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Studies on Spasmolytics. II.[1] Synthesis and Anticholinergic Activities of 4-Acyloxy-1-alkyl-1-(1,3-dioxolan-4-ylmethyl)piperidinium Compounds[2]

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Quaternization of 4-acyloxy-1-(1,3-dioxolan-4-ylmethyl)piperidine derivatives with methyl bromide afforded two diastereoisomers in equal amounts. The stereochemistry of these compounds was determined from the chemical shift of the N-methyl signals in the proton nuclear magnetic resonance (^{1}H-NMR) spectra. The quaternary salts showed high anticholinergic activities. The *trans* isomers tended to be more potent than the corresponding *cis* isomers.

Keywords——4-acyloxy-1-(1,3-dioxolan-4-ylmethyl)piperidine; quaternization; 4-acyloxy-1-(1,3-dioxolan-4-ylmethyl)-1-methylpiperidinium salt; diastereoisomer; isomeric ratio; ^{1}H-NMR; stereochemistry; anticholinergic activity; structure–activity relationship

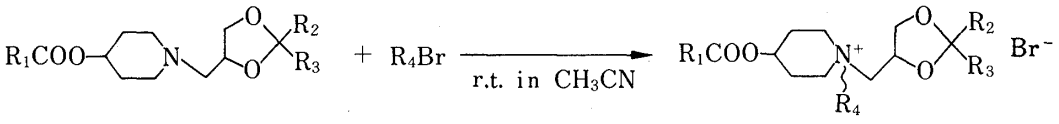
In the preceding paper,[1] we reported that many 4-acyloxy-1-(1,3-dioxolan-4-ylmethyl)piperidine derivatives (**1**) have potent spasmolytic, particularly papaverine-like, activity. In connection with the structure–activity relationship, we became interested in the pharmacological activities of their quaternary piperidinium derivatives (**2**). This report concerns the stereochemistry and spasmolytic (anticholinergic) activities of the quaternary salts (**2**). 3-Benziloyloxy-1-methyl-1-(2,2-dimethyl-1,3-dioxolan-4-ylmethyl)piperidinium bromide (BMP) was also synthesized and tested for spasmolytic activity in order to further elucidate the structure–activity relationship.

Results and Discussion

Synthesis

Quaternization of the compounds (**1**)[3] was performed by using methyl or ethyl bromide in acetonitrile at room temperature to give the corresponding piperidinium salts (**2**) in nearly quantitative yields (Chart 1).

These piperidinium salts (**2**) were usually obtained as a mixture of two diastereoisomers due to *cis–trans* isomerism attributable to tetravalent nitrogen and C-4 on the piperidine ring; the diastereomers were easily separated by fractional crystallizations and/or by silica-gel column chromatography. A typical procedure is as follows. A diastereoisomeric mixture of *trans*- and *cis*-**2a** was crystallized from acetone to give initially *trans*-**2a** in 41.4% yield; after evaporation of the mother liquor, crystallization of the residue from acetonitrile afforded the other isomer (*cis*-**2a**) in 33.0% yield. It was found that the *trans* isomers always showed larger *Rf* values in thin-layer chromatography (silica gel, CH_2Cl_2: MeOH = 5 : 1) than the corresponding *cis* isomers. These isomers are differentiated here by using the prefixes *trans* and *cis* with the compound number (Chart 2). Compound **1k** consists of two diastereoisomers, one (**1k**-A) with mp 160—161 °C and the other (**1k**-B) with mp 83.0—85.0 °C.[4] Quaterniza-



