Approaches to Short-Acting Neuromuscular Blocking Agents: Nonsymmetrical Bis-tetrahydroisoquinolinium Mono- and Diesters

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Nonsymmetrical bisquaternary mono- and diesters combining the potency-enhancing properties of the (1*R*)-laudanosinium group with a second unhindered quaternary ammonium moiety have been studied as a means of promoting short action with high-potency neuromuscular block. Atracurium-related nonsymmetrical diesters showed high potency, freedom from vagal blockade at neuromuscular blocking doses, and short action. Nonsymmetrical monoesters were short acting but showed varying degrees of vagal block.

Introduction

Studies of the effects of structural, electronic, and steric factors on the duration and potency of short-acting neuromuscular blocking agents[1−4] have shown that a relatively short duration of action can be achieved in such compounds as the symmetrical bisquaternary ester **1** but at the expense of inadequate potency and an undesirable level of vagal blockade.

In the present study, the nonsymmetrical bisquaternary diesters **2** embody the advantages of the (1*R*)-laudanosinium function with respect to potency and freedom from vagal block.[1] However, the 1-(3,4-dimethoxybenzyl) group hinders attack at adjacent β-CH and β-ester functions and could thereby increase the duration of neuromuscular blockade. The nonsymmetrical bisquaternary monoesters **3** and **4** attempt to overcome this disadvantage. In these, the (1*R*)-laudanosinium unit is distanced from a single ester function and linked through it to either an unhindered 1,2,3,4-tetrahydroisoquinolinium function (**3**), typical of compound **1**, or a rigid 6-*O*-methylcodeinium group (**4**).

Accordingly, the countereffect on Hofmann elimination and hydrolysis (and hence duration) of the potency-enhancing 1-(3,4-dimethoxybenzyl) group should be removed. However, the single β-quaternary ester function retains the potential for facile Hofmann elimination and unhindered rapid ester hydrolysis *in vivo*. The bis-(1*R*)-laudanosinium monoester **5** provides a direct comparison with (1*R*,1′*R*)-atracurium (**6a**).[5]

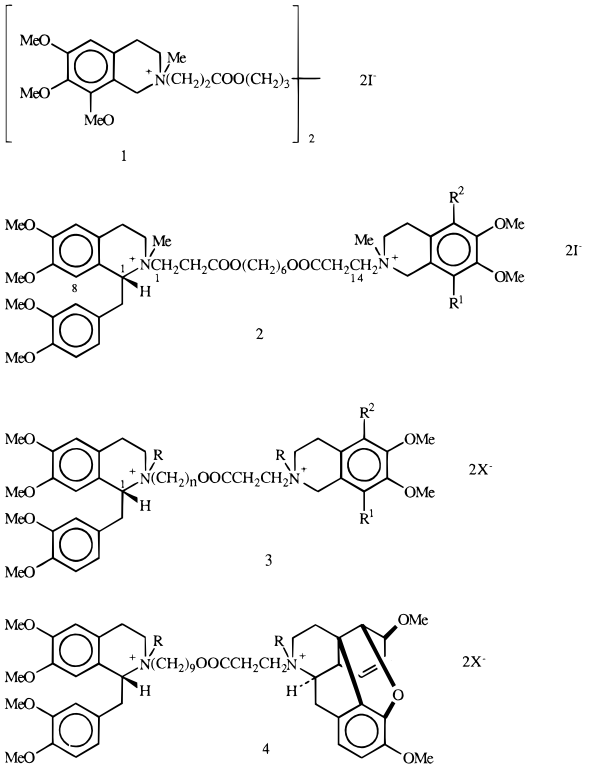
The nonsymmetrical bisquaternary nonsymmetrical diester **7** combines the potency-enhancing laudanosinium group in a mivacurium-type[6] acylcholine ester function (structurally favorable to butyrylcholinesterase hydrolysis),[7] with a second unhindered β-quaternary ester intrinsically capable of both facile Hofmann elimination and rapid hydrolysis.

Chemistry

The nonsymmetrical diesters **2a**,**b** (Scheme 1, Table 1) were prepared by condensing **8**, obtained in the same manner as its 1*S* homologue,[5] with **9a** or **9b** to give the nonsymmetrical ditertiary bases **10** and **11**, respectively, followed by quaternization. The monoesters **3a**−**e** (Scheme 2, Table 1) were obtained from (1*R*)-tetrahydropapaverine (**12**) (or its racemate **13**) via the amino alcohols **14**−**16**, the acrylate esters **17**−**19**, and the nonsymmetrical diamino esters **20**−**23**. 6-*O*-Methylnorcodeine (**24**) was prepared from 6-*O*-methylcodeine[8] via 6-*O*-methylnorcodeine *N*-phenylcarbamate. Reaction of the latter with hydrazine hydrate, as described for the *N*-demethylation of codeine,[9] yielded **24**. Addition of **24** to **17** produced the diamino ester **25** (Scheme 3). Similar addition of **12** to **17** gave **26** (Scheme 4).

