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Neuromuscular blocking agents. Some approaches to short acting compounds

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Summary — A series of amidic and *N*-methylamidic methyl and trideuteromethyl quaternary analogues of atracurium have been prepared. All were less potent and longer acting neuromuscular blocking agents than atracurium, and all showed appreciable vagal blockade at neuromuscular blocking doses. Replacement of NCH_3 by NCD_3 failed to affect potency. Fluorosubstitution in the central chain did not reduce duration of action. Attachment of acyloxy substituents to the interquaternary chain of atracurium and related compounds adjacent to their ester groups shortened the duration of action significantly. Diformyloxy substitution was the most effective in reducing duration without adversely affecting other properties apart from potency, which was significantly less than that of atracurium.

quaternary ammonium compound / amide / acyloxy ester / neuromuscular blocking agent

Introduction

Although suxamethonium **1** is still widely used, it has long been recognised that its actions as a short-acting neuromuscular blocking agent are far from ideal [1]. Its rapid onset, no doubt due to its action as a partial agonist, is accompanied by muscle twitching and as a result patients experience post-operative muscle pain [2]. Its mechanism of neuromuscular blockade by depolarisation, although undesirable, is not a serious disadvantage in the great majority of patients because paralysis is rapidly terminated through molecular cleavage by normal plasma esterase metabolism. However, defective metabolism, due to abnormally low levels of plasma cholinesterase in certain disease states [1] or genetically determined deficiencies, can prolong drug action to an unacceptable degree [3, 4] and lack of reversibility by neostigmine then becomes a serious disadvantage. In the search for a replacement for suxamethonium, we have studied ways in which the onset time and duration of the competitive skeletal muscle relaxant, atracurium, **13** (X = H, Y = 0, Z = $(CH_2)_3$) [5], might be reduced. We report a number of approaches, none completely successful. These include attempts to improve the fit of quaternary ammonium centres with acetylcholine receptors at the neuromuscular junction to enhance uptake and potency, and increasing lipophilicity as a means of reducing onset time. Ways of enhancing the rates of Hofmann elimination and ester hydrolysis to shorten duration have also been examined.

$Me_3N^+—CH_2CH_2OCOCH_2CH_2COOCH_2CH_2—^+NMe_3$ $2\,X^-$

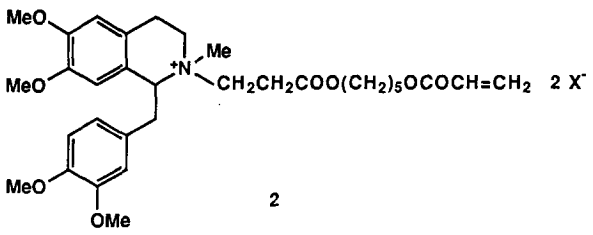
1

Rates of uptake and binding of antagonists at acetylcholine receptors are influenced by the nature and size of the quaternary ammonium substituents [6]. Since the carbon-deuterium bond is shorter than the C–H bond, CD_3 is more compact than CH_3. N–CD_3 substituents may therefore lead to tighter receptor binding and a shorter onset time. Thus, norcoralydine *N*-trideuteromethiodides [7] are marginally more potent neuromuscular blocking agents than the corresponding methiodides. The effect of incorporating trideuteromethyl substituents in some atracurium-related (**13** Z = $(CH_2)_4$, Y = NH and NMe, X = D) and other (**15** Y = NMe, X = D) bis-quaternary amides has, therefore, been examined. The latter compounds and a related series of esters **15** (Y = D) based on piperidine, 2,6-dimethylpiperidine, homopiperidine and morpholine were prepared to test the further concept that smaller heterocyclic rings, as in pancuronium and vecuronium [12, 13] favour more rapid onset of action.

Potency of neuromuscular blocking agents is enhanced by lipid substituents at or near their quat-

ernary ammonium groups [6]. These facilitate receptor-binding by hydrophobic interaction at lipophilic subcentres of the acetylcholine receptor, as is evident in the increasing potency of alkyltrimethylammonium compounds with increasing chain length [8–10]. We have, therefore, prepared a number of compounds, **13** (X = H or D, Y = NMe, Z = $(CF_2)_3$) incorporating hydrophobic fluorocarbon substituents in an endeavour to enhance both cross-membrane diffusion and receptor-affinity, and hence reduce onset time.

At the same time, we have also examined ways of increasing the rate of decomposition of atracurium-related compounds under physiological conditions of pH (7.4) and temperature (37°C) both by Hofmann elimination alone or in combination with ester hydrolysis. Fragmentation of atracurium **13** (X = H, Y = O, Z = $(CH_2)_3$) by Hofmann elimination to laudanosine **7** R = Me and the monoacrylate **2** is assisted *in vivo* by the β-positioned ester groups. However, concurrent hydrolysis of the latter [5, 11] also fragments the molecule to inactive components, and slows the initial rate of Hofmann elimination [5] due to formation of the quaternary acid **3**, in which the ester group (COOR) has been replaced by the less powerfully electron-withdrawing carboxylic acid group (COOH). We have, therefore, replaced ester functions by more stable amido groups in an attempt to enhance the overall rate of Hofmann elimination without concurrent hydrolytic chain cleavage. The hydrolytically more stable amido group (NH-CO) is less powerfully electron-withdrawing than the ester group due to amido-imido tautomerism, but this effect is countered by *N*-substitution in the *N*-methylamides **13** (X = H or D, Y = NMe, Z = $(CH_2)_4$) and their fluoro-substituted analogues **13** (Y = NMe, Z = $(CF_2)_3$).



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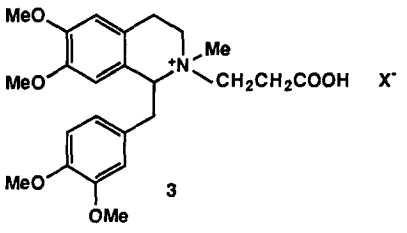

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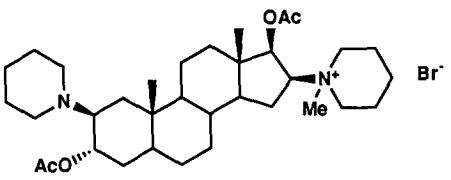
Attempts to prepare the corresponding hexafluoro esters **9** (Y = O, Z = $(CF_2)_3$) to enhance chain fragmentation by hydrolysis were unsuccessful, but bisquaternary esters of 1,3-dihydroxyacetone **13** (X = H, Y = O, Z = CO) and the corresponding 5,5'-dimethoxy compound were readily obtained.

Additional electron-withdrawing substituents in the heterocyclic ring or central chain of bis-quaternary polyalkylene diesters offer a further means of shortening duration of action. Compounds so substituted with readily hydrolysable carbethoxy or acyloxy groups adjacent to quaternary nitrogen are capable of rapidly forming either inactive hydrophilic bis-quaternary metabolites or inactive non-quaternary fragmentation products at enhanced rates of Hofmann elimination and ester hydrolysis. We report three series of compounds. Series **17** and **26** are based on piperidine and related bases in recognition of the generally favourable neuromuscular blocking properties of vecuronium **4** [12, 13], the short-acting bis-piperidinium compounds **5** [14], and the acyclic prodeconium **6** [15] that is also short-acting. The tetrahydropapaverine-derived compounds **24**, **32** and **34**, similarly capable of rapid fragmentation, were also prepared.

Chemistry

Attempts to prepare the intermediate **9** (Y = NH, Z = $(CH_2)_4$) by condensation of hexamethylene-1,6-diacrylamide **8** (Y = NH, Z = $(CH_2)_4$) with tetrahydro-



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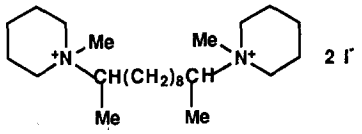

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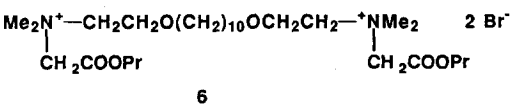

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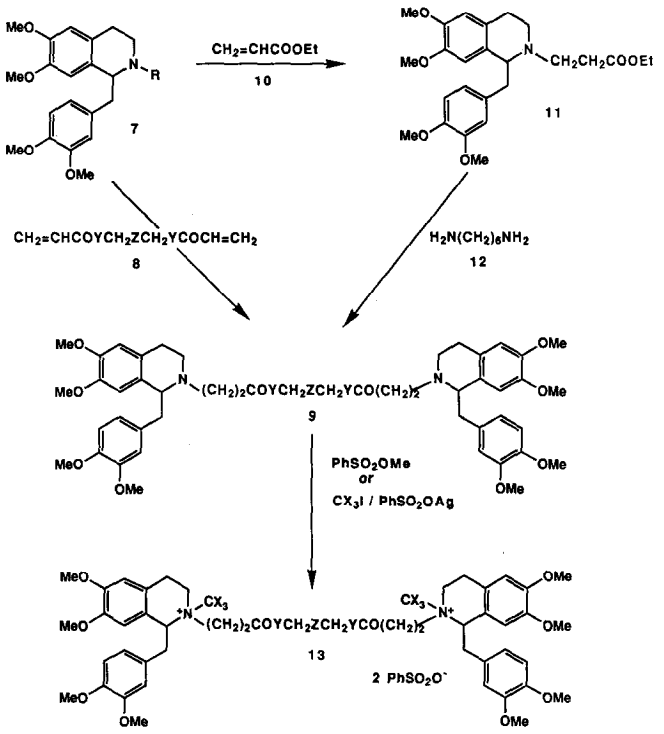
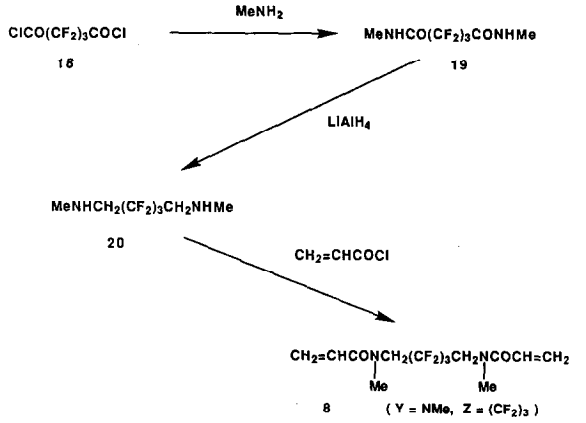
papaverine **7** (R = H) in the presence of glacial acetic acid yielded only a small amount of a product corresponding to $CH_3CO\text{-}O\text{-}CH_2CH_2CONH(CH_2)_6NHCO\text{-}CH_2CH_2O\text{-}CO\text{-}CH_3$. The nature of this compound was confirmed when hexamethylene-1,6-diacrylamide was heated with glacial acetic acid in the absence of tetrahydropapaverine.