1 R_4=Me, Et 2

Compd. 1	R_1	R_2	R_3	Compd. 2	R_4
1a	$Ph_2C(OH)$	H	H	**2a**	Me
1b	9-xanthenyl	H	H	**2b**	Me
1c	$Ph_2C(OH)$	Me	Me	**2c1**	Me
				2c2	Et
1d	$Ph_2C(OH)$	Ph	Ph	**2d**	Me
1e	$Ph_2C(OH)$	$-(CH_2)_5-$		**2e**	Me
1f	9-xanthenyl	Me	Me	**2f**	Me
1g	PhC(c-Hex)(OH)	Me	Me	**2g**	Me
1h	9-fluorenyl	Me	Me	**2h**	Me
1i	$CH_3CH(OH)$	Ph	Ph	**2i**	Me
1j	Et	Ph	Ph	**2j**	Me
1k-A	$Ph_2C(OH)$	Me	Ph	**2k-A**	Me
1k-B	$Ph_2C(OH)$	Me	Ph	**2k-B**	Me
1l	$Ph_2C(OH)$	Et	Et	**2l**[a]	Me
1m	$Ph_2C(OH)$	iso-Pr	iso-Pr	**2m**[a]	Me
1n	Ph_2CH	Me	Me	**2n**[a]	Me
1o	$Ph_2C(OH)$	*n*-Pr	*n*-Pr	**2o**[a]	Me
1p	$Ph_2C(OH)$	c-Hex	c-Hex	**2p**	Me
1q	$Ph_2C(OH)$	$PhCH_2$	$PhCH_2$	**2q**	Me
1r	PhCH(OH)	Me	Me	**2r**	Me
1s	PhCH(OH)	Ph	Ph	**2s**	Me
1t	$PhCH_2$	Ph	Ph	**2t**	Me

a) Cl anion.

Chart 1

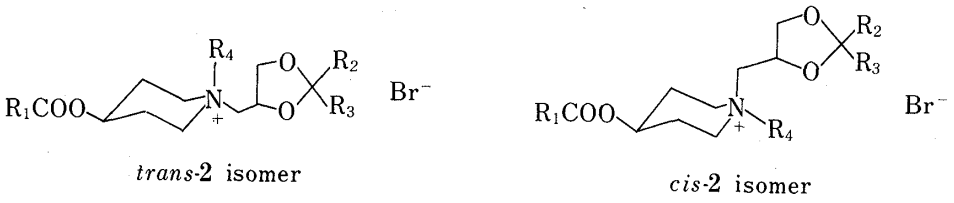


Chart 2

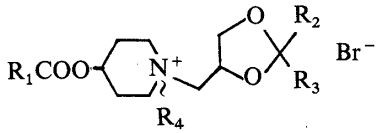
tion of each of these isomers produced two diastereoisomers. Thus four isomeric compounds (*trans*-**2k**-A, *cis*-**2k**-A; *trans*-**2k**-B, *cis*-**2k**-B) were obtained from **1k**. These compounds were separated by silica-gel column chromatography (CH_2Cl_2 : CH_3CN = 5 : 1). The yields, melting points and crystallization solvents of the quaternary salts (**2**) are shown in Table I.

Stereochemistry

The configurations and ratios of the diastereoisomers were determined from the proton nuclear magnetic resonance (^{1}H-NMR) spectra based on the fact that in piperidinium derivatives, axial N-methyl hydrogens usually resonate at higher field than equatorial N-methyl hydrogens[5] (see Table II).

In the compounds **2**, the C_4-proton of the piperidine ring appeared as a multiplet (half-width[6] 18—24 Hz) at 4.95—5.20 ppm, suggesting that RCOO group is in an equatorial

TABLE I. Yields, Melting Points and Recrystallization Solvents of the Diastereoisomers (**2**)