The amino alcohol **28**, which was obtained by reduction of ethyl 4-*N*-[(1*R*)-tetrahydropapaverin-2-yl]succinamide (**27**), was esterified with 5-bromovaleryl chloride to form the bromo ester **29**. Condensation of **29** with potassium acrylate in HMPA in the presence of 18-

Chart 1



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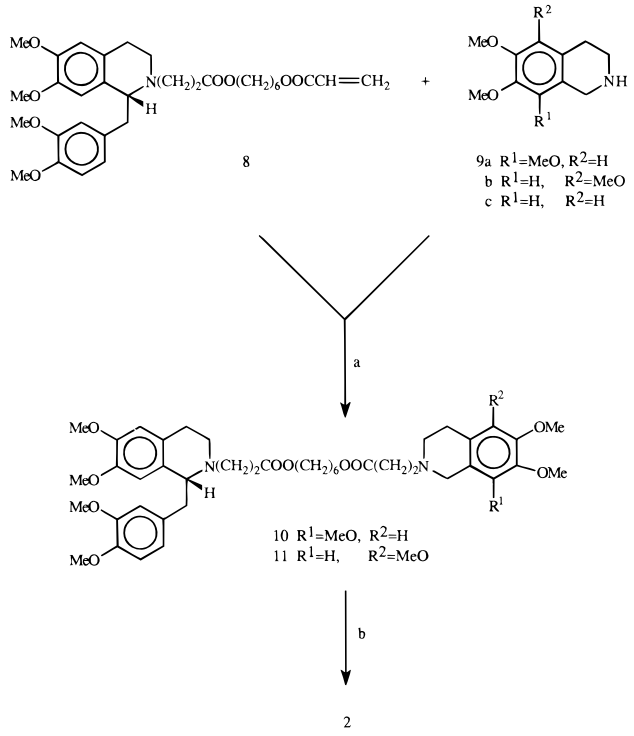
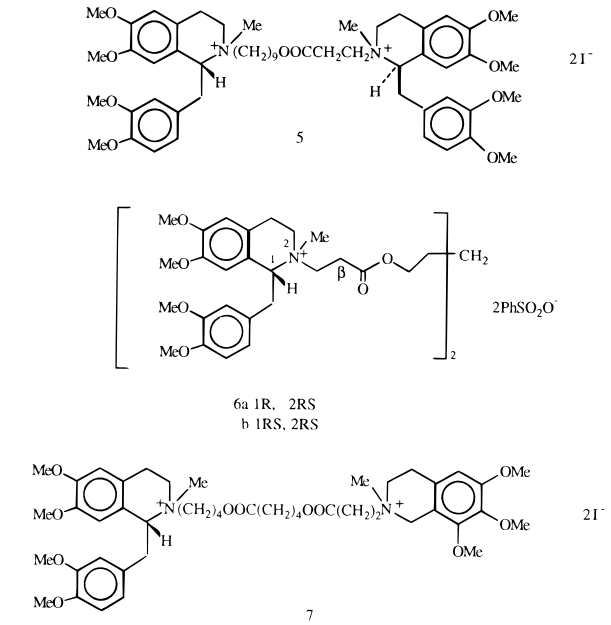
Scheme 1[a]



[a] Reagents: (a) AcOH, C_6H_6; (b) MeI, CH_3CN.

Chart 2



crown-6 produced the unsaturated diester **30**, which on treatment with **9a** yielded **31**. Quaternization of **31** with methyl iodide gave **7** (Scheme 5). The comparator symmetrical bisquaternary diester **1** was prepared as shown in Scheme 6. The nonsymmetrical bisquaternary esters **2**, **3b**−**d**, **4**, **5**, and **7** are mixtures of quaternary ammonium stereoisomers generated in the final *N*-alkylation step. The proportions of (1*R*,2*R*)-*cis*- and (1*R*,2*S*)-*trans*-papaverinium isomers were determined by both NMR and HPLC.

Pharmacological Results

Neuromuscular blocking potencies, duration, spontaneous reversibility, reversibility with neostigmine, and vagal block of compounds **1**−**5** and **7** relative to atracurium (**6b**) in anesthetized cats are given in Table 1.

The actions of the nonsymmetrical bisquaternary diesters **2a** (R^1 = H, R^2 = MeO) and **2b** (R^1 = MeO, R^2 = H) are spontaneously reversible. They are also readily reversed by anticholinesterases. However, in contrast to the corresponding symmetrical diester **1**, they are more potent and free from vagal block at neuromuscular blocking doses.

All four methoquaternary monoesters **3a**−**d** were less potent neuromuscular blocking agents than the corresponding diesters **2**. Their actions were also spontaneously reversible and readily reversed by neostigmine, but unlike the diesters, they showed vagal block at neuromuscular blocking doses. Their durations of action appeared to be shorter than those of atracurium (**6b**) and **5**.

The potency of the bis-methoquaternary monoester **4a** was similar to those of **3a**−**d**, but that of the bisallyl compound **4b** was substantially lower. The action of **4a** was spontaneously reversible and reversed by neostigmine, but it showed vagal block at neuromuscular blocking doses. The potency of **5** was comparable to those of **2a**,**b** and atracurium. The pharmacological profile of the nonsymmetrical bisquaternary nonsymmetrical diester **7** was similar to those of compounds **3a**−**d**, but it exhibited greater vagal block at neuromuscular blocking doses.

