 mm i.d. μBondapak C_{18} 10 μm steel column was used (both columns from Waters Associates). The analytical gradient solvent system consisted of solvent A (water/3% formic acid) and solvent B (methanol/3% formic acid) with a linear gradient elution of 10–100% solvent B over 40 min at a flow rate of 2·5 ml/min, unless otherwise stated. The semipreparative gradient solvent system consisted of the same eluent components as above except a gradient elution of 0–100% solvent B over 2 h at a flow rate of 3 ml/min was used. U.v./vis. diode array h.p.l.c. was performed on a Waters Millipore liquid chromatograph consisting of a U6K injector, a dual M-45 pump system, a 660E solvent programmer and a model 990 photodiode array detector connected to an NEC Powermate 386/20 computer. Gradient profiles were recorded with an NEC Pinwriter P5200 printer. The analytical column and solvent conditions used were as described above. All eluents were degassed immediately before use. The methanol used was ChromAR h.p.l.c. grade (Mallinckrodt), the water Milli-Q grade, and the formic acid 90% AR grade (Ajax Chemicals).

T.l.c. was performed on silica gel 60 G_{254} containing a fluorescent indicator (Macherey–Nagel) and the t.l.c. plates were visualized by u.v. light (366 nm). The t.l.c. eluent consisted of 90% dichloromethane/10% methanol.

F.a.b. mass spectra were obtained on a Jeol JMS-DX 300 mass spectrometer with a Jeol JMA-3100 mass data analysis system (Victorian College of Pharmacy Ltd, Parkville). The

atom gun was operated at 3 kV with xenon as the bombardment gas. The ion source was operated at ambient temperature with a 3 kV acceleration voltage and low resolution. The matrix consisted of glycerol, unless otherwise stated.

Commercially available propane-1,3-diamine (Aldrich), benzyloxycarbonyl chloride (Fluka), hydrogen bromide (HBr) in glacial acetic acid (45% w/v, BDH), BOP (Auspep) and HOBt (Aldrich) were used as supplied. Dimethyl sulfoxide (ME_2SO) was dried over molecular sieves type 4A for 48 h before use, and triethylamine (Et_3N) was purified and dried by distillation over KOH.

Protoporphyrin-IX (16) was prepared from commercially available hematoporphyrin dihydrochloride[15] (Roussel) and its structure was confirmed by ^1H and ^{13}C n.m.r. spectroscopy. The porphyrins (17)–(19) were prepared as described in Karagianis *et al.*[16]

The buffer 0·1 PIPES (ionic strength 0·1 M) contained 4 mM piperazine-1,4-bis(ethanesulfonic acid) dipotassium salt (PIPES) (Sigma), 1 mM ethylenediaminetetraacetic acid (Sigma) and 0·09 M NaCl. The pH was adjusted to 6·8 with dilute NaOH. The buffer 0·01 PIPES (ionic strength 0·01 M) was prepared by a 10-fold dilution of 0·1 PIPES with Milli-Q water, with no significant change to pH. Sodium dodecyl sulfate (Sigma) was prepared as a 20% w/v solution in 0·01 PIPES buffer.

2-Phenylaminobenzoic acid (1) was obtained in 90% yield, m.p. 180–181°C (lit.[5] 82–93%, 179–181°C). 9-Chloroacridine (2) was obtained in 87% yield, m.p. 117–118°C (lit.[6] 100%, 117–118°C). 9-Phenoxyacridine (3) was purified by Soxhlet extraction (hexane), followed by recrystallization from hexane to give (3) as pale yellow clusters in 75% yield, m.p. 125–126°C [lit.[7] 98% (crude), 127–128°C]. *N*-Benzyloxycarbonylpropane-1,3-diamine monohydrochloride (4) was obtained in 38% yield, m.p. 185–186°C (lit.[8] 57%, 189·5–190·5°C). 2-Iodobenzoic acid (7) was obtained in 90% yield, m.p. 162°C (lit.[9] >95%, 162°C). Diphenyliodonium-2-carboxylate (8) was obtained as coarse prisms in 70% yield, m.p. 220°C (dec.) [lit.[10] 77%, 220°C (dec.)]. 2-(2-Methoxycarbonylphenylamino)benzoic acid (9) was obtained as pale green prisms in 60% yield, m.p. 193–195°C [lit.[11] 65%, 196–198°C (benzene/acetone)]. 9-Oxoacridan-4-carboxylic acid (10) was obtained in 88% yield, m.p. 323–325°C (lit.[11] 87%, 324–325°C). 9-Chloroacridine-4-carbonyl chloride (11) was obtained as a bright yellow solid in 87% yield. The product was used immediately to avoid decomposition. 9-Chloro-*N*-[2-(dimethylamino)ethyl]acridine-4-carboxamide (12) was obtained in 84% yield [lit.[13] 71% (crude)]. The product was used immediately to avoid decomposition.