cis and *trans* isomers

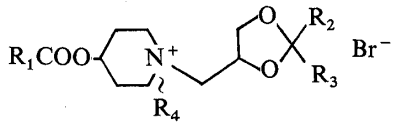
Compd. **2**	Quaternization Yield[a] (%)	*trans* Isomer			*cis* Isomer		
		Yield[a] (%)	mp (°C)	Recrystn. solvent	Yield[a] (%)	mp (°C)	Recrystn. solvent
2a	96.0	41.4	215.0—217.0	Me_2CO	33.0	190.0—192.0	MeCN
2b	93.6	44.3	212.0—215.0	MeCN	29.6	Amorphous	Me_2CO
2c1	94.7	36.5	225.0—227.0	MeCN	32.7	203.0—205.0	Me_2CO
2c2	90.1	40.6	225.5—226.5	MeCN	28.8	189.5—191.5	Me_2CO
2d	98.4	33.3	243.0—245.0	MeCN	37.6	194.0—195.5	Me_2CO
2e	96.6	40.0	202.0—204.0	MeCN	31.7	179.8—182.0	Me_2CO
2f	97.2	45.3	125.0—128.0	Me_2CO	34.3	Amorphous	MeCN
2g	93.8	27.3	211.0—213.0	MeCN	39.7	221.0—222.9	$MeNO_2$
2h	93.9	41.7	196.8—198.0	Me_2CO	37.6	166.0—168.0	Me_2CO
2i	95.9	36.5	171.5—172.5	Me_2CO	—[b]		
2j	95.0	32.4	176.5—178.5	MEK[c]	19.8	156.0—158.0	Me_2CO
2k-A	91.8	32.4	215.0—217.0	—[d]	27.1	178.5—180.0	—[d]
2k-B	96.4	35.5	206.0—207.0	—[d]	32.0	204.0—205.5	—[d]
2l[e]	92.7	26.3	98.0—102.0	Me_2CO	32.2	197.0—198.5	iso-PrOH
2m[e]	94.0	31.4	122.0—125.0	MEK	27.5	191.5—194.0	MeCN
2n[e]	91.8	36.7	218.0—220.0	MEK	32.5	194.0—196.0	Me_2CO

a) Isolated yield.
b) Not separated cleanly.
c) Methyl ethyl ketone.
d) A mixture of acetone and cyclohexane.
e) Chloride prepared from the exchange reaction of the bromide with chloride anion.

position in both *trans*- and *cis*-**2** isomers. On the other hand, the C_3-proton of 3-benziloyl-8-(2,2-dimethyl-1,3-dioxolan-4-ylmethyl)-8-methylnortropinium bromide[7] whose ester group has axial orientation, appeared as a pseudo-triplet[8] (half-width 10 Hz) at 5.23 ppm. Consequently, the stable conformational structures of the two diastereoisomers of **2** are considered to be as shown in Chart 2.

It is known that the quaternization of a 1-alkyl-4-alkyl or aryl substituted piperidine with methyl iodide affords the axially oriented N-methyl isomer predominantly (67—95%).[9] However, in the quaternization of **1** with methyl bromide, the ratios of the two isomers (*trans* and *cis*) were nearly 1 : 1 (Table II), showing that the selectivity of the quaternization for **1** is low. The only exception is the quaternization of the 4-lactoyloxy derivative (**1i**), which gave mainly the axially bonded N-methyl isomer (*trans*-**2i**) in a ratio of 59 : 41. In contrast to the quaternization of 4-acyloxy derivatives, that of 3-benziloyloxy-1-(2,2-dimethyl-1,3-dixolan-4-ylmethyl)piperidine proceeded with higher selectivity, giving the axially bonded N-methyl isomer (*cis*-BMP) as the major product in a ratio of 83 : 17. In order to clarify the above result, 4-benziloyloxy-1-methylpiperidine was quaternized using trideuteriomethyl bromide (CD_3Br) and it was found that the reaction proceeds preferentially by attack of the CD_3 group from the equatorial direction, giving rise to the equatorial isomer (*trans*-**3**) in 60% relative yield (Chart 3).

TABLE II. ^{1}H-NMR Chemical Shifts of N-Methyl and Product Ratios of the Diastereoisomers (**2**)



cis and *trans* isomers

Compd. **2**	Chemical shift[a] of N-methyl (δ ppm, in CD_3OD)		Ratio *trans*/*cis*
	trans	*cis*	
2a	3.03 (s)	3.15 (s)	50/50
2b	3.19 (s)	3.20 (s)	51/49
2c1	3.08 (s)	3.18 (s)	52/48
2c2	3.45 (q)[b]	3.60 (q)[b]	48/52
2d	3.14 (s)	3.25 (s)	47/53
2e	3.10 (s)	3.20 (s)	52/48
2f	3.13 (s)	3.17 (s)	50/50
2g	3.25 (s)	3.26 (s)	51/49
2h	3.28 (s)[c]	3.39 (s)[c]	52/48
2i	3.28 (s)	3.32 (s)	59/41
2j	3.33 (s)	3.36 (s)	55/45
2k-A	3.11 (s)	3.23 (s)	50/50
2k-B	3.13 (s)	3.23 (s)	52/48
2l[d]	3.08 (s)	3.20 (s)	46/54
2m[d]	3.12 (s)	3.23 (s)	46/54
2n[d]	3.13 (s)	3.22 (s)	48/52