Discussion

The atracurium analogue **5** is potent, is free from vagal block, and, not unexpectedly, has a similar duration of action to that of atracurium. However, the objective of attaining high potency and freedom from vagal block at neuromuscular blocking doses with shorter duration of action was met only in compounds **2a**,**b**. Although the differences are not capable of statistical validation, compounds **3a**−**e**, **4a**, and **7** appeared to be less potent.

The differences between **2a**,**b** and the remaining monoester compounds **3a**−**d**, **4a**, and **7** may well be a consequence of their stereochemical composition. All are mixtures of stereoisomers with either (1*R*,2*R*)- or (1*R*,2*S*)-laudanosinium (*cis* or *trans*) configurations in which the *cis*-isomers predominate (Table 1). This preponderance of *cis*-isomers favors high potency in compounds **2a**,**b** with atracurium-related β-ester configurations.[5,10] In contrast, the respective 9-, 11-, and 4-acyloxy functions of compounds **3**, **4**, and **7** are akin to the 3-acyloxy function of mivacurium, in which the 1*R*,2*R*-isomers (*cis*) are some 10 times less potent than the 1*R*,2*S*-isomers (*trans*).

The durations of action of compounds **1**, **3**, and **7** are all similar (*ca.* 8 min) and shorter than that of atracurium. This supports the hypothesis that absence of steric effects due to bulky C-1 substituents in the tetrahydroisoquinoline nucleus favors faster metabolic degradation and hence shorter duration. Restraint of the C-1 substituent in the methoquaternary (**4a**) seems to be ineffective.

Experimental Section

Melting points were recorded on either a Kofler Heizbank or Gallenkamp melting point apparatus and are uncorrected. IR spectra were obtained on either a Perkin-Elmer 710B or Perkin-Elmer 781 spectrometer using liquid film or KBr disks

Table 1. Neuromuscular Blocking Properties and Vagal Effects of Compounds **1**−**5** and **6** in Chloralose Anesthetized Cats

compd	*N*-alkyl	R^1	R^2	*n*	anion	configuration	1,2-*cis*/*trans* ratio	yield (%)	mp (°C)	$[\alpha]^{20}_D$ (in $CHCl_3$, deg)	formula	anal.	neuromuscular ED_{95} (mg/kg [mmol/kg × 10^4])	blockade duration (min)[a]	complete spontaneous reversal	neostigmine reversal[b]	vagal response[c]
1[d]	Me				I	2*RS*,2′*RS*							0.3−0.5 [3.3−5.6] (3)[e]	8	+	+	++
2a	Me	H	MeO		I	1*R*,2*RS*,2′*RS*	1.99/1	86	108−110	−34.7 (*c* 1.04)	$C_{46}H_{66}N_2O_{11}I_2 \cdot {}^1/_2H_2O$	C,H,N	0.12−0.20 [1.1−1.8] (3)	8−12	+	+	0
2b	Me	MeOH	H		I	1*R*,2*RS*,2′*RS*	2.36/1	89	109−113	−37.4 (*c* 0.93)	$C_{46}H_{66}N_2O_{11}I_2 \cdot {}^1/_2H_2O$	C,H,N	0.12−0.15 [1.1−1.4] (3)	8−12	+	+	0
3a	Me	H	H	11	I	1*RS*,2*RS*,2′*RS*	3.47/1	72	135		$C_{47}H_{70}N_2O_8I_2 \cdot H_2O$	C,H,N	0.3 [2.8] (2)	7−8	+	+	++
3b	Me	MeO	H	11	I	1*R*,2*RS*,2′*RS*	3.46/1	55	100 dec	−43.0 (*c* 0.62)	$C_{48}H_{72}N_2O_9I_2 \cdot 2H_2O$	C,H,N	0.3−0.4 [2.7−3.6] (2)	8	+	+	++
3c	Me	H	MeO	11	I	1*R*,2*RS*,2′*RS*	3.24/1	95	95 dec	−35.0 (*c* 0.60)	$C_{48}H_{72}N_2O_9I_2$	C,H,N	0.5−0.7 [4.6−6.5] (2)	8−9	+	+	++
3d	Me	H	MeO	9	I	1*R*,2*RS*,2′*RS*	2.9/1	95	110−113	−34.3 (*c* 1.12)	$C_{46}H_{68}N_2O_9I_2 \cdot {}^1/_2H_2O$	C,H;N[f]	0.26 [2.5] (2)	10	+	+	++
3e	allyl	H	MeO	9	Br	1*R*,2*RS*,2′*RS*	NR[i]	98	111−114	−33.5 (*c* 0.30)	$C_{50}H_{72}N_2O_9Br_2 \cdot H_2O$	C,H,N	0.7−0.8 [6.8−7.8] (2)	7−8	+	+	++++
4a	Me			9	I	1*R*,2*RS*,17*R*	3.42/1	57	134	−65.4 (*c* 0.62)	$C_{52}H_{72}N_2O_9I_2 \cdot 2H_2O$	H,N;C[g]	0.3−0.4 [2.6−3.5] (2)	12−13	+	+	+++
4b	allyl			9	Br	1*R*,2*RS*,17*R*	NR	26	97	−79.6 (*c* 0.58)	$C_{56}H_{76}N_2O_9Br_2$	C,H,N	4.0−7.0 [37.0−64.7] (2)	3	+	+	++++
5	Me			9	I	1*R*,2*RS*,1′*R*,2′*RS*	1.53/1	88	129 dec	−26.0 (*c* 0.21)	$C_{54}H_{76}N_2O_{10}I_2 \cdot {}^1/_2H_2O$	C,N;H[h]	0.1 [0.9] (2)	15	+	NR	0
7	Me				I	1*R*,2*RS*,2′*RS*	3.15/1	80	101 dec	−34.6 (*c* 0.21)	$C_{46}H_{66}N_2O_{11}I_2$	C,H,N	0.5 [4.6] (3)	8	+	+	+++
6b (atracurium)													0.16 [1.3]	14.6 (onset 4.3)			0