9-[3-(Benzyloxycarbonylamino)propyl]acridine Hydrochoride (5)

This compound was prepared by modification of the method of Dupré *et al.*[17] In general, 9-phenoxyacridine (3) (1 equiv.) and the protected diamine (4) (1 equiv.) were refluxed in methanol for 1 h. After cooling to room temperature the product was precipitated by the addition of ether to give (5) as a bright yellow solid in 86% yield, m.p. 143–144°C. This compound was used without further purification. I.r. ν_{max} 3200 (NH st), 1728 (CO st), 1642 (NH def), 1598 and 1570 (aromatic CC st), 1278 and 1248 cm^{-1} (CO st). ^1H n.m.r. [199·50 MHz, $(CD_3)_2SO$] δ 14·2, s, 1H, proton on ring N; 9·98, br, 1H, AcrN**H**CH_2; 8·59, br, 2H, AcrH 4; 7·95, d, *J* 8 Hz, 2H, AcrH 1; 7·89, t, *J* 8 Hz, 2H, AcrH 2; 7·47, overlapping pair t, *J* 8 Hz, 3H, AcrH 3 and NHCO; 7·33, s, 5H, ArH; 5·05, s, 2H, OCH_2Ar; 3·87, t, *J* 7 Hz, 2H, AcrNHC**H**$_2CH_2$; 3·20, q, *J* 7 Hz, 2H, CH_2CH_2NHCO; 1·92, m, *J* 7 Hz, 2H, $CH_2CH_2CH_2$. ^{13}C n.m.r. [50·1 MHz, $(CD_3)_2SO$] δ 157·1, C 9; 156·0, NHCO; 139·5, C 4a; 136·9, C 1′; 134·4, C 3; 128·1, 127·5, 127·4, C 2′, C 3′, C 4′; 125·8, C 4; 122·9, C 1; 118·3, C 2; 112·1, C 9a; 65·1, OCH_2Ar; 46·0, $AcrNHCH_2$; 37·6, CH_2NHCO; 29·2, CH_2CH_2NHCO.

9-(3-Aminopropylamino)acridine (6)

The Cbz group was removed from compound (5) by using HBr in glacial acetic acid[18] to give (6) as the dihydrobromide salt. Recrystallization from ethanol gave bright yellow *needles*

[15] Dinello, R. K., and Chang, C. K., in 'The Porphyrins' (Ed. D. Dolphin) Vol. 1, p. 293 (Academic: New York 1978).
[16] Karagianis, G., Reiss, J. A., and Scourides, P. A., *Aust. J. Chem.*, 1993, **46**, 1755.
[17] Dupré, D. J., and Robinson, F. A., *J. Chem. Soc.*, 1945, 549.
[18] Ben-Ishai, D., and Berger, A., *J. Org. Chem.*, 1952, **17**, 1564.