In contrast, the more strongly electron-withdrawing tertiary *N*-methylamides, *N,N'*-dimethylhexamethylene-1,6-diacrylamide **8** (Y = NMe, Z = $(CH_2)_4$) and *N,N'*-dimethyl-2,2,3,3,4,4-hexafluoro-1,5-pentamethylene diacrylamide **8** (Y = NMe, Z = $(CF_2)_3$) prepared as shown in scheme 2, condensed readily with tetrahydropapaverine (scheme 1) to form compounds **9** (Y = NMe, Z = $(CH_2)_4$) and **9** (Y = NMe, Z = $(CF_2)_3$) respectively. The di-tertiary base precursors **14** (Y = NMe, n = 6) were prepared similarly.

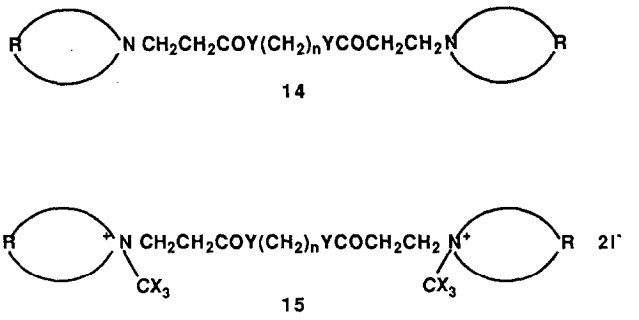
The di-tertiary base **9** (Y = NH, Z = $(CH_2)_4$) was prepared (scheme 1) from tetrahydropapaverine **7** (R = H), *via* ethyl 3-*N*-tetrahydropapaverinylpropionate **11**, by condensation of the latter with hexamethylenediamine **12** in xylene in the presence of sodium hydride. Methyl quaternary salts **13** (X = H) and **15** (X = H) were prepared by reaction with methyl benzenesulphonate and methyl iodide respectively. Quaternisation of the bases **9** and **14** (Y = NMe, n = 6) with trideuteromethyl iodide followed by treatment



Scheme 1.

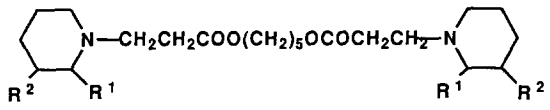


Scheme 2.



of the product with silver benzenesulphonate in methanol gave the corresponding trideuteromethyl besylates **13** (X = D) and **15** (Y = NMe, n = 6, X = D).

The esters **15** (Y = O, n = 5) **17** (R^1 = H, R^2 = COOEt) and **17** (R^1 = COOEt, R^2 = H) were prepared as for atracurium [6] by condensation of the appropriate secondary amine with pentamethylene diacrylate and quaternisation with either methyl iodide or trideuteromethyl iodide. The 3-*O*-acylpiperidinium compounds **17** (R^1 = H, R^2 = *O*-acyl) and 2-*O*-acylmethylpiperiodinium compounds **17** (R^1 = CH_2O-acyl, R^2 = H) were prepared likewise by condensation of pentamethylene diacrylate with 3-hydroxypiperidine and 2-hydroxymethylpiperidine respectively, followed by acylation with the appropriate acyl chloride and quaternisation. The quaternary salts **13**, **15a–k** and **17a–g** have four, four and six chiral centres respectively. They were prepared from racemic intermediates without recourse to separation methods. Each is assumed to be a mixture of all possible stereoisomers [16], and in the light of their biological activities, which were not of sufficient interest to warrant further development, no attempt was made to prepare individual stereoisomers.



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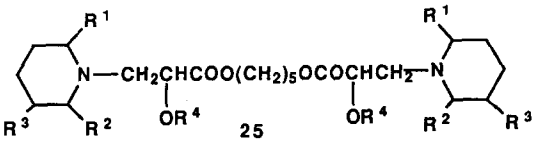

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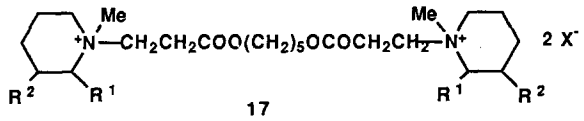

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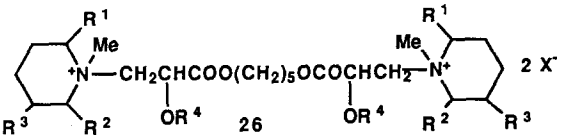

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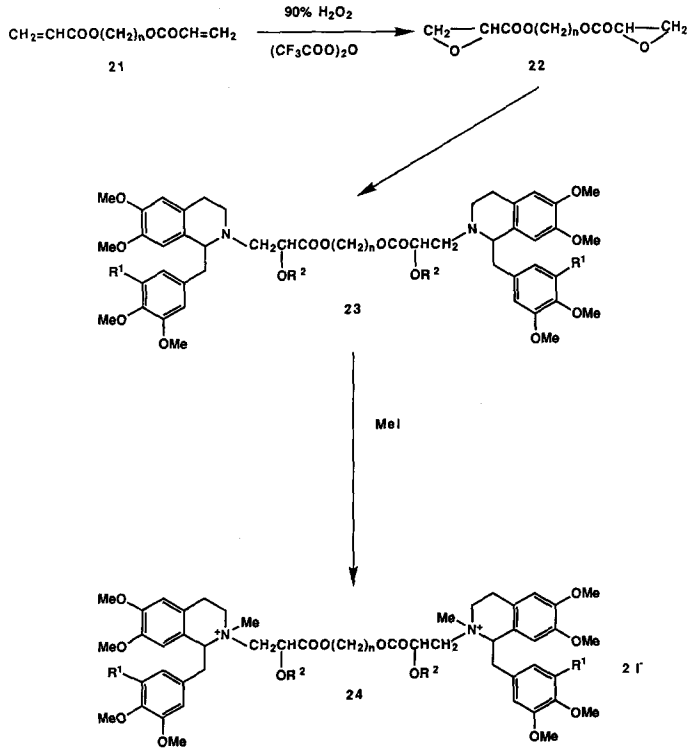
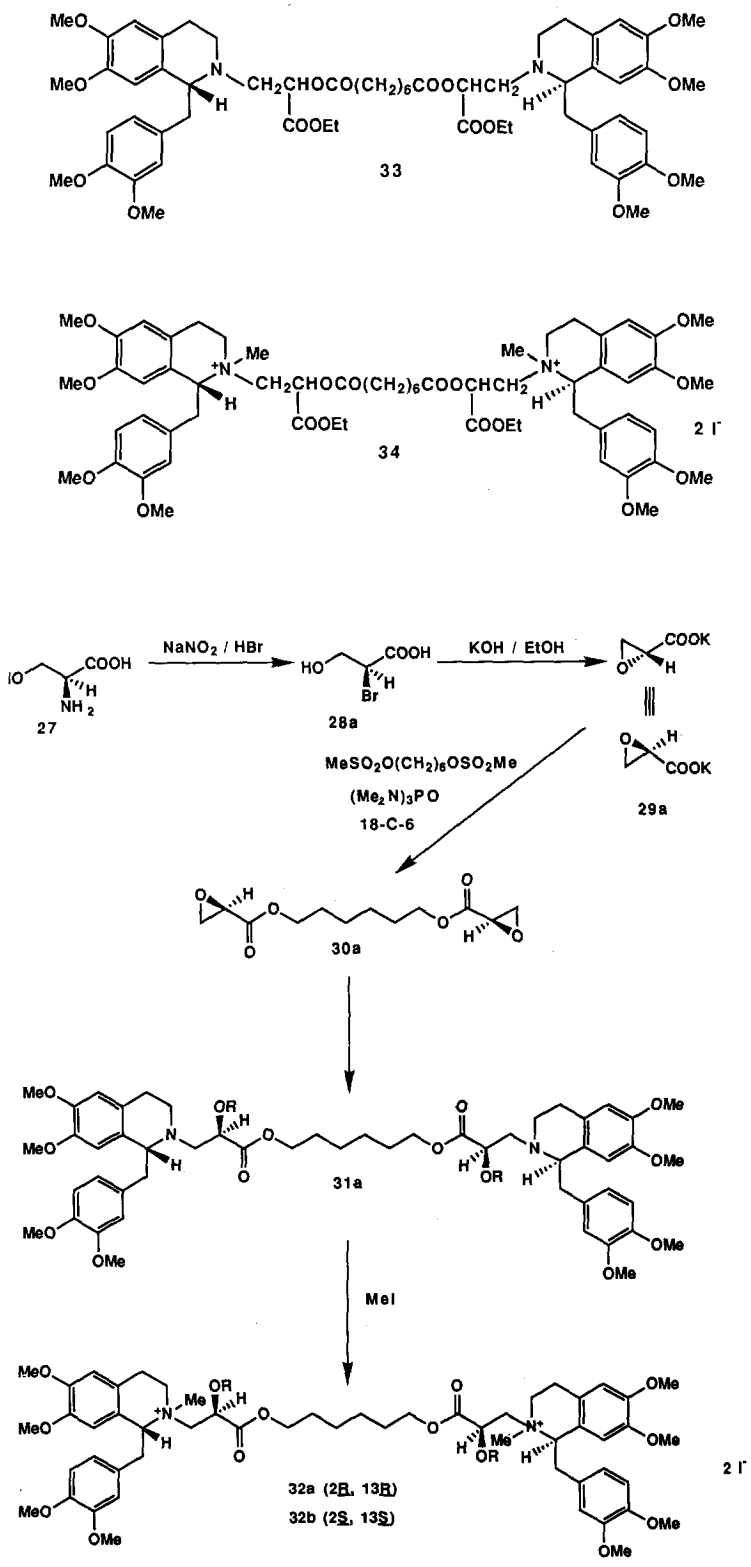
The key intermediates in the synthesis of compounds **24** (n = 5–7) and **26**, the polymethylene di-2-epoxypropionates **22** (n = 5–7) were prepared (scheme 3) by epoxidation of the corresponding polymethylene diacrylates **21** with peroxytrifluoroacetic acid obtained from 90% hydrogen peroxide and trifluoroacetic anhydride [17]. Treatment of the diepoxides **22** with the appropriate secondary amines [18] gave the dihydroxydiamines **23** and **25**, which when acylated and methylated gave the di-acyloxy bis-quaternary compounds **24** and **26**. The 2,13-diethoxycarbonyl analogue **34** of compounds **24** was prepared by condensation of *(1R)*-tetrahydropapaverine **7** (R = H) with ethyl glycidate to yield ethyl *(2RS)*-2-hydroxy-3-*(1R)*-tetrahydropapaverinylpropionate **7** (R = $CH_2CH(OH)COOEt$), condensation of the latter with suberoyl chloride, and quaternisation of the resulting base **33** with methyl iodide.



Scheme 3.