a) Abbreviations are as follows: s, singlet; q, quartet.
b) N-Ethyl.
c) Measured in $CDCl_3$ because of the coincidence of the N-methyl signals in CD_3OD.
d) Cl anion.

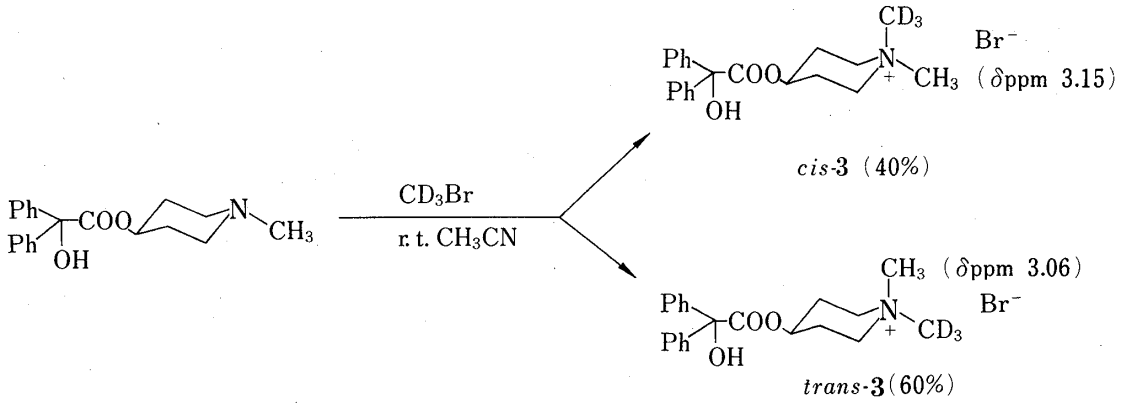
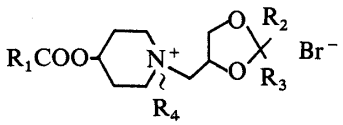


Chart 3

It is well-known that a 4-acyloxy group in *N*-alkylpiperidines takes the energetically more favorable equatorial orientation.[5c,10] If we assume that the quaternization occurs in this conformation, the above results indicate that the approach of a methyl group from the axial direction to the nitrogen of the compound **1** is more hindered than that from the equatorial direction. On the other hand, for the 3-acyloxy derivative, an axial approach is still preferred.

No effect of the solvent on the selectivity of quaternization was observed.[11]

TABLE III. Anticholinergic Activities of the Diastereoisomers (**2**)

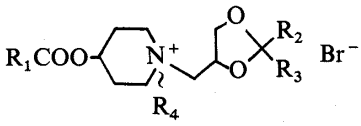


cis and *trans* isomers

Compd. **2**	pA_2		Compd. **2**	pA_2	
	trans	*cis*		*trans*	*cis*
2a	8.08		**2i**	5.78	
2b	8.65		**2k**-A	7.29	7.07
2c1	7.76	6.17	**2k**-B	7.38	6.23
2c2[a]	6.88		**2l**[b]	7.38	6.12
2d	6.43	6.62	**2m**[b]	6.66	
2e	6.43		**2n**[b]	7.43	5.80
2f	8.64		BMP[c]	6.50	
2g	8.28		Atropine methobromide		
2h	7.96	6.06		9.28	

a) N-Ethyl.
b) Cl anion.
c) 3-Benziloyloxy-1-methyl-1-(2,2-dimethyl-1,3-dioxolan-4-ylmethyl)piperidinium bromide.