[a] Time from injection to 95% control. [b] Dose of 0.55 mg/kg. [c] ++++ = 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. [d] Dhar et al.[4] [e] Number of animals. [f] N: calcd, 2.65; found, 2.18. [g] C: calcd, 53.89; found, 53.41. [h] H: calcd, 6.59; found, 7.11. [i] NR = not recorded.

for solid samples. ^{1}H-NMR spectra were recorded on either a Perkin-Elmer R32 or Bruker WM 250 (250 MHz) spectrometer and ^{13}C-NMR on a Bruker WM250 (250 MHz) spectrometer in $CDCl_3$, unless otherwise indicated, using either TMS or the center of the $CDCl_3$ peak as reference standard. IR, ^{1}H-NMR, and ^{13}C-NMR spectra were in accord with the structures given. Optical rotations were measured in $CHCl_3$ on a Perkin-Elmer 241 polarimeter. Elemental analytical results are within ±0.4% of the calculated values, except where indicated.

Column chromatography was carried out on silica gel 60 (Merck; 70−230 mesh) and flash chromatography on silica gel 60 (Merck; 230−400 mesh). TLC was performed on Polygram Sil G/UV254 250 μm plates in either dichloromethane/ethanol/ammonia (DEA) or chloroform/methanol (CM), with visualization by exposure to iodine vapor. Analytical HPLC was performed on a Spectraphysics Spectraseries P100 instrument using a 4.6 × 250 mm column packed with partisil silica (10 μm) and methanol/ethyl acetate/trifluoroacetic acid/98% H_2SO_4 (61.1/38.5/0.3/0.1) as mobile phase. Detection was at 280 nm.

1-[(1*R*)-Tetrahydropapaverin-2-yl]-4,11-dioxa-3,12-dioxotetradec-13-ene (8). (1*R*)-Tetrahydropapaverine (1.04 g, 3.028 mmol) in dry benzene (15 mL) was added dropwise over 1 h to hexamethylene diacrylate (3.43 g, 15.16 mmol) in dry benzene (5 mL) containing glacial acetic acid (1 drop, *ca.* 20 mg) with constant stirring at 80 °C. The solution was refluxed for 5 h. The solvent was removed, the viscous residue dissolved in ether (200 mL), and the solution extracted with dilute HCl. The aqueous solution was washed with ether (100 and 50 mL), made alkaline with NaOH solution, and extracted with ether. The ethereal solution was dried (Na_2SO_4) and evaporated to give **8** as a viscous oil (1.55 g, 93%), which showed a single spot on TLC: TLC in CM (9/1), R_F 0.88; $[\alpha]^{20}_D$ −40.8° (*c* 0.564); IR; ^{1}H-NMR.

1-[(1*R*)-Tetrahydropapaverin-2-yl]-14-(6,7,8-trimethoxytetrahydroisoquinolin-2-yl)-4,11-dioxa-3,12-dioxotetradecane (10). Compound **8** (0.62 g, 1.09 mmol) and 6,7,8-trimethoxytetrahydroisoquinoline (**9a**) (0.26 g, 1.16 mmol) were dissolved in dry benzene (15 mL) containing glacial acetic acid (1 drop), and the mixture was heated at 80 °C for 20 h. Evaporation of the solvent gave a viscous oil (0.9 g) which was purified by column chromatography in CM (99/1) to yield **10** as a lightly colored viscous oil (0.71 g, 84%): $[\alpha]^{20}_D$ −32.3° (*c* 0.726); TLC in CM (98/2), R_F 0.64; IR; ^{1}H-NMR.

1-[(1*R*)-Tetrahydropapaverin-2-yl]-14-(5,6,7-trimethoxytetrahydroisoquinolin-2-yl)-4,11-dioxa-3,12-dioxotetradecane (11). Prepared from compound **8** and 5,6,7-trimethoxytetrahydroisoquinoline (**9b**) as described for **10**: yield 90%; $[\alpha]^{20}_D$ −29.5° (*c* 0.604); TLC in CM (98/2), R_F 0.68; IR; ^{1}H-NMR.