Compounds **24**, **26**, **32** and **34** each have either six (**24**, **26c–e**, **32** and **34**) or eight (**26a–b**) chiral centres. Compounds **24a**, **c**, **e–l**, **o–r**, **t** and **u** and **26a–e** were prepared from racemic intermediates by non-stereoselective methods and without recourse to isomer separation methods. They are assumed to be mixtures of all possible isomers. Compound **34**, formed from *(1R)*-tetrahydropapaverine, is assumed to be a mixture of the ten possible isomers.

Some of the effects of stereochemistry in this series were studied in compounds **24b**, **d**, **n** and **q** and **32a** and **b**, on lines similar to those used in earlier studies of atracurium and related compounds [16]. The latter showed that the *(1R,1'R)*-isomer mixtures consisting of 1,2-*cis-cis*, 1,2-*cis-trans* and 1,2-*trans-trans* isomers derived from *(1R)*-tetrahydropapaverine are more potent than the corresponding *(1R,1'S)*- and *(1S,1'S)*-isomer mixtures. Accordingly, the *(1R)*-tetrahydropapaverinyl-*(2RS,13RS)*-2,13-chain-substituted compounds **24b**, **d**, **n** and **q** were prepared from *(1R)*-tetrahydropapaverine (scheme 3). The corresponding *(1R,1'R)*-ditetrahydropapaverinyl-*(2R,13R)*- and *(2S, 13S)*-chain-substituted formyloxy compounds **32a** and **32b** were also prepared as shown in scheme 4. In this, *(R)*-potassium glycidate **29a**, prepared from *(S)*-serine



Scheme 4.

27a *via (2S)*-2-bromo-3-hydroxypropionic acid **28a** [19], was condensed with 1,6-hexamethylene dimesylate in the presence of 18-crown-6 and hexamethylphosphoramide to yield *(2R,13R)*-1,2,13,14-diepoxy-4,11-dioxa-3,12-dioxotetradecylene **30a**. Condensation of the latter with *(1R)*-tetrahydropapaverine gave the *(2R,13R)*-2,13-dihydroxy-*(1R,1'R)*-diamine **31a** (R = H). Acylation with formic-acetic anhydride and quaternisation with methyl iodide gave the *(2R,13R)*-2,13-diformyloxy-bis-*(1R)*-tetrahydropapaverinyl dimethiodide **32a** (R = CHO). The corresponding *(2S,13S)*-2,13-diformyloxy-di*(1R)*-tetrahydropapaverinyl dimethiodide **32b** (R = CHO) was prepared similarly from *(R)*-serine.

Experience with atracurium and related compounds [16] has shown that quaternisation yield mixtures of 1,2-*cis-cis*-, 1,2-*cis-trans*- and 1,2-*trans-trans*-isomers are of consistent composition. Compounds **24a–u** and **32a** and **b** are therefore assumed to consist of similar mixtures of 1,2-*cis-cis*-1,2-*cis-trans*- and 1,2-*trans-trans*-isomers, the composition of which is determined by the methylating agent, solvent and temperature used.

Pharmacological results and discussion

Preliminary assessments of neuromuscular blocking potency, duration, spontaneous reversibility, reversibility with neostigmine and vagal blockade relative to atracurium besylate in anaesthetised cats are given in tables I–V. These show that the amido compounds **13** (Y = NH or Me) are competitive neuromuscular blocking agents, undergoing spontaneous reversal and ready reversal with neostigmine (table I). All, however, are less potent and somewhat longer acting than atracurium, and in contrast to atracurium, all show a significant degree of vagal blockade at neuromuscular blocking doses – apparently a characteristic feature of their amidic structures. No appreciable difference was seen between pairs of trideuteromethyl and methyl quaternary compounds. Also, fluorosubstitution in the central interquaternary chain failed to influence duration of action in this series.

The *N*-methylamides **15a–f** (Y = NMe) were also less potent and longer acting than atracurium. In common with the corresponding tetrahydropapaverine derivatives **13**, all showed a significant degree of vagal blockade, but in contrast to the former all produced non-competitive neuromuscular blockade which was not reversed by neostigmine.

Similarly, the esters **13g** (Y = O) and **13h** (Y = O) and those of the series **15**, **17** and **26** with the exception of the piperidinium compound **15g** and the morpholinium compound **15j** also showed significant vagal blockade (tables II, III and IV). Only the 2,6-

Table I. Neuromuscular blocking properties and vagal effects of compounds **13** in anaesthetised cats.

Cpd	*X*	*Y*	*Z*	*mp (°C)*	*Yield (%)*	*Formula*	*Anal*	*Neuromuscular blockade* ED_{95} *(n)*[a] *(mg/kg)*	*Duration*[b] *(min)*	*Complete spontaneous*[c] *reversal*	*Neostigmine reversal*	*Vagal response*[d]
13a	H	NH	$(CH_2)_4$	115–120	82	$C_{66}H_{84}N_4O_{16}S_2$, H_2O	CHNS	3.5 (4)	> 20	+	+	+++
13b	D	NH	$(CH_2)_4$	105–110	69	$C_{66}H_{78}D_6N_4O_{16}S_2$, H_2O	CH+DNS	4.0 (2)	20–25	+	+	+++
13c	H	NMe	$(CH_2)_4$	106–110	75	$C_{68}H_{90}N_4O_{16}S_2$, H_2O	CHNS	0.85 (7)	18–20	+	+	++
13d	D	NMe	$(CH_2)_4$	92–98	85	$C_{68}H_{84}D_6N_4O_{16}S_2$, H_2O	CH+DNS	0.85 (3)	18	+	+	++
13e	H	NMe	$(CF_2)_3$	121–126	93	$C_{67}H_{82}F_6N_4O_{16}S_2$, H_2O	CHNS	3.5 (4)	> 20	+	+	+++
13f	D	NMe	$(CF_2)_3$	102–106	79	$C_{67}H_{76}D_6F_6N_4O_{16}S_2$, H_2O	CH+DNS	2.0–4.5 (4)	> 25	+	+	++++
13g	H	O	CO	94–96	75	$C_{63}H_{72}N_2O_{19}S_2$, H_2O	CHNS	> 11 (2)	NT[e]	NT	NT	+++
13h[f]	H	O	CO	89–93	71	$C_{65}H_{80}N_2O_{21}S_2$, H_2O	CHNS	> 10 (2)	NT	NT	NT	++++
Atracurium[g]	H	O	$(CH_2)_5$									

[a]Number of animals; [b]Time from injection to 95% of control; [c]Dose 0.05 mg/kg iv; [d]++++ Significant inhibition in the absence of neuromuscular blockade; +++Significant inhibition at doses that produce neuromuscular blockade; ++Significant inhibition at ED_{95} or slightly higher doses; [e]Not tested; [f]5',5"-Dimethoxy compound; [g]ED_{95} 0.162 ± 0.015 mg/kg. Onset 4.3 ± 0.1 min. Duration 14.6 ± 0.7 min.

Table II. Neuromuscular blocking properties and vagal effects of compounds **15** in anaesthetised cats.

Cpd	*X*	*Y*	*n*	*R*	*mp (°C)*	*Yield (%)*	*Tlc*[a] R_f	*Formula*	*Anal*	*NMR*	*Neuromuscular blockade* ED_{95} *(n)*[b] *(mg/kg)*	*Duration*[c] *(min)*	*Complete spontaneous reversal*	*Neostigmine reversal*[d]	*Vagal response*[e]
15a	H	NMe	6	$(CH_2)_5$	*[f]	55	0.65	$C_{26}H_{52}N_4O_2I_2$	CHNI	+	6.0–10.0 (3)	> 20	–	–	++++
15b	D	NMe	6	$(CH_2)_5$	*	56	0.60	$C_{26}H_{46}D_6N_4O_2I_2$	CH+DNI	+	10.0–15.0 (2)	> 20	–	–	++++
15c	H	NMe	6	$(CH_2)_6$	67–73	54	0.56	$C_{28}H_{56}N_4O_2I_2$	CHNI	+	4.0–6.0 (2)	> 20	–	–	+++
15d	D	NMe	6	$(CH_2)_6$	*	55	0.53	$C_{28}H_{50}D_6N_4O_2I_2$, H_2O	CH+DNI	+	4.0–8.0 (2)	> 12	–	–	+++
15e	H	NMe	6	$CH_2CH_2OCH_2CH_2$	98–104	54	0.78	$C_{24}H_{48}N_4O_4I_2$	CHNI	+	15.0–18.0 (2)	> 15	–	–	+++
15f	D	NMe	6	$CH_2CH_2OCH_2CH_2$	*	50	0.78	$C_{24}H_{42}D_6N_4O_4I_2$, H_2O	CH+DNI	+	> 15.0 (3)	> 15	–	–	+++
15g	H	O	5	$(CH_2)_5$	*	59		$C_{23}H_{44}N_2O_4I_2$, $2H_2O$	CHNI	+	0.2–0.8 (2)	> 25	+	–	0
15h	H	O	5	$(CH_2)_6$	167–171	79		$C_{25}H_{48}N_2O_4I_2$	CHNI	+	8.0–10.0 (2)	8–15	+	–	++++
15j	H	O	5	$CH_2CH_2OCH_2CH_2$	*	45		$C_{21}H_{40}N_2O_6I_2$	CHNI	+	2.0–4.0 (2)	*ca*15	+	–	0–(+)
15k	H	O	5	CHMe $(CH_2)_3$CHMe	*	66		$C_{27}H_{52}N_2O_4I_2$	CHNI	+	1.5–2.5 (2)	12–30	+	+	+++
Atracurium[g]															

[a]0.5 M NaCl-CH_3CN (60:40) on Whatman $MKC_{18}F$; [b]Number of animals; [c]Time from injection to 95% of control; [d]Dose 0.05 mg/kg iv; [e]++++ Significant inhibition in the absence of neuromuscular blockade; +++Significant inhibition at doses that produce neuromuscular blockade; ++Significant inhibition at ED_{95} or slightly higher doses; [f]Non-crystalline; [g]ED_{95} 0.162 ± 0.015 mg/kg. Onset 4.3 ± 0.1 min. Duration 14.6 ± 0.7 min.

Table III. Neuromuscular blocking properties and vagal effects of compounds **17** in anaesthetised cats.