TABLE IV. Anticholinergic Activities of the Diastereoisomeric Mixtures of Piperidinium Compounds (**2j**, **2o**—**2t**)



cis and *trans* isomers

Compd.[a]	pA_2
	Mixture[b] of the *trans* and *cis* isomers
2j	5.92
2o[c]	6.71
2p	6.94
2q	6.51
2r	5.29
2s	6.69
2t	6.64
Atropine methobromide	9.28

a) Clean separation of the *cis* and *trans* isomers was not achieved.
b) Nearly 1 : 1 mixture as determined by ^{1}H-NMR spectroscopy.
c) Cl anion.

Pharmacology

The separated diastereoisomers (*trans* and *cis*) of 4-acyloxy-1-alkyl-1-(1,3-dioxolan-4-ylmethyl)piperidinium salts (**2**) along with the 3-benziloyloxy derivative (*cis*-BMP) were tested for spasmolytic activity according to the Magnus method using isolated ileum from guinea

pigs. The competitive antagonistic activity is expressed as the pA_2 value, calculated from the shift of the concentration–action curve of acetylcholine. These results are shown in Table III.

The anticholinergic activities (pA_2 values) of the diastereoisomeric mixtures of 4-acyloxy-1-(1,3-dioxolan-4-ylmethyl)-1-methylpiperidinium salts (**2j**, **2o**—**t**) are also listed in Table IV.

It is interesting that the conversion of the tertiary amines (**1**) to the quaternary salts (**2**) resulted in disappearance of the papaverine-like activity, and instead increased the atropine-like (anticholinergic) activity; *e.g.* **2a**, **2f**, **2h**, **2j**, **2l**, **2m**, **2n**, **2o**, **2p**, **2q**, and BMP.[1] A clear difference of anticholinergic activity between the two stereoisomers was observed; the *trans* isomer generally exhibits more potent activity than the *cis* isomer. For example, *trans*-**2h** was 80 times more active than *cis*-**2h**. This observation is particularly interesting from a structure–activity viewpoint, since few studies on this subject have been done.[12]

Barlow[13] reported that a compound with a flat and rigid structure could show high anticholinergic activity since it can easily and firmly cover the acetylcholine receptor. On this basis, the *trans* isomers of 4-acyloxypiperidinium salts (**2**) might be expected to bind to the receptor more firmly because they are flatter and more extended than the corresponding *cis* isomers.

On the other hand, the *trans* isomer of 4-benziloyloxypiperidinium salt (**2c1**) was approximately 19 times more potent than the *trans* isomer of the 3-benziloyloxy derivative (BMP). This also suggests that a suitable distance between the nitrogen and the oxygen atom on the piperidine ring is necessary for the activity.[14]

Experimental

All melting points are uncorrected. Infrared (IR) spectra were recorded with a JASCO IRA-1 spectrophotometer and ^{1}H-NMR spectra were taken with a Hitachi R-24 (60 MHz) spectrometer with tetramethylsilane as an internal standard (δ ppm). The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. For column chromatography, silica gel (Wako gel, C-200) was used.

General Procedure for the Preparation of 4-Acyloxy-1-(1,3-dioxolan-4-ylmethyl)piperidinium Bromide (2a—k)——A reaction mixture of **1** (0.01 mol) and methyl bromide (1.5 ml) in acetonitrile (30 ml) was allowed to stand at room temperature for 15 h, then concentrated *in vacuo*. The mixture of quaternary salts (*trans*-**2** and *cis*-**2**) obtained was washed with dry ether (30 ml × 2) and crystallized from acetonitrile/ether or acetone/ether to give the diastereoisomeric *trans*- and *cis*-**2** in nearly 1 : 1 ratio in 90.1—98.4% yield. Usually, the *trans* isomer of **2** was initially separated from the mixture by crystallization from acetonitrile or acetone in 27.3—45.3% yield as colorless needles. Next, the other isomer (*cis*-**2**) was obtained from the mother liquor by evaporation followed by similar crystallization of the residue in 19.8—39.7% yield as colorless needles.