in 90% yield, m.p. 240–242°C (dec.) (Found: C, 44·6; H, 5·0; N, 9·8. $C_{16}H_{17}N_3.2HBr/H_2O$ requires C, 44·7; H, 4·9; N, 9·8%). I.r. ν_{max} 3350 (NH st), 1593 and 1573 cm^{-1} (aromatic CC st). ^1H n.m.r. [199·50 MHz, $(CD_3)_2SO$] δ 13·60, br, 1H, proton on ring N (HBr); 9·77, br, 1H, AcrN**H**CH_2; 8·62, d, *J* 7 Hz, 2H, AcrH 4; 8·03–7·87, m, *J* 7 Hz, AcrH 1,2 and $CH_2N\mathbf{H}_2.\mathbf{H}Br$; 7·55, t, *J* 7 Hz, 2H, AcrH 3; 4·15, t, *J* 7 Hz, 2H, AcrNHC$\mathbf{H}_2CH_2$; 2·95, t, *J* 7 Hz, 2H, $CH_2C\mathbf{H}_2NH_2.HBr$; 2·19, m, *J* 7 Hz, 2H, $CH_2C\mathbf{H}_2CH_2$. ^{13}C n.m.r. [50·1 MHz, $(CD_3)_2SO$] δ 157·4, C 9; 139·4, C 4a; 134·9, C 3; 126·0, C 4; 123·3, C 1; 118·2, C 2; 112·2, C 9a; 45·6, AcrNHCH_2; 36·4, $CH_2NH_2.HBr$; 26·7, $CH_2\mathbf{C}H_2CH_2$. F.a.b. mass spectrum ([M^+] $C_{16}H_{17}N_3$ requires 251·14): *m/z* (relative intensity) 252 (100%, MH^+), 195 (35, $C_{13}H_{11}N_2^+$), 185 (55, $C_{13}HN_2^+$). U.v./vis. (0·01 PIPES, pH 6·8) λ_{max} 221 (ϵ 20000), 265 (56400), 390 (6400), 410 (9900), 431 (8200); (MeOH, pH 6·0) 222 (31600), 266 (70800), 392 (9300), 410 (13200), 432 nm (11000 dm^3 mol^{-1} cm^{-1}).

N-[2-(Dimethylamino)ethyl]-9-phenoxyacridine-4-carboxamide (13)

This compound was prepared by adopting the method of Albert.[7] Purification by Soxhlet extraction (hexane), followed by recrystallization from hexane gave (13) as yellow clusters in 70% yield, m.p. 162–163°C. I.r. ν_{max} 3250 (NH st), 1625 (CO st), 1570 (NH def), 1209 cm^{-1} (CO st). ^1H n.m.r. [199·50 MHz, $(CD_3)_2SO$] δ 11·74, t, *J* 4 Hz, 1H, CONH; 8·75, d, *J* 7 Hz, 1H, AcrH 5; 8·29, d, *J* 9 Hz, 8·22, d, *J* 9 Hz, 2H, AcrH 1,8; 8·04–7·95, overlapping d and t, *J* 9 Hz, 2H, AcrH 3, and 2; 7·69, t, *J* 8 Hz, 7·63, t, *J* 8 Hz, 2H, Acr 6,7; 7·31, t, *J* 8 Hz, 2H, ArH 3′,5′; 7·08, t, *J* 8 Hz, 1H, ArH 4′; 6·90, d, *J* 8 Hz, 2H, ArH 2′,6′; 3·62, q, *J* 6 Hz, 2H, NHC$\mathbf{H}_2$; 2·60, t, *J* 6 Hz, 2H, $NHCH_2C\mathbf{H}_2$; 2·36, s, 6H, $N(CH_3)_2$. ^{13}C n.m.r. [50·1 MHz, $(CD_3)_2SO$] δ 163·9, CONH; 158·7, C 9; 155·6, C 1′; 148·3, 146·7, C 4a, C 10a; 133·9, 131·2, C 3, C6; 130·5, C 4; 129·5, C 3′, 128·4, C 5; 126·1, C 4′; 125·2, 125·0, C 1, C 8; 122·4, 121·6, C 2, C 7; 119·7, 118·7, C 8a, C 9a; 115·0, C 2′, 57·6, $NHCH_2$; 44·4, $N(CH_3)_2$; 37·1, $\mathbf{C}H_2N(CH_3)_2$.

9-[3-(Benzyloxycarbonylamino)propylamino]-N-[2-(dimethylamino)ethyl]acridine-4-carboxamide Hydrochloride (14)

This compound was prepared as described for (5) except instead of precipitating the product with ether it was isolated as the crude oil and used without further purification.