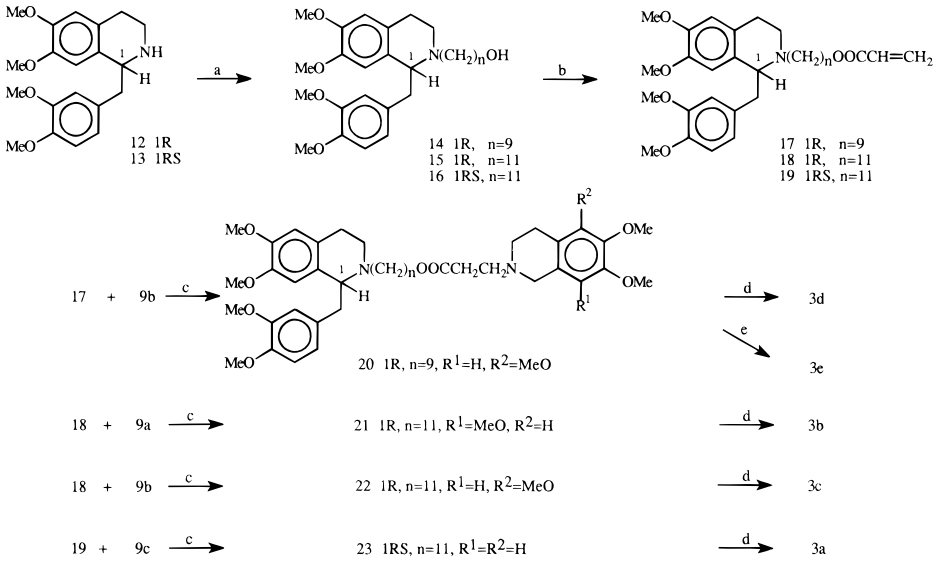
***N*-(9-Hydroxynonyl)-(1*R*)-tetrahydropapaverine (14).** 9-Bromononanol (1.03 g, 4.62 mmol) in acetonitrile (15 mL) was added dropwise to (*R*)-tetrahydropapaverine (**12**) (1.57 g, 4.57 mmol) in acetonitrile (20 mL) with constant stirring at 82 °C and the solution refluxed for 70 h. The solution was evaporated to give a yellow oil (2.58 g) and the crude product purified by column chromatography in DEA (100/8/1) to yield a viscous light brown oil. Crystallization from *n*-hexane gave **14** as colorless needles (0.83 g, 37%): mp 70 °C; $[\alpha]^{20}_D$ −61.0° (*c* 0.50); TLC in DEA (100/8/1), R_F 0.44; IR; ^{1}H-NMR. Anal. ($C_{29}H_{43}NO_5$) C, H, N.

***N*-(11-Hydroxyundecanyl)-(1*R*)-tetrahydropapaverine (15):** prepared as described for **14**; yield 70%; mp 58−59 °C (from *n*-hexane); TLC in DEA (150/8/1), R_F 0.35; IR; ^{1}H-NMR. Anal. ($C_{31}H_{47}NO_5$) H, N, C: calcd, 72.48; found, 72.0.

***N*-(11-Hydroxyundecanyl)-(1*RS*)-tetrahydropapaverine (16):** prepared as described for **14**; yield 85%; mp 82 °C (from *n*-hexane); IR; ^{1}H-NMR. Anal. ($C_{31}H_{47}NO_5$) C, H, N.

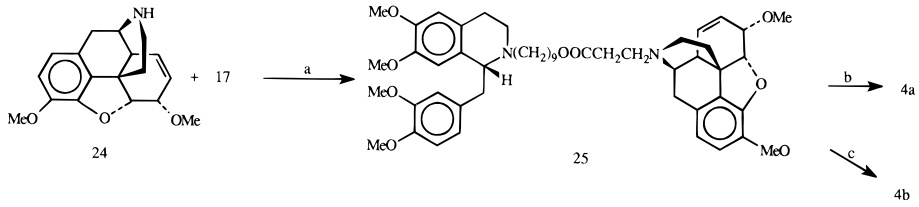
1-[(1*R*)-Tetrahydropapaverin-2-yl]-10-oxa-11-oxotridec-12-ene (17). Acryloyl chloride (0.146 g, 61 mmol) in dry benzene was added dropwise to compound **14** (0.56 g, 1.15 mmol) in dry benzene containing a trace of pyrogallol and maintained at 40 °C under nitrogen. After 1 h the solution was filtered and the solvent removed under vacuum. The oily residue was purified by flash chromatography in DEA (150/

Scheme 2[a]



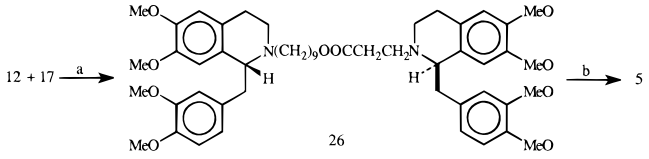
[a] Reagents: (a) $Br(CH_2)_nOH$, CH_3CN; (b) $CH_2{=}CHCOCl$, Et_3N, C_6H_6; (c) AcOH, C_6H_6; (d) MeI, CH_3CN; (e) $CH_2{=}CHCH_2Br$, CH_3CN.

Scheme 3[a]



[a] Reagents: (a) AcOH, C_6H_6; (b) MeI, CH_3CN; (c) $CH_2{=}CHCH_2Br$, CH_3CN.