4-Benziloyloxy-1-(1,3-dioxolan-4-ylmethyl)-1-methylpiperidinium Bromide (*trans*- and *cis*-2a)——*trans*-**2a**: ^{1}H-NMR (CD_3OD): 3.03 (3H, s, N–CH_3), 4.71, 5.25 (2H, dd, J=22 Hz, C_2–H of the dioxolane), 5.18 (1H, m, C_4–H of the piperidine), 7.35 (10H, m, Ph × 2). IR ν_{max}^{KBr} cm^{-1}: 3300 (OH), 1720 (C=O). *Anal.* Calcd for $C_{24}H_{30}BrNO_5$: C, 58.54; H, 6.14; N, 2.84. Found: C, 58.61; H, 6.11; N, 2.79. *cis*-**2a**: ^{1}H-NMR (CD_3OD): 3.15 (3H, s, N–CH_3), 4.70, 5.22 (2H, dd, J=22 Hz, C_2–H of the dioxolane), 5.19 (1H, m, C_4–H of the piperidine), 7.30 (10H, m, Ph × 2). IR ν_{max}^{KBr} cm^{-1}: 3320 (OH), 1720 (C=O). *Anal.* Calcd for $C_{24}H_{30}BrNO_5$: C, 58.54; H, 6.14; N, 2.84. Found: C, 58.38; H, 6.27; N, 2.85.

1-(1,3-Dioxolan-4-ylmethyl)-1-methyl-4-(xanthene-9-carbonyloxy)piperidinium Bromide (*trans*- and *cis*-2b)——*trans*-**2b**: ^{1}H-NMR (CD_3OD): 3.19 (3H, s, N–CH_3), 4.66, 5.20 (2H, dd, J=22 Hz, C_2–H of the dioxolane), 5.15 (1H, s, =CHCOO), 5.17 (1H, m, C_4–H of the piperidine), 6.98—7.54 (8H, m, aromatic). IR ν_{max}^{KBr} cm^{-1}: 1725 (C=O). *Anal.* Calcd for $C_{24}H_{28}BrNO_5$: C, 58.78; H, 5.76; N, 2.86. Found: C, 58.63; H, 5.99; N, 2.61. *cis*-**2b**: ^{1}H-NMR (CD_3OD): 3.20 (3H, s, N–CH_3), 4.66, 5.15 (2H, dd, J=22 Hz, C_2–H of the dioxolane), 5.15 (1H, s, =CHCOO), 5.18 (1H, m, C_4–H of the piperidine), 7.00—7.56 (8H, m, aromatic). IR ν_{max}^{KBr} cm^{-1}: 1725 (C=O). *Anal.* Calcd for $C_{24}H_{28}BrNO_5$: C, 58.78; H, 5.76; N, 2.86. Found: C, 58.81; H, 5.73; N, 2.79.

4-Benziloyloxy-1-methyl-1-(2,2-dimethyl-1,3-dioxolan-4-ylmethyl)piperidinium Bromide (*trans*- and *cis*-2c1)——*trans*-**2c1**: ^{1}H-NMR (CD_3OD): 1.35 (3H, s, CH_3), 1.42 (3H, s, CH_3), 3.08 (3H, s, N–CH_3), 5.18 (1H, m, C_4–H of the piperidine), 7.35 (10H, m, Ph × 2). IR ν_{max}^{KBr} cm^{-1}: 3275 (OH), 1735 (C=O). *Anal.* Calcd for $C_{26}H_{34}BrNO_5$: C, 60.00; H, 6.58; N, 2.69. Found: C, 59.89; H, 6.71; N, 2.65. *cis*-**2c1**: ^{1}H-NMR (CD_3OD): 1.35 (3H, s, CH_3), 1.42 (3H, s, CH_3), 3.18 (3H, s, N–CH_3), 5.19 (1H, m, C_4–H of the piperidine), 7.35 (10H, m, Ph × 2). IR ν_{max}^{KBr} cm^{-1}: 3380 (OH), 1738 (C=O). *Anal.* Calcd for $C_{26}H_{34}BrNO_5$: C, 60.00; H, 6.58; N, 2.69. Found: C, 59.92; H, 6.82; N, 2.74.