Cpd	*R'*	*R²*	*X*	*mp (°C)*	*Yield (%)*	*Formula*	*Anal*	*NMR*	*Neuromuscular blockade* ED_{95}[a] *(mg/kg)*	*Duration*[b] *(min)*	*Complete spontaneous reversal*	*Neostigmine reversal*[c]	*Vagal response*[d]
17a	H	Acetoxy	I	*[e]	89	$C_{27}H_{48}N_2O_8I_2$	CHNI	+	15.0 (1)	7–8	+	–	+++
17b	H	Benzoyloxy	I	72–77	53	$C_{37}H_{52}N_2O_8I_2$		+	5.0–10.0 (4)	5	+	–	+++
	H	Benzoyloxy	Bs	*	83	$C_{49}H_{62}N_2O_{14}S_2$	CHNS	+	5.0 (1)	5	+	–	+++
17c	H	4-Cl-benzoyloxy	Bs	*	79	$C_{49}H_{60}N_2O_{14}Cl_2S_2$	CHNClS	+	5.0–6.0 (1)	6	+	–	+++
17d	H	Veratroyloxy	I	*	81	$C_{41}H_{60}N_2O_{12}I_2$	CHNI	+	5.0–6.0 (2)	6–12	+	–	++++
	H	Veratroyloxy	Bs	*	76	$C_{53}H_{70}N_2O_{18}S_2$, H_2O	CHNS	+	4.0–6.0 (1)	12–14	+	–	++++
17e	H	Homoveratroyloxy	Bs	*	73	$C_{55}H_{74}N_2O_{18}S_2$	CHNS	+	5.0–10.0 (1)	8–10	+	NT[f]	+++
17f	H	Ethoxycarbonyl	I	*	76	$C_{29}H_{52}N_2O_8I_2$, H_2O	CHNI	+	> 10.0 (2)	6–8	+	–	++++
17g	Ethoxycarbonyl	H	I	*	94	$C_{29}H_{52}N_2O_8I_2$, $1/2H_2O$	CHNI	+	1.0–2.0 (2)	7–8	+	+	+++
Atracurium[g]													

[a]Number of animals; [b]Time from injection to 95% of control; [c]Dose 0.05 mg/kg iv; [d]++++ Significant inhibition in the absence of neuromuscular blockade; +++Significant inhibition at doses that produce neuromuscular blockade; ++Significant inhibition at ED_{95} or slightly higher doses; [e]Freeze-dried; [f]Not tested; [g]ED_{95} 0.162 ± 0.15 mg/kg. Onset 4.3 ± 0.1 min. Duration 14.6 ± 0.7 min.

Table IV. Neuromuscular blocking properties and vagal effects of compounds **26** in anaesthetised cats.

Cpd	*R'*	*R²*	*R³*	*R⁴*	*X*	*mp (°C)*	*Yield (%)*	*Formula*	*Anal*	*NMR*	*Neuromuscular blockade* ED_{95}[a] *(mg/kg)*	*Duration*[b] *(min)*	*Complete spontaneous reversal*	*Neostigmine reversal*[c]	*Vagal response*[d]
26a	Me	Me	H	Acetyl	I	103–106	86	$C_{31}H_{56}N_2O_8I_2$, $1/2H_2O$	CHNI	+	1.0–2.0 (2)	10	+	+	+++
26b	Me	Me	H	Benzoyl	Bs[e]	83–86	70	$C_{53}H_{70}N_2O_{14}S_2$, H_2O	CHNS	+	2.0–3.0 (1)	6	+	–	+++
26c	H	H	COOEt	Acetyl	I	86–89	87	$C_{33}H_{56}N_2O_{12}I_2$	CHNI	+	> 6.0 (2)	NR[f]	+	+	++
26d	H	H	COOEt	Benzoyl	I	111–115	98	$C_{43}H_{60}N_2O_{12}I_2$	CHNI	+	6.0–10.0 (2)	10–12	+	–	+++
26e	H	H	COOEt	Veratroyl	I	NR	96	$C_{47}H_{68}N_2O_{16}I_2$	CHNI	+	8.0 (2)	5–6	+	–	+++
Atracurium[g]															

[a]Number of animals; [b]Time from injection to 95% of control; [c]Dose 0.05 mg/kg iv; [d]++++ Significant inhibition in the absence of neuromuscular blockade; +++Significant inhibition at doses that produce neuromuscular blockade; ++Significant inhibition at ED_{95} or slightly higher doses; [e]BS = besylate; [f]NR = not recorded; [g]ED_{95} 0.162 ± 0.15 mg/kg. Onset 4.3 ± 0.1 min. Duration 14.6 ± 0.7 min.

Table V. Neuromuscular blocking properties and vagal effects of compounds **24**, **31** and **34** in anaesthetised cats.

Cpd	n	R'	R^2	Configuration Isoquinoline C–1	Configuration Chain	mp (°C)	Yield (%)	$[\alpha]_D^{20}$	Formula	Anal	NMR	Neuromuscular blockade ED_{95}[a] (mg/kg)	Neuromuscular blockade Duration[b] (min)	Complete spontaneous reversal	Neostigmine reversal[c]	Vagal response[d]
24a	5	H	Formyl	RS, RS	RS, RS	120–124	96		$C_{55}H_{72}N_2O_{16}I_2$	CHN		0.6–1.0 (3)	8–9	+	+	0–++
24b	5	H	Formyl	R, R	RS, RS	121–123	94	−51.4° (0.99)[e]	$C_{55}H_{72}N_2O_{16}I_2$	CHN		0.8–1.0 (1)	8–10	+	+	0
24c	5	H	Acetyl	RS, RS	RS, RS	124–128	100		$C_{57}H_{76}N_2O_{16}I_2$	CHN	+	1.5 (2)	8	+	+	0
24d	5	H	Acetyl	R, R	RS, RS	128–130	96	−55.6° (1.02)	$C_{57}H_{76}N_2O_{16}I_2$	CHN		0.7(2)	8–9	+	+	0
24e[f]	5	H	Benzoyl	RS, RS	RS, RS	83.5–86	59		$C_{75}H_{90}N_2O_{28}$	CHN	+	> 6.0 (2)	NR	NR	NR	+++
	5	H	Benzoyl	RS, RS	RS, RS		90		$C_{67}H_{80}N_2O_{16}I_2$	CHN						
24f[f]	5	H	4-Chlorobenzoyl	RS, RS	RS, RS	57–60	47		$C_{75}H_{88}N_2O_{28}Cl_2$	CHN	+	> 10.0 (2)	NR	NR	NR	++++
24g	5	H	2,4-Dichlorobenzoyl	RS, RS	RS, RS		89		$C_{67}H_{76}N_2O_{16}Cl_4I_2$	CHN		> 11.0 (2)	> 10	+	–	++
24h	5	H	3,5-Dichlorobenzoyl	RS, RS	RS, RS		96		$C_{67}H_{76}N_2O_{16}Cl_4I_2$	CHN		> 10.0 (2)	NR	NR	NR	+++
24j	5	H	4-Trifluoromethyl-benzoyl	RS, RS	RS, RS		98		$C_{69}H_{78}N_2O_{16}F_6I_2$	CHN	> 12.0 (2)	NR	NR	NR		++++
24k	5	H	Homoveratroyl	RS, RS	RS, RS		100		$C_{73}H_{92}N_2O_{20}I_2$	CHN		8.0–10.0 (2)	10–12	+	NR	+++
24l	5	H	3,4,5-Trimethoxy-phenylacetyl	RS, RS	RS, RS		97		$C_{75}H_{96}N_2O_{22}I_2$	CHN		9.0–10.0 (2)	16	+	–	++
24m	5	H	Cyclopropan-carbanoyl	R, R	RS, RS		94	−58.1° (1.03)	$C_{61}H_{74}N_2O_{16}I_2H_2O$	CHN		> 10.0 (1)	> 12	+	+	+++
24n	6	H	Formyl	R, R	RS, RS	112–114	85	−53.9° (0.99)	$C_{56}H_{74}N_2O_{16}I_2$	CHN	+	0.8 (2)	6	+	+	0
32a	6	H	Formyl	R, R	R, R	112–114	89	−50.1° (1.02)	$C_{56}H_{74}N_2O_{16}I_2$	CHN		0.4–0.5 (4)	8–10	+	+	0
32b	6	H	Formyl	R, R	S, S	112–114	73	−58.9° (1.04)	$C_{56}H_{74}N_2O_{16}I_2$	CHN		0.7–0.9 (3)	5–7	+	+	0
24o	6	MeO	Formyl	RS, RS	RS, RS	115–124	86		$C_{58}H_{78}N_2O_{18}I_2$	CHN	+	2.0–3.0 (2)	6	+	+	0
24p	6	H	Acetyl	RS, RS	RS, RS	105–114	90		$C_{58}H_{78}N_2O_{16}I_2$	CHN		0.9–1.5 (3)	9–13	+	+	0
24q	6	H	Acetyl	R, R	RS, RS	120–122	95	−55.4° (1.08)	$C_{58}H_{78}N_2O_{16}I_2$	CHN		0.8–1.0 (1)	8	+	+	0
24r	6	MeO	Acetyl	RS, RS	RS, RS	120–127	90		$C_{60}H_{82}N_2O_{18}I_2$	CHN		8.0–10.0 (1)	8–10	+	+	0–+
24s	6	H	Ethoxycarbonyl	R, R	RS, RS		93	−53.0° (1.0)	$C_{60}H_{82}N_2O_{18}I_2H_2O$	CHN		> 10.0 (1)	8–10	+	+	+++
24t	7	MeO	Formyl	RS, RS	RS, RS		83		$C_{59}H_{80}N_2O_{18}I_2$	CHN	+	2.0 (1)	7	+	+	0–+
24u	7	MeO	Acetyl	RS, RS	RS, RS	121–126	97		$C_{61}H_{84}N_2O_{18}I_2$	CHN	+	3.0–4.0 (1)	18	+	+	0
34				R, R	RS, RS	115–117	95	−50.9° (1.08)	$C_{60}H_{82}N_2O_{16}I_2$	CHN		10.0 (1)	10	+	+	++++
Atracurium[g]																

[a]No of animals; [b]Time from injection to 95% of control; [c]Dose 0.05 mg/kg; [d]++++ Significant inhibition of the response to vagal nerve stimulation in the absence of neuromuscular blockade; +++Significant inhibition at doses that produce neuromuscular blockade; ++Significant inhibition at ED_{95} or slightly higher doses; [e]Concentration in chloroform; [f]Hydrogen tartrate; [g]ED_{95} 0.162 ± 0.15 mg/kg. Onset 4.30 ± 0.1 min. Duration 14.6 ± 0.7 min.

dimethylpiperidinium compounds **15k** and **26a** and the 2-ethoxycarbonylpiperidinium compound **17g** with substituents on the β-carbon to the quaternary centre and the chain-substituted 3-ethoxycarbonylpiperidinium compound **26c** produced competitive neuromuscular blockade readily reversed by neostigmine. All were significantly less potent than atracurium.

Notwithstanding otherwise undesirable properties, most of the acyloxy- and ethoxycarbonyl-piperidinium compounds **17** (table III) and **26** (table IV) produced neuromuscular blockade of substantially shorter duration than that of atracurium. As anticipated, duration is related to the ease with which the compounds undergo hydrolysis and/or Hofmann elimination. Hydrolysis cleaves the lipophilic ethoxycarbonyl and acyloxy groups to the corresponding, less potent, monoquaternary acids and alcohols, which being hydrophilic also have reduced affinity for the acetylcholine receptor.