9-(3-Aminopropylamino)-N-[2-(dimethylamino)ethyl]acridine-4-carboxamide (15)

The crude oil of (14) was dissolved in the minimum volume of glacial acetic acid, and excess HBr in glacial acetic acid was added. Evolution of CO_2 was immediately evident and the mixture was allowed to stir for 1 h. Removal of the solvent under vacuum followed by the addition of methanol to the residue gave the product as a bright yellow solid. Recrystallization from methanol gave (15) as bright yellow *clusters* in quantitative yield, m.p. 210–213°C (dec.) (Found: C, 41·2; H, 5·0; N, 11·3. $C_{21}H_{27}N_5O.3HBr$ requires C, 41·5; H, 5·0; N, 11·5%). I.r. ν_{max} 3300 (NH st), 1630 (CO st), 1560 cm^{-1} (NH def). ^1H n.m.r. [199·50 MHz, $(CD_3)_2SO$] δ 13·47, br, 1H, proton on ring N (HBr); 12·27, t, *J* 4 Hz, 1H, CONH; 10·10, br, 1H, AcrN**H**CH_2; 8·58, d, *J* 8 Hz, 1H, AcrH 5; 8·45, d, *J* 8 Hz, 1H, 8·33, d, *J* 8 Hz, 1H, 8·21, d, *J* 8 Hz 1H, AcrH 1,3,8; 8·0–7·5, m, 7H, AcrH 2,6,7, $CH_2N\mathbf{H}_2.\mathbf{H}Br$ and $CH_2N(CH_3)_2.\mathbf{H}Br$; 4·21, t, *J* 7 Hz, 2H, AcrNHC$\mathbf{H}_2$; 3·70, q, *J* 6 Hz, 2H, CONHC$\mathbf{H}_2$; 2·89, m, 4H, $C\mathbf{H}_2NH_2.HBr$ and $C\mathbf{H}_2N(CH_3)_2.HBr$; 2·60, s, 6H, $N(C\mathbf{H}_3)_2.HBr$; 2·23, m, 2H, $CH_2C\mathbf{H}_2CH_2$. ^{13}C n.m.r. (50·1 MHz, D_2O) δ 169·9, CONH; 159·0, C 9; 139·2, 138·7, C 4a, C 10a; 136·9, 135·8, C 3, C 6; 130·6, C 4; 126·0, 125·6, 123·4, C 5, C 1, C 8; 119·9, 118·8, C 2, C 7; 113·7, 112·6, C 8a, C 9a; 57·4, CONH**C**H_2; 47·1, AcrNHCH_2; 44·2, $N(CH_3)_2$; 37·7, $\mathbf{C}H_2N(CH_3)_2$; 36·0, CH_2NH_2; 27·8, $\mathbf{C}H_2CH_2NH_2$. F.a.b. mass spectrum ([M^+] $C_{21}H_{27}N_5O$ requires 365·22): *m/z* (relative intensity) 366 (100%, MH^+), 309 (35, $MH^+ - CH_2CH_2CH_2NH$), 277 [100, $MH^+ - NHCH_2CH_2N(CH_3)_2 - 2H$], 251 [18, $MH^+ - CONHCH_2CH_2N(CH_3)$], 235 (10, $MH^+ - C_5H_{11}N_2O - NH_2$), 221 (16, $MH^+ - C_5H_{11}N_2O - CH_2NH_2$), 219 (30, $MH^+ - C_5H_{11}N_2O - CH_2NH_2 - 2H$), 207 (20, $MH^+ - C_5H_{11}N_2O - CH_2CH_2NH_2$), 195 (35, $C_{13}H_{11}N_2^+$), 186 (70, $C_{13}H_2N_2^+$), 185 (100, $C_{13}HN_2^+$). U.v./vis. (0·01 PIPES, pH 6·8) λ_{max} 265 (ϵ 55600), 418 (12500), 437 nm (12200 dm^3 mol^{-1} cm^{-1}).

General Procedure for the Preparation of compounds (20)–(24)

The appropriate porphyrin (1 equiv.), BOP (2·2 equiv.) and HOBt (2·2 equiv.) were dissolved in dry Me_2SO *c.* 5 mg porphyrin/ml), and stirred under nitrogen for 30 min. The required acridine (2 equiv.) and excess Et_3N were then added and the mixture was stirred under nitrogen for a further 1 h. The reaction mixture was separated by size-exclusion gel chromatography by using Sephadex LH-20 for compounds (20) and (22), and Sephadex G-15 for compounds (21), (23) and (24). In general, fraction sizes of 0·5 ml were collected and checked by analytical gradient h.p.l.c., a linear gradient solvent system being used consisting of solvent A (water/3% formic acid) and solvent B (methanol/3% formic acid), pH 2, with an elution of 0–100% solvent B over 20 min. The fractions containing the desired conjugate were combined and the product was precipitated with NaOH (5 M), collected by centrifugation, washed (3×distilled water) and dried under vacuum (0·01 mmHg, 41°C).