Scheme 4[a]



[a] Reagents: (a) AcOH, C_6H_6; (b) MeI, CH_3CN.

8/1) to yield **17** as a yellow oil (0.46 g, 74%): TLC in DEA (150/8/1); R_F 0.39; $[\alpha]^{20}_D$ −49.2° (*c* 0.81); IR; ^{1}H-NMR.

1-[(1*R*)-Tetrahydropapaverin-2-yl]-12-oxa-13-oxopentadec-14-ene (18): prepared as described for **17** and used without further purification; yield 99%; TLC in DEA (150/8/1); R_F 0.54; IR.

1-[(1*RS*)-Tetrahydropapaverin-2-yl]-12-oxa-13-oxopentadec-14-ene (19): prepared as described for **17** and used without further purification; yield 40%; TLC in DEA (150/8/1); R_F 0.54; IR.

1-[(1*R*)-Tetrahydropapaverin-2-yl]-15-(6,7,8-trimethoxytetrahydroisoquinolin-2-yl]-12-oxa-13-oxopentadecane (21). Compounds **9a** (0.345 g, 1.55 mmol) and **18** (0.586 g, 1.03 mmol) were heated in dry benzene with a trace of glacial acetic acid at 80 °C for 7 days. The solvent was removed; the residue was azeotroped with dry benzene to remove acetic acid and purified by flash chromatography in DEA (300/8/1) to give **21** as a yellow oil (0.36 g, 45%): TLC in DEA (150/8/1), R_F 0.41; IR; ^{1}H-NMR.

1-[(1*R*)-Tetrahydropapaverin-2-yl]-15-(5,6,7-trimethoxytetrahydroisoquinolin-2-yl]-12-oxa-13-oxopentadecane (22): prepared from **9b** and **18** as described for **21**; yield 56%; TLC in DEA (150/8/1), R_F 0.47; IR; ^{1}H-NMR.

1-[(1*RS*)-Tetrahydropapaverin-2-yl]-15-(6,7-dimethoxytetrahydroisoquinolin-2-yl]-12-oxa-13-oxopentadecane (23): prepared from **9c** and **19** as described for **21**; yield 27%; TLC in DEA (150/8/1), R_F 0.42; IR; ^{1}H-NMR.

1-[(1*R*)-Tetrahydropapaverin-2-yl]-13-(5,6,7-trimethoxytetrahydoisoquinolin-2-yl]-10-oxa-11-oxotridecane (20): prepared from **9b** and **17** as described for **21**; yield 85%; TLC in DEA (150/8/1), R_F 0.61; $[\alpha]^{20}_D$ −37.2° (*c* 0.25); ^{1}H-NMR.

1-[(1*R*)-Tetrahydropapaverin-2-yl]-13-(6-*O*-methylnorcodein-17-yl)-10-oxa-11-oxotridecane (25): prepared from **24** and **17** as described for **21**; yield 82%; TLC in DEA (150/8/1), R_F 0.41; IR; ^{1}H-NMR.

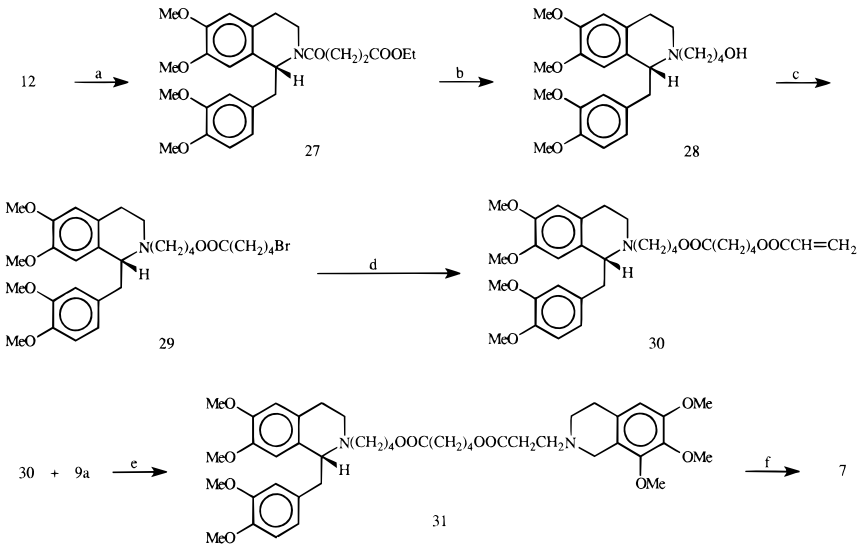
1,13-Bis[(1*R*)-tetrahydropapaverin-2-yl]-10-oxa-11-oxotridecane (26): prepared from **12** and **17** as described for **21**; yield 15%; TLC in DEA (150/8/1), R_F 0.51; IR; ^{1}H-NMR.

6-*O*-Methylnorcodeine (24). 6-*O*-Methylcodeine[8] (10.8 g, 34.5 mmol), phenyl chloroformate (12.6 g, 138 mmol), and potassium carbonate (3.45 g, 34.5 mmol) were refluxed in dry dichloromethane under nitrogen for 18 h. The reaction mixture was filtered, and the solvent and excess phenyl chloroformate were removed under vacuum to yield 6-*O*-methylnorcodeine phenylcarbamate as a white solid (13.6 g, 94%): mp 134−135 °C (from *n*-hexane); ^{1}H-NMR. Anal. ($C_{25}H_{25}NO_5$) C, H, N.