Duration of action should, therefore, reduce roughly in parallel with the electron withdrawing power of the acylating group. Other factors, however, such as the bulk of the acylating acid impede hydrolysis of the chain ester and the substituent acylaoxy groups, so that the parallel between the pK_a of the acylating acid and duration is inexact. It is even more so in compounds **24** (table V) where the bulk of the larger chain-acylating groups combines with that of the tetrahydropapaverine groups to reduce potency, enhance vagal blockade and minimise the reduction in duration of action.

Of the compounds **24** (table V), only the formyloxy and acetyloxy chain-substituted compounds were free from vagal blockade at neuromuscular blocking doses. Their action underwent complete spontaneous reversal, and was readily reversed by neostigmine showing it to be competitive. Introduction of additional methoxyl groups in the 5'-methoxytetrahydropapaverine compounds **24o**, **r**, **t** and **u** markedly reduced potency as found in the 5,5'-methoxy derivatives of the atracurium-related compounds **13** (X = H, Y = O, Z = O) [5]. The additional methoxyl group had little effect on duration except in the acetoxy compound **24u** which was of approximately the same duration as atracurium.

The *(1R,1'R)*-isomers of atracurium [16] and *N,N*-1,10-decamethylenetetrahydropapaverines [20] are more potent than their *(1R,1'S)*- and *(1S,1'S)*-isomers. Likewise, the *(1R,1'R)*-ditetrahydropapaverinyl-*(RS,RS)*-diacetyloxy compound **24d** was more potent than the corresponding *(1RS,1'RS)*-compound **24c**, though of similar duration. The *(1R,1'R)*-ditetrahydropapaverinyl-*(RS,RS)*-diformyloxy compound **24b**, however, was equipotent with and had the same duration as its corresponding *(1RS,1'RS)*-compound **24a**. Increasing the interquaternary distance by one atom unit (*ie* from $n = 5$ to $n = 6$) had little effect on the potency of either acetyloxy or formyloxy compounds, but duration of action was shortened in the *(1R,1'R)*-ditetrahydropapaverinyl-*(RS,RS)*-diformyloxy compound **24n**, indicating an effect that may in part be attributable to the smaller bulk and lower pK_a of formic acid (pK_a 3.77) compared with acetic acid (pK_a 4.75). On the other hand, it is evident that steric effects are equally if not more important since potency was significantly increased in the *(1R,1'R)*-ditetrahydropapaverinyl-*(2R,13R)*-diformyloxy dimethiodide **32a**, although with a smaller increase in the duration of action. The corresponding *(1R,1'R)*-ditetrahydropapaverinyl-*(2S,13S)*-diformyloxy dimethiodide **32b**, however, was of similar potency and duration to the *(1R,1'R)*-ditetrahydropapaverinyl-*(2RS,13RS)*-diformyloxy compound **24n**.

Experimental protocols

Chemistry

Melting points were recorded on a Koffler Heizbach 184321 melting point apparatus, and are uncorrected. Infrared spectra were obtained on either a Perkin-Elmer 710B or a Perkin-Elmer 781 infrared spectrometer using liquid films or KCl discs (for solids). Routine proton magnetic resonance spectra were recorded on a Perkin-Elmer R32 (90 MHz) or a Bruker (250 MHz) using TMS as internal standard. Mass spectra were recorded on a Mass Spectrometry Services Ltd MS9 spectrometer. IR, NMR, MS data were in accordance with the structures given. Microanalytical results (C, H, N except where stated otherwise) were within ± 0.4% of theoretical values. Thin layer chromatography was run, unless otherwise specified, on Polygram Sil G/UV254 250 μm plates, with visualisation by exposure to iodine vapour.

*Ethyl 3-(tetrahydropapaverin-2'-yl)propionate **11***

(RS)-Tetrahydropapaverine (8.53 g, 0.025 mol) was heated at 70°C for 4 h with ethyl acrylate **9** (2.5 g, 0.025 mol) and glacial acetic acid (0.3 g, 0.005 mol). The reaction mixture was dissolved in toluene (70 ml), the solution stirred with silca gel (Merck column chromatography grade 70–230 mesh 0.6 g), filtered and evaporated to give a light brown viscous oil (10.7 g). The product was purified by column chromatography on silica gel 60 (Merck 70–230 mesh) eluting with ethyl acetate (600 ml). Evaporation gave **11** as a light brown viscous oil (9.9 g, 90%). R_f 0.82 in ethanol:ethyl acetate (1:1). IR ν 1735 cm^{-1} (ester CO). Hydrochloride, mp 176–179°C from methanol–ether (yield 78%). Anal $C_{25}H_{34}ClNO_6$ (C, H, N, Cl).

*{N,N'-4,11-Diaza-3,12-dioxotetradecylene-1,14-diyl-bis-(RS)-tetrahydropapaverine **9** (Y = NH, Z = $(CH_2)_4$)*

Ethyl 3-(tetrahydropapaverin-2-yl)propionate (8.8 g, 0.02 mol), hexamethylenediamine (1.13 g, 0.01 mol) and sodium hydride (60% dispersion in oil, 0.75 g) were stirred in dimethyl sulphoxide (20 ml) at room temperature for 24 h. Unreacted sodium hydride was decomposed by adding ice-cold water dropwise with stirring, and the mixture extracted with chloroform (300 ml, 150 ml). The chloroform extracts were centri-

fuged, washed with water, dried (anhydrous Na_2SO_4) and evaporated to yield a light viscous oil (8.96 g after vacuum drying at 60°C for 18 h). The product was purified by column chromatography on silica gel 60 (Merck 70–230 mesh) eluting with ethyl acetate (300 ml) followed by ethyl acetate:ethanol (4:1, 500 ml). The latter yielded **9** (Y = NH, Z = $(CH_2)_4$) as a lightly coloured viscous oil (6.44 g, 71.2%). R_f 0.35 in ethyl acetate:ethanol (1:1). IR ν 1650 cm^{-1} (amide CO). Dioxalate, mp 178–180°C from methanol (3.6 g, yield 33%). Anal $C_{56}H_{74}N_4O_{18}$, H_2O (C, H, N).

N,N'-Dimethylhexamethylene-1,6-diacrylamide 8 (Y = NMe, Z = $(CH_2)_4$)

Acryloyl chloride (18.1 g, 0.2 mol) in dry benzene (60 ml) was added to a stirred solution of *N,N'*-dimethyl-1,6-hexanediamine (14.3 g, 0.1 mol) in dry benzene (150 ml) containing triethylamine (20.24 g, 0.2 mol) and pyrogallol (0.1 g) at 45°C over a period of 30 min. After the addition was complete, triethylamine (10 ml) in dry benzene (80 ml) was added and stirring continued for a further 30 min. The reaction mixture was cooled and filtered to remove triethylamine hydrochloride. A trace of *p*-methoxyphenol was added, the solvent evaporated, and the oily residue distilled, bp 163–164°C/0.06 mm to yield **8** (Y = NMe, Z = $(CH_2)_4$) as a lightly coloured viscous oil (9.4 g, 36%). A second batch, purified by flash chromatography [17] in ethanol on Kieselgel 60 (Merck, 230–400 mesh ASTM) gave the product in 69% yield. R_f 0.69 in methanol. IR 2443 (CH_2) 2863 (N–CH_3) 1655 (amide CO), ν 1620 (-CH=CH_2) cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$) δ ppm; 1.50 (m, 8H, $(CH_2)_4$); 3.0 (d, 6H, N-CH_3); 3.32 (q, 4H, N-CH_2); 5.64 (m, 2H, CH=CH_2); 6.40 (m, 4H, CH=CH_2).

N,N-4,11-Dimethyl-4,11-diaza-3,12-dioxotetramethylene-1,14-diyl-bis-(RS)-tetrahydropapaverine 9 (Y = NMe, Z = $(CH_2)_4$)

(RS)-Tetrahydropapaverine (1.66 g, 4.8 mmol) and *N,N'*-dimethylhexamethylene-1,6-diacrylamide (0.58 g, 2.2 mmol) were heated with glacial acetic acid (0.16 g) at 70°C for 4 h. The reaction mixture was dissolved in toluene, solution stirred for 5 h with silica gel 60 (Merck, column chromatography grade, 70–230 mesh), filtered and evaporated to give a light brown viscous oil (2.18 g). The oil in dry acetone was treated with oxalic acid in dry acetone to yield the *(RS)*-dioxalate, mp 128–133°C from methanol (1.3 g, 53%). Anal $C_{58}H_{78}N_4O_{18}$, H_2O (C, H, N). The dioxalate (1.2 g) in water was basified with a saturated solution of sodium hydrogen carbonate, and the precipitated base extracted with dry ether (200 ml, 100 ml) to yield the *(RS)*-base **9** (Y = NMe, Z = $(CH_2)_4$) (1 g). *(S)* (+)-Base **9** (Y = NMe, Z = $(CH_2)_4$) was prepared from *(S)* (–)-tetrahydropapaverine. $[\alpha]_D^{20}$ + 50.2° (c, 0.95 in $CHCl_3$). *(S)* (+)-Base dioxalate **9** (Y = NMe, Z = $(CH_2)_4$), mp 119–122°C, $[\alpha]_D^{20}$ + 22.1° (c, 1.106 in water). Anal $C_{58}H_{78}N_4O_{18}$, H_2O (C, H, N). *(R)* (–)-Base **9** (Y = NMe, Z = $(CH_2)_4$) was prepared from *(R)* (+)-tetrahydropapaverine. $[\alpha]_D^{20}$ – 49.9° (c, 0.72 in $CHCl_3$). *(R)* (–)-Base dioxalate **9** (Y = NMe, Z = $(CH_2)_4$), mp 117–122°C, $[\alpha]_D^{20}$ – 22.0° (c, 1.036 in water). Anal $C_{58}H_{78}N_4O_{18}$, H_2O (C, H, N). The corresponding *N,N*-1,14-diyl-bis-piperidine **14a** (Y = NMe, *n* = 6), -bis-homopiperidine **14c** (Y = NMe, *n* = 6) and -bis-morpholine **14e** (Y = NMe, *n* = 6) diamido base dioxalates and bases were prepared similarly, and characterised as shown in tables VI and VII.