N,N′-*Bis[3-(acridin-9-ylamino)propyl]-7,12-diethenyl-3,8,13,17-tetramethyl-21*H,*23*H-*porphine-2,18-dipropanamide (20)*

This compound was obtained in 20% yield and 90% purity by h.p.l.c. ^{1}H n.m.r. [400·14 MHz, $(CD_3)_2SO$] partial assignment: δ 10·26, s, 1H, 10·12, s, 1H, 10·10, s, 1H, 10·06, s, 1H, 4×*meso* CH; 8·42, overlapping pair dd, *J* 12, 18 Hz, 2H, 2×C**H**CH$_2$; 8·02, overlapping pair d, 2×AcrH 4; 7·5–7·3, m, 2×AcrH 1,2; 6·74, unresolved, 2×AcrH 3; 6·40, dd, *J* 18 Hz, 2H, 2×CHC**H**$_2$; 6·19, overlapping pair dd, *J* 12 Hz, 2H, 2×CHC**H**$_2$; 4·28, unresolved, 4H, 2×C**H**$_2$CH$_2$CONH; 3·67, s, 3·64, s, 3·57, s, 3·55, s, 4×ring CH$_3$. F.a.b. mass spectrum (MeOH/HCl/glycerol/thioglycerol) ([M$^+$] $C_{66}H_{64}N_{10}O_2$ requires 1028·52): *m/z* (relative intensity) 1029 (100%, M$^+$), 752 [30, M$^+$ – $(CH_2)_3$NHAcr – CHCH$_2$ – CH$_3$], 751 (20, M$^+$ – $C_{19}H_{21}N_2$ – H), 445 (20, M$^+$ – 2×$C_{16}H_{15}N_2$ – 2×C_2H_3 – 4×CH$_3$). U.v./vis. (MeOH, pH 6·0) λ_{max} 221 (ϵ 55000), 258 (66000), 401 (95500), 506 (11200), 540 (10000), 576 (7600), 630 nm (5400 dm^3 mol^{-1} cm^{-1}).

N,N′-*Bis[3-[4-[2-(dimethylamino)ethylaminocarbonyl]acridin-9-ylamino]propyl]-7,12-diethenyl-3,8,13,17-tetramethyl-21*H,*23*H-*porphine-2,18-dipropanamide (21)*

This compound was obtained in 25% yield and 85% purity by h.p.l.c. F.a.b. mass spectrum (Me_2SO/glycerol) ([M$^+$] $C_{76}H_{84}N_{14}O_4$ requires 1256·68): *m/z* (relative intensity) 1257 (100%, M$^+$), 938 (25, M$^+$ – Acr – CHCH$_2$), 937 (55, M$^+$ – $C_{18}H_{18}N_3O$ – C_2H_3 – H), 936 (20, M$^+$ – $C_{20}H_{21}N_3O$ – 2H). U.v./vis. (0·01 PIPES, pH 6·8) λ_{max} 265, 402, 506, 541, 574, 625 nm (ϵ not determined).

N,N′-*Bis[3-(acridin-9-ylamino)propyl]-7,12-bis[1-[(2-dimethylaminoethyl)thio]ethyl]-3,8,13,17-tetramethyl-21*H,*23*H-*porphine-2,18-dipropanamide (22)*