The phenylcarbamate (4.0 g, 9.52 mmol) was treated first with 65% (10 mL) and then with 98% hydrazine hydrate (15 mL) with nitrogen bubbled through the mixture, which then was heated at 150 °C for 5 h. Further 65% hydrazine hydrate (10 mL) and 98% hydrazine hydrate (10 mL) were added, and heating was continued for a further 19 h. The solution was evaporated to dryness, the residue dissolved in chloroform, and the solution extracted with KOH solution (30%, ×4). The chloroform solution was dried (Na_2SO_4) and evaporated to give a yellow oil. Flash chromatography in DEA (100/8/1) followed by trituration with *n*-hexane gave **24** as a flaky white solid (65%): mp 98−100 °C; TLC in DEA (100/8/1), R_F 0.25; IR; ^{1}H-NMR; ^{13}C-NMR. Anal. ($C_{18}H_{21}NO_3$) C, H, N.

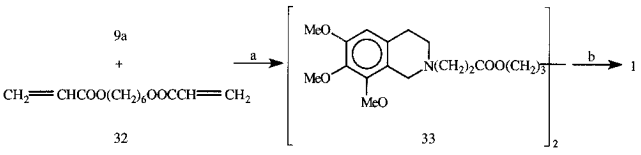
Ethyl 4-[*N*-(1*R*)-Tetrahydropapaverin-2-yl]succinamide (27). Ethyl succinoyl chloride (6.01 g, 17.5 mmol) in dry THF was added dropwise (50 min) to compound **12** (6.01 g, 17.5 mmol) and triethylamine (5.3 g, 52.5 mmol) under nitrogen in dry benzene, and the mixture was refluxed for 1.25 h. The cooled reaction mixture was filtered and evaporated, the resulting oil was extracted with diethyl ether, and the

Scheme 5[a]



[a] Reagents: (a) $EtOOC(CH_2)_2COCl$, Et_3N, C_6H_6; (b) $LiAlH_4$, THF; (c) HCl, $Br(CH_2)_4COCl$, CH_3CN; (d) CH_2=CHCOOK, 18-crown-6, HMPA; (e) AcOH, C_6H_6; (f) MeI, CH_3CN.

Scheme 6[a]



[a] Reagents: (a) AcOH, C_6H_6; (b) MeI, CH_3CN.

solution was cooled to yield **27** (7.34 g, 89%): mp 94 °C; $[\alpha]^{20}_D$ −73.3° (*c* 0.52); TLC in DEA (150/8/1), R_F 0.42; IR; ^{1}H-NMR. Anal. ($C_{21}H_{33}NO_7$) C, H, N.

***N*-(4-Hydroxybutyl)-(1*R*)-tetrahydropapaverine (28).** Compound **27** (7.37 g, 15.62 mmol) in dry THF was added dropwise to a refluxing suspension of $LiAlH_4$ (2.96 g, 78.13 mmol) in dry THF under nitrogen, and the mixture was refluxed for 2.5 h. The reaction mixture was cooled in ice, and water (10 mL) was added cautiously followed in turn by 4 M NaOH (10 mL) and then water (200 mL). The resulting suspension was filtered through Kiesel gel and the THF evaporated and extracted with $CHCl_3$ (150 mL × 3). The combined $CHCl_3$ extracts were washed with saturated NaCl solution, dried (Na_2SO_4), and concentrated to give a yellow oil. Treatment with hexane gave **28** as a white solid (5.8 g, 90%): mp 53−55 °C; TLC in DEA (150/8/1), R_F 0.32; IR; ^{1}H-NMR. Anal. ($C_{24}H_{33}NO_5$) C, H, N.

***N*-(10-Bromo-5-oxa-6-oxodecyl)-(1*R*)-tetrahydropapaverine (29).** 5-Bromovaleryl chloride (2.44 g, 12.2 mmol) in acetonitrile (20 mL) was added dropwise to **28** hydrochloride (5.03 g, 11.1 mmol) in acetonitrile (40 mL) at 80 °C. The mixture was heated at 80 °C for 5.25 h and left at room temperature overnight and the solvent removed. Flash chromatography in DEA (200/8/1) gave **29** as a yellow oil (5.8 g, 90%): TLC in DEA (200/8/1), R_F 0.45; IR; ^{1}H-NMR.

***N*-(5,11-Dioxa-6,12-dioxotetradec-13-enyl)-(1*R*)-tetrahydropapaverine (30).** Potassium acrylate (0.133 g, 1.21 mmol) and 18-crown-6 (17 mg, 0.067 mmol) were added to a solution of **29** (0.588 g, 1.01 mmol) in HMPA (25 mL) under nitrogen, and the suspension was stirred for 24 h at 40 °C. The reaction mixture was filtered, the filtrate diluted with water (150 mL), and the solution extracted with ether (100 mL × 4). The combined ether extracts were washed with saturated NaCl solution (100 mL × 2) and evaporated to yield **30** as a brown oil (0.42 g, 73%): TLC in DEA (150/8/1), R_F 0.50; IR; ^{1}H-NMR.