N,N'-Dimethyl-2,2,3,3,4,4-hexafluoro-1,5-pentamethylene diamine 20

Hexafluoroglutaryl chloride **18** (5 g, 0.018 mol) was added dropwise to stirred aqueous methylamine (0.24 g; 0.072 mol) over a period of 1 h at room temperature, and stirring continuously for a further 1 h. The reaction mixture was evaporated and the residue dissolved in hot ethanol (30 ml). Crystalline methylamine hydrochloride separated on cooling. Concentration of the filtrate yielded *N,N'*-dimethylhexafluoroglutarimide **17** (44 mg) as fine needles mp 142–143°C. IR ν 3325 (NH), 1700 (CO) cm^{-1}. ^1H NMR (90 MHz $CDCl_3$/DMSO-d_6) δ ppm; 8.7 (d, 6H, N-CH_3); 2.6 (q, 2H, N-H). The filtrate was evaporated to dryness, and the residue (4.2 g), consisting of a mixture of methylamine hydrochloride and the amide **19**, was extracted with boiling dry ether (500 ml) in a Soxhlet apparatus for 30 h onto lithium aluminium hydride (1.8 g, 3 M ratio). Excess hydride was decomposed by dropwise addition of water (15 ml). The suspension was filtered, the filtrate evaporated, and the residue distilled, bp 70–73°C/12 mm to yield **20** as a colourless oil (2.1 g, 49%). Anal $C_7H_{12}F_6N_2$ (C, H, N).

N,N'-Dimethyl-2,2,3,3,4,4-hexafluoropentamethylene-1,5-diacrylamide 8 (Y = NMe, Z = $(CF_2)_3$)

It was prepared from **20** (2.1 g) as for *N,N'*-dimethylhexamethylene-1,6-diacrylamide. The crude product (2.2 g) was purified by flash chromatography (column 18 x 3.5 cm) using silica gel 60 (110 g 230–400 mesh) and ethanol, to yield the diacrylamide **8** (Y = NMe, Z = $(CF_2)_3$) as a lightly coloured oil. R_f 0.70 in ethanol. IR ν 1655 (CO), 1630 (CH=CH_2) cm^{-1}.

Table VI. Characteristics of diaminodiamido (**14a, c** and **e**) and diaminodiester (**14g–k** and **16f**) dioxalates.

Dioxalate	*Yield (%)*	*mp (°C)*	*Tlc* (R_f)*	*Formula*	*Anal*	*IR*	*NMR*
14a	65	192–194	0.54	$C_{28}H_{50}N_4O_{10}$	CHN	+	+
14c	51	173	0.48	$C_{30}H_{54}N_4O_{10}$	CHN	+	+
14e	56	193–194	0.57	$C_{26}H_{46}N_4O_{10}$	CHN	+	+
14g	80	144–145	0.41	$C_{25}H_{42}N_2O_{12}$	CHN		+
14h	81	146–148	0.16	$C_{27}H_{46}N_2O_{12}$	CHN		+
14j	61	170–172	–	$C_{23}H_{38}N_2O_{14}$	CHN		+
16f	33	82–95	0.42	$C_{31}H_{50}N_2O_{16}, H_2O$	CHN		+

*Tlc in 0.5 M NaCl-CH_3CN (60:40) on Whatman $MKC_{18}F$.

Table VII. Characteristics of diaminodiamides (**14a**, **c** and **e**) and diaminodiesters (**14g–k** and **16a–k**).

Base	*Yield (%)*	*Tlc*[1] *(R_f)*	*IR*	*NMR*	*MS (m/e M^+)*
14a	63	0.60	+	+	+
14c	84	0.56	+	+	+
14e	99	0.61	+	+	+
14g	79		+	+	+
14h	75		+	+	+
14j	80	0.55	+	+	+
14k[2]	12		+	+	+
16a[2]	34	0.28	+	+	+
16b[2]	29	0.40	+	+	+
16c[2]	28	0.24	+	+	+
16d[2]	38	0.46	+	+	+
16e[2]	43	0.48	+	+	+
16f[3]	84		+	+	+
16g[3]	34		+	+	+
16h[4]	92		+		
16k[2]	10	0.43	+	+	

[1]Tlc in $CHCl_3$:EtOH (20:1); [2]Purified by flash chromatography in $CHCl_3$-MeOH (100:2) on Merck Kieselgel 60 (230–400 mesh ASTM); [3]Purified by column chromatography on MN neutral alumina in $CHCl_3$-EtOH (100:1 ranging to 100:6); [4]Crude product used without purification.

N,N'-4,10-Dimethyl-4,10-diaza-3,11-dioxo-6,6,7,7,8,8-hexafluorotridecylene-1,13-diyl-bis-(RS)-tetrahydropapaverine **9** *(Y = NMe, Z = $(CF_2)_3$)*

(RS)-Tetrahydropapaverine (2.47 g, 0.72 mol) and the diacrylamide **8** (Y = NMe, Z = $(CF_2)_3$) (1.25 g, 0.0036 mol) were heated with glacial acetic acid (0.25 g) at 70°C for 4 h. The reaction mixture in toluene was stirred for 5 h with silica gel 60 (Merck, column chromatography grade, 70–230 mesh), filtered and evaporated to give the base as an oil, purified *via* the base dioxalate, mp 174–176°C from methanol–ether (1.12 g, 30%). Anal $C_{57}H_{70}F_6N_4O_{18}$, H_2O (C, H, N, F).

N,N-4,10-Dioxa-3,11-dioxotridecylene-1,13-diyl-bis-piperidine ***14g*** *(Y = O, n = 5)*

Pentamethylene 1,5-diacrylate (4.78 g, 22.5 mmol), piperidine (4.7 ml, 47.5 mmol), distilled from calcium hydride, and glacial acetic acid (1 drop) were stirred together at 70°C for 16.5 h. The mixture was cooled, dissolved in sodium-dried toluene (10 ml), stirred with MN-Kieselgel 60 (70–230 mesh ASTM, 200 mg) for 17 h, filtered, and the filtrate concentrated *in vacuo* to yield a pale yellow oil. The product in dry acetone was treated with oxalic acid in dry acetone to yield the base dioxalate mp 144–145°C from anhydrous ethanol (10.19 g, 80%). Tlc in 0.5 M NaCl: CH_3CN (60:40) on Whatman $MKC_{18}F$ R_f 0.41. Anal $C_{25}H_{42}N_2O_{12}$ (C, H, N). ^{1}H NMR (90 MHz D_2O) δ ppm; 4.09 (4H, t, CH_2-O); 3.65–3.20 (8H, m, CH_2-N); 3.10–2.60 (8H, m, CH_2-N and CH_2-CO); 2.10–1.0 (18H, CH_2).

The dioxalate (2.0 g) in water was basified with a saturated solution of sodium hydrogen carbonate, and the precipitated base extracted with chloroform (3 x 15 ml) to yield the base as a pale amber oil (1.075 g, 79%). IR (liquid film) ν 1740 cm^{-1} (ester CO). ^{1}H NMR (90 MHz; D_2O) δ ppm; 4.07 (4H, t, CH_2-O); 2.80–2.20 (16H, m, CH_2-N and CH_2-CO); 1.80–1.20 (18H, m, CH_2). $C_{21}H_{38}N_2O_4$ requires M 382.2831. Found: *m/e* 382.2852 (M^+). The corresponding, *N,N*-1,13-diyl-bis-homopiperidine (**14h** Y = O, *n* = 5), -bis-morpholine (**14j** Y = O, *n* = 5) and -bis-2,6-dimethylpiperidine (**14k** Y = O, *n* = 5) diester base dioxalates and bases were prepared similarly, and characterised as shown in tables VI and VII.

N,N-4,10 dioxa-3,11-dioxotridecylene-1,13-diyl-bis(3-hydroxypiperidine) ***16*** *(R^1 = H, R^2 = OH)*

The compound was prepared as for **14g** (Y = O, *n* = 5) from 3-hydroxypiperidine (1.84 g, 18.2 mmol). The crude product was purified by column chromatography on MN neutral alumina (120 g) in $CHCl_3$-ethanol (100:1 ranging to 100:6) to yield the diol as a pale green oil (2.6 g, 72%). Tlc in $CHCl_3$-EtOH (20:1) on Merck aluminium oxide 60 F_{254} (neutral type E) R_f 0.62. IR (liquid film) ν 3700–3075 (OH); 1738 cm^{-1} (ester CO). ^{1}H NMR (90 MHz, $CDCl_3$) δ ppm; 4.08 (4H, t, CH_2-O); 3.60–3.95 (2H, broad, CH-O); 3.24 (2H, s, OH); 2.85–2.20 (16H, m, CH_2-N and CH_2-CO); 1.95–1.10 (14H, m, CH_2). $C_{21}H_{38}N_2O_6$ requires M 414.2730. Found: *m/e* 414.2732 (M^+).

The corresponding *N,N*-1,13-diyl-bis(3-ethoxycarbonylpiperidine) **16f** (R^1 = H, R^2 = COOEt), -bis(2-ethoxycarbonylpiperidine) **16g** (R^1 = COOEt, R^2 = H) and -bis(2-hydroxymethylpiperidine) **16h** (R^1 = CH_2OH, R^2 = H) diester bases were prepared similarly, and characterised as shown in table VII.

N,N-4,10-dioxa-3,11-dioxopentadecylene-1,13-diyl-bis(3-acetyloxypiperidine) ***16a*** *(R^1 = H, R^2 = $OCOCH_3$)*

Acetyl chloride (0.56 ml; 7.89 mmol) was added to a solution of *N,N*-4,10-dioxa-3,11-dioxo-1,13-diyl-bis(3'-hydroxypiperidine) (0.543 g; 1.315 mmol) in ethanol-free, dry chloroform (4 ml) and the mixture stirred first at room temperature for 16 h and then at 45°C for 24 h. The mixture was cooled, concentrated *in vacuo*, and the semisolid residue dissolved in water. The solution was extracted with ether (2 x 5 ml) to remove colour, basified with sodium hydrogen carbonate, and the precipitated base extracted with ether (4 x 10 ml). The solution was evaporated, and the product purified by flash chromatography in $CHCl_3$:MeOH (100:2) on Merck Kieselgel 60 (230–400 mesh ASTM) to yield the base **16a** as a pale green viscous oil (0.22 g, 34%). The corresponding *N,N*-1,13-diyl-bis(3-benzoyloxypiperidine) **16b**, -bis(3-[4'-chlorobenzoyl]piperidine) **16c**, -bis(3-veratroyloxypiperidine) **16d**, -bis(3-homoveratroyloxypiperidine), **16e** and -bis(2-homoveratroyloxymethylpiperidine **16k** (R = CH_2Oacyl) were prepared similarly and characterised as shown in table VII.

2-Oxotrimethylene 1,3-diacrylate ***8*** *(Y = O, Z = CO)*

2-Oxotrimethylene 1,3-diacrylate was prepared from acryloyl chloride (18.1 g; 0.2 mol) and 1,3-dihydroxyacetone (9.01 g; 0.1 mol) as described for 1,5-pentamethylene diacrylate [5]. Flash chromatography on silica gel 60 (mesh size 230–400; column 7.5 x 15 cm) eluting with ethanol-chloroform (20:80) gave the product (13.1 g; 66%), mp 51–52°C from petroleum ether (bp 40–60°C). R_f 0.56 in *n*-hexane:ethyl acetate (1:1). IR ν 1735 (ester CO); 1750 (CO); 1632 and 805 cm^{-1} (CH_2=CH–). ^{1}H NMR (90 MHz, $CDCl_3$) δ ppm; 4.9 (s, 4H, OCH_2COCH_2O); 5.9–6.6 (m, 6H, 2 x CH_2=CH). Anal $C_9H_{10}O_5$ (C, H).