This compound was obtained in 30% yield and 88% purity by h.p.l.c. Further purification was achieved by semipreparative h.p.l.c. to give (22) in 98% purity. ^{1}H n.m.r. [400·14 MHz, $(CD_3)_2SO$] partial assignment: δ 10·54, s, 10·50, s, 10·31, s, 10·18, s, 4×*meso* CH; 8·06, unresolved, 2×AcrH 4; 7·85, unresolved, 2×AcrH 1; 7·75, unresolved, 2×CONH; 7·44, unresolved, 2×AcrH 2; 6·96, unresolved, 2×AcrH 3; 5·98, unresolved, 2×SCH; 4·27, unresolved, 2×C**H**$_2$CH$_2$CONH; 3·76, s, 3·70, s, 3·61, s, 3·59, s, 4×ring CH$_3$; 3·10, unresolved, 2×CH$_2$C**H**$_2$CONH; 2·90, unresolved, SC**H**$_2$C**H**$_2$N; 2·70, unresolved, C**H**$_2$NHCO; 2·40, unresolved, 2×SCHC**H**$_3$; 2·10, s, 2×N(CH$_3$)$_2$; −3·90, s, 2×ring NH. F.a.b. mass spectrum (thioglycerol/glycerol) ([M$^+$] $C_{74}H_{86}N_{12}O_2S_2$ requires 1238·64): *m/z* (relative intensity) 1239 (70%, M$^+$), 1135 [25, M$^+$ – S(CH$_2$)$_2$N(CH$_3$)$_2$], 1134 (22, M$^+$ – $C_4H_{10}NS$ – H), 1031 (23, M$^+$ – 2×$C_4H_{10}NS$), 1030 (14, M$^+$ – $C_8H_{20}N_2S_2$ – H), 753 [22, M$^+$ – 2×$(CH_2)_3$NHAcr – CH$_3$ – H], 752 (15, M$^+$ – $C_{33}H_{33}N_4$ – 2H), 445 [100, M$^+$ – 2×CH(CH$_3$)S(CH$_2$)$_2$ – N(CH$_3$)$_2$ – 2×$(CH_2)_3$NHAcr – 4×CH$_3$], 444 (62, M$^+$ – $C_{48}H_{64}N_6S_2$ – H). U.v./vis. (0·01 PIPES, pH 6·8) λ_{max} 221 (ϵ 38000), 264 (86500), 396 (78000), 507 (8000), 542 (4800), 574 (4000), 625 nm (1800 dm^3 mol^{-1} cm^{-1}).

*N,N′-Bis[3-[4-[2-(dimethylamino)ethylaminocarbonyl]acridin-9-ylamino]propyl]-7,12-bis[1-[(2-dimethylaminoethyl)thio]ethyl]-3,8,13,17-tetramethyl-21*H,*23*H*-porphine-2,18-dipropanamide (23)*

This compound was obtained in 35% yield and 90% purity by h.p.l.c. Further purification was achieved by semipreparative h.l.p.c. to give (23) in 98% purity. ^{1}H n.m.r. [400·14 MHz, $(CD_3)_2SO$] partial assignment: δ 12·10, unresolved, 2×AcrCONH; 10·50, s, 10·32, s, 10·05, s, 4×*meso* CH; 8·41, d, *J* 8 Hz, 2×AcrH 5; 8·13, overlapping pair d, *J* 8 Hz, 2×AcrH 1,8; 7·87, d, *J* 8 Hz, 7·70, d, *J* 8 Hz, 2×AcrH 3; 7·80, overlapping pair t, *J* 8 Hz, 2×AcrH 2; 7·50, overlapping pair t, *J* 8 Hz, 2×AcrH 6,7; 6·93, m, 2×CONH; 5·95, unresolved, 2×SCH; 4·28, unresolved, 2×CH_2CH_2CONH; 3·73, s, 3·60, s, 3·55, s, 3·52, s, 4×ring CH_3; 3·15, unresolved, 2×CH_2CH_2CONH; 2·70, m, 2×SCH_2CH_2N/2×CH_2NHCO; 2·32, unresolved, 2×$SCHCH_3$; 2·05, s, 2×$N(CH_3)_2$; −3·96, s, 2×ring NH. F.a.b. mass spectrum ([M^+] $C_{84}H_{106}N_{16}O_4S_2$ requires 1466·80): *m/z* (relative intensity) 1467 (45%, M^+), 1466 (36, $M^+ - H$), 1363 [16, $M^+ - S(CH_2)_2N(CH_3)_2$], 1259 (5, $M^+ - 2\times C_4H_{10}NS$), 1175 [12, $M^+ - (CH_2)_3NHAcr$], 735 (10, $M^+ - 2\times C_{21}H_{25}N_4O - 2\times CH_3 - 4H$), 444 [60, $M^+ - 2\times CH(CH_3)S(CH_2)_2N(CH_3)_2 - 2\times C_{21}H_{25}N_4O - 4\times CH_3$), 444 (40, $M^+ - C_{58}H_{90}N_{10}O_2S_2 - H$). U.v./vis. (0·01 PIPES, pH 6·8) λ_{max} 265 (ϵ 72000), 401 (91700), 506 (7100), 540 (4200), 572 (3900), 623 nm (1900 dm^3 mol^{-1} cm^{-1}).