1-[[(1*R*)-Tetrahydropapaverin-2-yl]-14-(6,7,8-trimethoxytetrahydroisoquinolin-2-yl]-5,11-dioxa-6,12-dioxotetradecane (31). Compounds **30** (0.42 g, 0.74 mmol) and **9a** (0.26 g, 1.16 mmol) were refluxed in dry benzene (40 mL) and glacial acetic acid (2 drops) for 23 h. The solvent was removed and the residue azeotroped with dry benzene (×2) to remove acetic acid to yield a brown oil. Purification by flash chromatography in DEA (200/8/1) gave **31** as a viscous yellow oil (0.33 g, 56%): IR; ^{1}H-NMR.

1,14-Bis[6,7,8-trimethoxytetrahydropapaverin-2-yl]-4,-11-dioxa-3,12-dioxotetradecane (33). 6,7,8-Trimethoxytetrahydroisoquinoline (**9a**) (1.12 g, 5.0 mmol), hexamethylene diacrylate (**32**) (0.55 g, 2.4 mmol), and glacial acetic acid (2 drops, *ca*. 40 mg) were heated together at 80 °C for 20 h. The reaction mixture was cooled, dissolved in dry toluene (15 mL), stirred with Merck Kieselgel 60 (70−230 mesh, 200 mg) for 4 h, filtered, and evaporated to give a light viscous oil. Column chromatography in chloroform on silica gel (70−230 mesh) gave **33** as a viscous oil (1 g, 62%): TLC in CM (94/6), R_F 0.76; ^{1}H-NMR.

Quaternary Salts. Ditertiary amino mono- and diesters were treated with the appropriate alkyl halide by methods previously described.[1,2] Yields, stereoisomer ratios, physical constants, and elemental analyses are reported in Table 1. NMR data are available as supporting information.

Pharmacology. Neuromuscular blocking properties and vagal effects were measured in cats. The results are recorded in Table 1.

Mongrel cats weighing 2.0−5.0 kg were anesthetized with a mixture of pentobarbitone sodium (17 mg/kg ip) and α-chloralose (80 mg/kg ip). Adequate levels of anesthesia 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 Statham P23 transducer. Heart rate was determined from the ECG. The right vagus was exposed, crushed *ca*. 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 of 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 a 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 pentobarbitone sodium.

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Supporting Information Available: NMR spectral data of quaternary compounds (3 pages). Ordering information is given on any current masthead page.

References

(1) Stenlake, J. B.; Waigh, R. D.; Dewar, G. A.; Hughes, R.; Chapple, D. J.; Coker, G. G. Biodegradable neuromuscular blocking agents. Part 4. Atracurium besylate and related polyalkylene di-esters. *Eur. J. Med. Chem.* **1981**, *16*, 515−524.

(2) Stenlake, J. B.; Dhar, N. C.; Haddow, J.; McDonald, I. M.; Maehr, R. B.; Wastila, W. B. Neuromuscular blocking agents. Some approaches to short acting compounds. *Eur. J. Med. Chem.* **1992**, *27*, 463−477.

(3) Stenlake, J. B.; Dhar, N. C.; Henderson, C. F.; Maehr, R. B.; Scharver, J.; Wastila, W. B.; Midgley, J. M. Neuromuscular blocking agents. Approaches to short-acting compounds 2. Bisthiazolium salts. *Eur. J. Med. Chem.* **1993**, *28*, 415−418.

(4) Dhar, N. C.; Maehr, R. B.; Masterson, L. A.; Midgley, J. M.; Stenlake, J. B.; Wastila, W. B. Unpublished observations.

(5) Stenlake, J. B.; Waigh, R. D.; Dewar, G. H.; Dhar, N. C.; Hughes, R.; Chapple, D. J.; Lindon, J. C.; Ferrige, A. G.; Cobb, P. Biodegradable neuromuscular blocking agents. Part 6. Stereochemical studies on atracurium and related polyalkylene di-esters. *Eur. J. Med. Chem.* **1984**, *19*, 441−450.

(6) Swarington, R. A.; El-Sayed, H. A.; Yeowell, D. A.; Savarese, J. J. U.S. Patent 4,761,418, 1988.

(7) Kharkevich, D. A.; Skoldinov, A. P.; Lemina, E. Y.; Igumnova, N. D. Relations between structure, hydrolysis rate and activity of dicarboxylic esters. *Farmikol. Toksikol. (Moscow)* **1989**, *52*, 34−37; *Chem. Abstr. 110*, 205078t.

(8) Barber, R. B.; Rapoport, H. Synthesis of thebaine and oripavine from codeine and morphine. *J. Med. Chem.* **1975**, *18*, 1074−1077.

(9) Rice, K. C.; May, E. L. Procedural refinements in the *N*-demethylation of morphine and codeine using phenyl chloroformate and hydrazine. *J. Heterocycl. Chem.* **1977**, *14*, 665−666.

(10) Maehr, R. B.; Wastila, W. B. Comparative pharmacology of atracurium and six isomers in cats. *Anesthesiology* **1993**, *79*, A950.

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