N,N-4,8-Dioxa-3,6,9-trioxoundecylene-1,11-diyl-bis(RS-tetrahydropapaverine ***9*** *(Y = O, Z = CO)*
The compound was prepared from tetrahydropapaverine (2.22 g; 0.0065 mol) and 2-oxotrimethylene diacrylate (0.63 g, 0.0031 mol) by methods already described [5]. Chromatography on silica gel G (70–230 mesh) eluting with acetone (300 ml) followed by methanol 150 l) gave the product (1.66 g; 58%), mp 103–105°C. R_f 0.24 in methanol. Anal $C_{49}H_{60}N_2O_{13}$, H_2O (C, H, N). *N,N*-4,8-Dioxa-3,6,9-trioxoundecylene-1,11-diyl-bis(*RS*-5'-methoxytetrahydropapaverine), prepared similarly, was obtained as a viscous oil (yield 63.5%), R_f 0.31. Anal $C_{51}H_{66}N_2O_{15}$, H_2O (C, H, N).

1,2,12,13-Diepoxy-4,10-dioxa-3,11-dioxotridecane ***22*** *(n = 5)*
The method of Emmons and Pergano [17] was followed. Trifluoroacetic anhydride (55 ml; 0.39 mol) was added dropwise over 30 min to a stirred suspension of hydrogen peroxide (85% w/w; 8.2 ml; 0.324 mol) in dichloromethane (70 ml) at 0°C. After stirring for a further 30 min, the mixture was dried (Na_2SO_4) and added dropwise over 40 min to a stirred slurry of Na_2HPO_4 (149.2 g; 1.04 mol) and pentamethylene diacrylate **21** (10.18 g; 0.048 mol) in dichloromethane (250 ml) at 42°C. The mixture was heated at 42°C for 3 h, cooled, and diluted with water (40 ml) to dissolve the inorganic salts. The organic layer was separated, washed with 10% aqueous sodium hydrogen carbonate (150 ml x 2), brine (200 ml x 3) and dried (Na_2SO_4). Evaporation of the solvent *in vacuo* gave a yellow oil (13.13 g) which was purified by flash chromatography in ethyl acetate:hexane (1:2) on silica gel 60 (Merck 230–400 mesh; column 8 x 6 cm). Elution gave, in order, unchanged diacrylate (1.15 g), monoepoxide (3.02 g) and the diepoxide **22** *n* = 5 (6.42 g; 55%). IR (liquid film) ν 1750 (ester CO); 1410 (CH_2); 1200 (epoxide); 1030 (cyclic CH_2); 750 (CH_2) cm^{-1}. ^1H NMR (90 MHz $CDCl_3$) δ ppm 1.3–1.9 (6H, m, CH_2); 3.0 (4H, d, CH_2-O); 3.45 (2H, t, CH-O); 4.2 (4H, t, CO_2CH_2). 1,2,13,14-Diepoxy-4,11-dioxa-3,12-dioxotetradecane **22** (*n* = 6) and 1,2,14,15-diepoxy-4,12-dioxa-3,13-dioxopentadecane **22** (*n* = 7) were prepared similarly.

N,N-(2RS,12RS)-2,12-Dihydroxy-4,10-dioxa-3,11-dioxotridecylene-1,13-diyl-bis(RS)-tetrahydropapaverine ***23a*** *(R^1 = R^2 = H, n = 5)*
The method of Conda *et al* [18] was followed. *(RS)*-Tetrahydropapaverine (4.97 g; 14.48 mmol) and the diepoxide **22** (1.57 g; 6.42 mmol) were heated in isopropanol (70 ml) at 50°C for 48 h. The solution was concentrated *in vacuo* to give a gummy solid. Flash chromatography on silica gel (Merck 7734) with acetone-toluene gave an oil (5.3 g; 81%). Concentration of a solution in acetone-ether gave the diol as a fluffy yellow solid. Flash chromatography in acetone-toluene (1:2 changing to 1:4) on silica gel 60 (Merck 7734 230–400 mesh; column 22 x 5 cm) gave the *RS,RS*-diol **23a** (R^1 = R^2 = H, *n* = 5).

The related bis(*RS*-tetrahydropapaverinyl)-*(RS,RS)*-diols **23b–d**, bis(*R*-tetrahydropapaverinyl)-*(RS,RS)*-diols **23e** and **f** and bis(*RS*-piperidinyl-*(RS,RS)*-diols **25a** and **b** (R^4 = H) were prepared similarly and characterised as shown in table VIII.

N,N-(2RS,12RS)-2,12-Diacetoyl-4,10-dioxa-3,11-dioxotridecylene-1,13-diyl-bis-(RS)-tetrahydropapaverine ***23g*** *(R^1 = H, R^2 = acetyl, n = 5)*
The diol **23a** (1.058 g; 1.14 mmol) was heated in ethanol-free chloroform with acetyl chloride (1.62 ml; 2.28 mmol) at 50°C for 17 h, and the product solution evaporated *in vacuo*. The residue was dissolved in chloroform (30 ml), the solution washed with saturated aqueous sodium hydrogen carbonate solution (25 ml x 2), water (30 ml x 2), dried ($MgSO_4$), and evaporated. The crude product was purified by flash chromatography in acetone-toluene (1:4) on silica gel 60 (Merck 9385 230–400 mesh) to yield the diacetate as a yellow oil (468 mg; 67%), characterised as shown in table IX.

The related bis(*RS*-tetrahydropapaverinyl)-*(RS,RS)*-diacoyl-diols **23h–q** (*n* = 5), **23u–w** (*n* = 6), **23aa** and **23bb** (*n* = 7), bis(*R*-tetrahydropapaverinyl)-*(RS,RS)*-diacyldiols **23r–t** (*n* = 5) and **23x–z** (*n* = 6) and bis(*RS*-piperidyl)-*(RS,RS)*-diacyldiols **25a–e** were prepared similarly and characterised as shown in table IX.

Ethyl (2RS)-2-hydroxy-3-N-(R-tetrahydropapaverinyl)propionate ***7*** *(R = $CH_2CH(OH)COOEt$)*
Ethyl glycidate (272 mg; 2.34 mmol) [20] and (R)–(+)–tetrahydropapaverine (692 mg; 2 mmol) were heated in isopropanol (20 ml) at 60°C for 18 h. The solution was evaporated *in vacuo* to yield **7** as a clear yellow oil (872 mg; 95%). IR (film) ν 3500 (s) (OH); 1750–1720 (ester CO); 1605, 1590 (aromatic C-C) cm^{-1}. NMR (250 MHz; $CDCl_3$) δ ppm 2.2 (3H, 2t, CH_3); 2.5–3.5 (10H, m, 4$ArCH_2$, 5NCH, OH); 3.7 (3H, CH_3O); 3.8 (9H, s, CH_3O); 4.0 (1H, q, CH(OH)COOEt); 4.2 (2H, q, OCH_1); 6.1 and 6.3 (1H, 2s, Ar–(8)H); 6.6–6.8 (4H, m, ArH).

Table VIII. Characteristics of bis(*RS*-tetrahydropapaverinyl)-*(RS,RS)*-diols **23a–d**, bis(*R*-tetrahydropapaverinyl)-(*RS, RS*)-diols **23e** and **f** and bis(*RS*-piperidinyl)-*(RS, RS)*-diols **25a** and **b**.

Cpd	*R'*	*R²*	*R³*	*n*	*Yield (%)*	*mp (°C)*	*Tlc (R_f)*	*$[\alpha]_D^{20}$ (conc)[1]*	*Formula*	*Anal*	*IR*	*NMR*
23a	H	H	–	5	80	47–48			$C_{51}H_{66}N_2O_{14}$	CHN	+	+
23b	H	H	–	6	50	49–55	0.43[2]		$C_{52}H_{68}N_2O_{14}$	CHN	+	+
23c	MeO	H	–	6	62	46–53	0.18[2]		$C_{54}H_{72}N_2O_{16}$	CHN	+	+
23d	MeO	H	–	7	90	52–54			$C_{55}H_{74}N_2O_{16}$	CHN	+	+
23e	H	H	–	5	66	49–50.5	0.35[2]	– 69.6° (1.04)	$C_{51}H_{66}N_2O_{14}$	CHN		+
23f	MeO	H	–	6	61	48–49.5	0.38[3]	– 66.9° (0.97)			+	+
25a	Me	Me	H			84–96	0.32[3]		$C_{25}H_{46}N_2O_6$	CHN		+
25b	H	H	COOEt		90	oil					+	+

[1]Chloroform; [2]Tlc in acetone-toluene 1:2; [3]Tlc in $CHCl_3$-MeOH 9:1.

Table IX. Characteristics of bis(*RS*-tetrahydropapaverinyl)-*(RS, RS)*-diacoyldiols **23g–q** ($n = 5$), **23u–w** ($n = 6$), **23aa** and **23bb** ($n = 7$), bis(*R*-tetrahydropapaverinyl)-*(RS, RS)*-diacoyldiols **23r–t** ($n = 5$) and **23x–z** ($n = 6$) and bis(*RS*-piperidyl)-*(RS, RS)*-diacoyldiols **25a–e**.

Cpd	*R'*	*R^2*	*Yield (%)*	*mp (°C)*	*Formula*	*Anal*	*IR*	*NMR*
23g	H	Acetyl	67	oil	$C_{55}H_{70}N_2O_{16}$	CHN		
23h	H	Formyl	92		*		+	
23j	H	Benzoyl	42		*		+	
23k	H	4-Chlorobenzoyl	93		*			
23l	H	Homoveratroyl	80	74–78	*		+	
23m	H	2,6-Dichlorobenzoyl	52	58–61	$C_{65}H_{70}N_2O_{16}Cl_4$	Cl	+	+
23n	H	2,4-Dichlorobenzoyl	72	55–58	$C_{65}H_{70}N_2O_{16}Cl_4$	CHNCl	+	+
23o	H	3,5-Dichlorobenzoyl	76	64–66	$C_{65}H_{70}N_2O_{16}Cl_4$	CHN	+	+
23p	H	Trifluoromethylbenzoyl	71	59–62	$C_{67}H_{72}N_2O_{16}F_6$	CHN	+	+
23q	H	3,4,5-Trimethoxyphenylacetoyl	70		$C_{73}H_{90}N_2O_{22}$	CHN		
23r	H	Formyl	44		*			
23s	H	Acetyl	74	46–47	*			
23t	H	Cyclopropancarbonoyl	62		*		+	+
23u	MeO	Formyl			*			
23v	H	Acetyl	54	[1]Tlc R_f 0.41	*		+	+
23w	MeO	Acetyl	50	[2]Tlc R_f 0.22	*			
23x	H	Formyl	93		*			
23y	H	Acetyl	79		*			
23z	H	Ethoxycarbonyl	97		*		+	+
23aa	H	Formyl	95		*		+	
23bb	H	Acetyl	73		*		+	+

	R'	*R^2*	*R^3*	*R^4*				
25a	Me	Me	H	Acetyl		[3]Tlc R_f 0.29*	+	
25b	Me	Me	H	Benzoyl		[4]Tlc R_f 0.37*	+	
25c	H	H	COOEt	Acetyl	31		+	+
25d	H	H	COOEt	Benzoyl	65		+	+
25e	H	H	COOEt	Veratroyl	51		+	+

*Used without further characterisation; [1]Tlc in acetone-toluene 1:4; [2]Tlc in acetone-toluene 1:5; [3]Tlc in acetone-toluene 1:19; [4]Tlc in acetone-toluene 3:17.