*7,12-Bis[1-[(2-acetylamino-2-carboxyethyl)thio]ethyl]-*N,N′*-bis[3-[4-[2-(dimethylamino)ethylaminocarbonyl]acridin-9-ylamino]propyl]-3,8,13,17-tetramethyl-21*H,*23*H*-porphine-2,18-dipropanamide (24)*

This compound was obtained in 23% yield and 60% purity by h.p.l.c. F.a.b. mass spectrum (MeOH/thioglycerol/glycerol) ([M^+] $C_{86}H_{102}N_{16}O_{10}S_2$ requires 1582·74): *m/z* (relative intensity) 1583 (100%, M^+), 1582 (26, $M^+ - H$), 1439 [30, $M^+ - 2\times(CH_2)_2N(CH_3)_2$], 1438 (29, $M^+ - C_8H_{20}N_2 - H$), 1437 (17, $M^+ - C_8H_{20}N_2 - 2H$), 1303 (17, $M^+ - C_4H_{10}N - SCH_2CH(NHCOCH_3)CO_2H - 3\times CH_3 - H$), 1302 (25, $M^+ - C_{12}H_{27}N_2O_3S - 2H$). U.v./vis. (0·01 PIPES, pH 6·8) λ_{max} 266, 402, 506, 541, 573, 623 nm (ϵ not determined).

*N,N′-Bis[3-[4-[2-(dimethylamino)ethylaminocarbonyl]acridin-9-ylamino]propyl]-7,12-bis[1-[2-[3-[4-[2-(dimethylamino)ethylaminocarbonyl]acridin-9-ylamino]propylaminocarbonyl]ethylthio]ethyl]-3,8,13,17-tetramethyl-21*H,*23*H*-porphine-2,18-dipropanamide (25)*

This compound was prepared as described for the preparation of compounds (20)–(24) except that the amounts of added BOP and HOBt were each increased to 5 equiv. and the acridine to 4 equiv. The porphyrin–tetrakisacridine conjugate was isolated by size-exclusion chromatography on Sephadex G-15 gel. The yield was 20% with 75% purity by h.p.l.c. F.a.b. mass spectrum (thioglycerol/glycerol) ([M^+] $C_{124}H_{146}N_{24}O_8S_2$ requires 2163·12): *m/z* (relative intensity) 2164 (36%, MH^+), 1900 [26, $MH^+ - 3\times(CH_2)_2N(CH_3)_2 - 2\times CH_3 - 3H$], 1899 (18, $MH^+ - C_{14}H_{36}N_3 - 4H$), 1872 (30, $MH^+ - Acr$), 1871 (29, $MH^+ - C_{18}H_{18}N_3O - H$), 1870 (22, $MH^+ - C_{18}H_{18}N_3O - 2H$), 1817 [100, $MH^+ + 2H - (CH_2)_3NHAcr$], 1712 [22, $MH^+ - S(CH_2)_2CONH(CH_2)_3NHAcr$], 1711 (34, $MH^+ - C_{21}H_{23}N_4O_2S - H$), 1710 (18, $MH^+ - C_{21}H_{23}N_4O_2S - 2H$), 1366 [20, $MH^+ - C_{21}H_{23}N_4O_2S - (CH_2)_3NHAcr - 3H$], 1365 (12, $MH^+ - C_{42}H_{48}N_6O_3S - 4H$), 1072 (10, $MH^+ - 3\times(CH_2)_3NHAcr - 3\times CH_3$). U.v./vis. (0·01 PIPES, pH 6·8) λ_{max} 265, 400, 506, 540, 572, 623 nm (ϵ not determined).