*N,N-(2RS,13RS)-2,13-Di(ethoxycarbonoyl)-3,12-dioxa-4,11-dioxotetradecylene-1,14-diyl-bis(R-tetrahydropapaverine) **33***

Suberoyl chloride (0.13 ml; 0.72 mmol) in benzene (6 ml) was added slowly over 10 min to a cooled (ice/salt) solution of the 2-hydroxyamine **7** (694 mg; 1.5 mmol) and trimethylamine (0.21 ml; 1.5 mmol) in benzene (12 ml), and the mixture refluxed for 1.5 h. The cooled solution was filtered, and concentrated *in vacuo*. The oily product was purified by chromatography on silica gel (Merck 7734) to give **33** as a yellow fluffy solid (248 mg; 33%). IR ν 1755–1730 (ester CO); 1605, 1590 (aromatic C-C); 730, 695 cm^{-1}. NMR (250 MHz; $CDCl_3$) δ ppm 1.2 (6H, t, CH_3); 1.35 (4H, bs, CH_2; 1.65 (4H, bs, CH_2; 2.3–2.6 (6H, m, 2 x CH_2CO, x 2 NCHAr); 2.7–3.4 (16H, m, 2 x $CH_2NCH_2CH_2$, 2 x $ArCH_2$); 3.6 (6H, s, 2 x OCH_3); 3.85 (18H, m, 6 x OCH_3); 4.2 (4H, q, 2 x OCH_2); 5.2 (2H, dd, 2 x EtOOC-CH-O); 6.05 (2H, 2s, 2 x Ar-(8)H); 6.6–6.8 (8H, m, ArH).

*(2S)-2-bromo-3-hydroxypropionic acid **28a***

Sodium nitrite (9.8 g; 0.14 mol) was added portionwise at 15-min intervals over 2 h to a cooled solution (ice/salt) of *(S)*-serine (9.3 g; 0.088 mol) in 6 M hydrobromic acid (100 ml). The mixture was allowed to warm to ambient temperature overnight (14 h), and then extracted with ether (2 x 150 ml). The combined extracts were washed with brine (2 x 200 ml), dried (Na_2SO_4) and evaporated to give **28a** as a pale green oil (10 g; 67%), which was used without further purfication. *(2R)*-2-bromo-3-hydroxypropionic acid **28b** was prepared similarly from *(R)*-serine (yield 58%).

*Potassium (2R)-2,3-epoxypropionate **29a***

Potassium hydroxide (6.24 g; 0.11 mol) in dry methanol (30 ml) was added dropwise over 1.5 h to a cooled (ice/salt) rapidly stirred solution of *(2S)*-2-bromo-3-hydroxypropionic acid **28a** (9.0 g; 0.055 mol) in dry methanol (20 ml). The sol-

ution was stirred at 5°C for 15 h, and filtered to remove precipitated potassium bromide. The methanolic solution was added dropwise with stirring to anhydrous ether to precipitate the potassium salt **29a** as a white amorphous solid (4.93 g; 70%), mp 138.5–139°C (from absolute ethanol). $[\alpha]_D^{20}$ + 31.8° (c, 1.05, H_2O). NMR (250 MHz; D_2O) δ ppm 2.77 (1H, dd, CHO); 2.94 (1H, dd, CHO); 3.36 (1H, dd, OCH-COOK). Potassium *(2S)*-2,3-epoxypropionate **29b** was prepared similarly (yield 80%), mp 135.5–137°C, $[\alpha]_D^{20}$ – 27.1° (c, 0.94, H_2O).

(2R,13R)-1,2,13,14-Diepoxy-4,11-dioxa-3,12-dioxotetradecylene ***30a***
Potassium *(2R)*-2,3-epoxypropionate (1.48 g; 11.7 mmol) and 18-crown-6 (167 mg; 0.63 mmol) were stirred in acetonitrile (40 ml) for 1 h at room temperature. 1,6-Diiodohexane (0.87 ml; 5.1 mmol) was added and the mixture heated under reflux for 5 days. The solution was evaporated, the residue purified by chromatography on silica gel (Merck 7734) eluting with ethyl acetate-hexane (1:5 changing to 1:2) to yield **30a** as a colourless oil (190 mg; 5.8%). Yield when prepared using hexamethylene dimesylate 57%. Tlc in ethyl acetate-hexane (1:1) R_f 0.30. $[\alpha]_D^{20}$ + 25.6° (c, 1.04, $CHCl_3$). IR (film) ν 1730 (ester CO); 1200 (epoxide); 1030 (cyclic OH); 750 (epoxide) cm^{-1}. *(2S, 13S)*-1,2,13,14-Diepoxy-4,11-dioxa-3,12-dioxotetradecylene) **30b** was prepared similarly (yield 10%). Yield when prepared using hexamethylene dimesylate 31%. Tlc in ethyl acetate-hexane (1:1) R_f 0.33. $[\alpha]_D^{20}$ – 19.2° (c, 0.05, $CHCl_3$). IR (film) ν 1740 (ester CO); 1200 (epoxide); 1025 (cyclic CH); 750 (epoxide) cm^{-1}. NMR (90 MHz; $CDCl_3$) δ ppm 1.2–1.8 (8H, m, CH_2); 2.9 (4H, d, CH_2O); 3.4 (2H, t, CHO); 4.2 (4H, t, $COOCH_2$).

N,N-(2R,13R)-2,13-Dihydroxy-4,11-dioxa-3,12-dioxotetradecylene-diyl-bis(R)-tetrahydropapaverine ***31a*** *(R = H)*
R(+)-Tetrahydropapaverine (531 mg; 1.55 mmol) and the diepoxide **30a** (147 mg; 0.57 mmol) were heated in isopropanol (40 ml) at 60°C for 18 h. The cooled solution was evaporated, and the resulting oil chromatographed, and the resulting oil chromatographed on silica gel (Merck 7734) eluting with acetone-toluene (1:5 changing to 1:2) to yield **31a** as a fluffy white solid (321 mg; 60%), mp 50°C, $[\alpha]_D^{20}$ – 76.5° (c, 0.945, $CHCl_3$), which was used without further purification. *N,N-(2S,13S)*-2,13-Dihydroxy-4,11-dioxa-3,12-dioxo-tetradecylene-1,14-diyl-bis(R)-tetrahydropapaverine **31b** (R = H) was prepared similarly (yield 70%), mp 49°C, $[\alpha]_D^{20}$ – 58.0°.

N,N-(2R,13R)-2,13-Diformyloxy-4,11-dioxa-3,12-dioxotetradecylene-1,14-diyl-bis(R)-tetrahydropapaverine ***31a*** *(R = formyl)*
Acetic anhydride (0.14 ml; 1.47 mmol) was added to a cooled (– 45°C) solution of the diol **31a** R = H (224 mg; 0.24 mmol), formic acid (33 l; 0.87 mmol), triethylamine (0.16 ml; 1.17 mmol), and *N,N*-dimethylaminopyridine (18 mg; 0.15 mmol) in dichloromethane (8 ml). The solution was stirred at – 45°C for 1 h and then at room temperature for 1.5 h. The solution was diluted with dichloromethane (12 ml), washed with 2 M HCl (20 ml), saturated aqueous sodium hydrogen carbonate solution (20 ml), water (3 x 25 ml) and dried (Na_2SO_4). Evaporation of the solvent yielded **31a** (R = formyl) as a tacky solid (240 mg; 100%), Tlc in acetone-toluene (1:2) R_f 0.41, which was dried *in vacuo* and used without further purification. N,N-*(2S,13S)*-2,13-Diformyloxy-4,11-dioxa-3,12-dioxotetradecylene-1,14-diyl-bis*(R)*-tetrahydropapaverine **31b** (R = formyl) was prepared similarly (yield 90%), Tlc in acetone-toluene R_f 0.38.

Quaternary salts
(a) Tertiary bases were quaternised with either methyl iodide or methyl benzenesulphonate by methods previously described [5]. (b) Dihydrogen tartrates were prepared by adding silver dihydrogen tartrate (1 mol equivalent) to a solution of the quaternary ammonium iodide in methanol and stirring the slurry in the dark for 3 h. Filtration, evaporation of the solvent, and trituration of the residue with anhydrous ether gave the dihydrogen tartrate. Yields, physical constants, and pharmacological properties are shown in tables I–V.

Pharmacology

Mongrel cats weighing 2.0–5.0 kg were anaesthetised with a mixture of pentobarbitone sodium (7 mg/kg ip) and α-chloralose (80 mg/kg ip). Adequate levels of anaesthesia were maintained with supplemental doses of α-chloralose administered intravenously as needed. The trachea was cannulated and the animals were ventilated with room air (20 ml/kg) *via* a Harvard Apparatus respiration pump adjusted to deliver 20 strokes/min. Arterial blood pressure was measured *via* a cannula to the right femoral artery connected to a Stathum P23 transducer. Heart rate was determined from the ECG. The right vagus was exposed, crushed approximately 2 cm distal to the nodose ganglia, and placed on a shielded bipolar platinum electrode. The vagus nerve was stimulated for 10 s every 5 min with a Grass S88 stimulator using the following parameters: 20 Hz, 0.5 ms duration, and supramaximal voltage (10–15 V).

The left hind limb was rigidly secured and the tibialis tendon was isolated and attached to a Grass FT 03 force displacement transducer. After sectioning the sciatic nerve trunk, the peroneal nerve was placed on a shielded bipolar platinum electrode. Stimuli of 0.2 ms duration and at a supramaximal voltage were applied to the nerve at the rate of 0.15 Hz using a Grass S88 stimulator. Twitch tension in the anterior tibialis was recorded during a resting tension of 50 g. Core temperature was maintained between 37 and 38°C with radiant heat. All recordings were made on a Grass Model 7 polygraph. At the end of the experiments cats were killed with intravenously administered saturated KCl or pentobarbital sodium.

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