4-Benziloyloxy-1-ethyl-1-(2,2-dimethyl-1,3-dioxolan-4-ylmethyl)piperidinium Bromide (*trans*- and *cis*-2c2)——*trans*-**2c2**: ^{1}H-NMR (CD_3OD): 1.32 (3H, s, CH_3), 1.39 (3H, s, CH_3), 3.45 (2H, q, J=7.5 Hz, N–C$\underline{H}_2$CH$_3$), 7.38 (10H, m, Ph×2). IR ν_{max}^{KBr} cm^{-1}: 3280 (OH), 1730 (C=O). *Anal.* Calcd for $C_{27}H_{36}BrNO_5$: C, 60.67; H, 6.79; N, 2.62. Found: C, 60.58; H, 6.89; N, 2.47. *cis*-**2c2**: ^{1}H-NMR (CD_3OD): 1.32 (3H, s, CH_3), 1.39 (3H, s, CH_3), 3.60 (2H, q, J=7.5 Hz, N–C$\underline{H}_2$CH$_3$), 7.39 (10H, m, Ph×2). IR ν_{max}^{KBr} cm^{-1}: 3300 (OH), 1730 (C=O). *Anal.* Calcd for $C_{27}H_{36}BrNO_5$: C, 60.67; H, 6.79; N, 2.62. Found: C, 60.38; H, 6.91; N, 2.55.

4-Benziloyloxy-1-methyl-1-(2,2-dimethyl-1,3-dioxolan-4-ylmethyl)piperidinium Bromide (*trans*- and *cis*-2d)——*trans*-**2d**: ^{1}H-NMR (CD_3OD): 3.14 (3H, s, N–CH_3), 5.20 (1H, m, C_4–H of the piperidine), 7.38 (20H, m, Ph×4). IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1740 (C=O). *Anal.* Calcd for $C_{36}H_{38}BrNO_5$: C, 67.08; H, 5.94; N, 2.17. Found: C, 67.11; H, 5.89; N, 2.21. *cis*-**2d**: ^{1}H-NMR (CD_3OD): 3.25 (3H, s, N–CH_3), 5.18 (1H, m, C_4–H of the piperidine), 7.35 (20H, m, Ph×4). IR ν_{max}^{KBr} cm^{-1}: 3250 (OH), 1730 (C=O). *Anal.* Calcd for $C_{36}H_{38}BrNO_5$: C, 67.08; H, 5.94; N, 2.17. Found: C, 66.77; H, 6.03; N, 2.15.

4-Benziloyloxy-1-methyl-1-(2,2-pentamethylene-1,3-dioxolan-4-ylmethyl)piperidinium Bromide (*trans*- and *cis*-2e)——*trans*-**2e**: ^{1}H-NMR (CD_3OD): 3.10 (3H, s, N–CH_3). IR ν_{max}^{KBr} cm^{-1}: 3380 (OH), 1730 (C=O). *Anal.* Calcd for $C_{29}H_{38}BrNO_5$: C, 62.14; H, 6.83; N, 2.50. Found: C, 61.89; H, 6.91; N, 2.37. *cis*-**2e**: ^{1}H-NMR (CD_3OD): 3.20 (3H, s, N–CH_3). IR ν_{max}^{KBr} cm^{-1}: 3380 (OH), 1735 (C=O). *Anal.* Calcd for $C_{29}H_{38}BrNO_5$: C, 62.14; H, 6.83; N, 2.50. Found: C, 62.25; H, 6.81; N, 2.47.

1-Methyl-1-(2,2-dimethyl-1,3-dioxolan-4-ylmethyl)-4-(xanthene-9-carbonyloxy)piperidinium Bromide (*trans*- and *cis*-2f)——*trans*- **2f**: ^{1}H-NMR (CD_3OD): 1.33 (3H, s, CH_3), 1.38 (3H, s, CH_3), 3.13 (3H, s, N–CH_3), 4.95 (1H, m, C_4–H of the piperidine), 5.15 (1H, m, =CHCOO), 7.19 (8H, m, aromatic). IR ν_{max}^{KBr} cm^{-1}: 1735 (C=O). *Anal.* Calcd for $C_{26}H_{32}BrNO_5$: C, 60.23; H, 6.22; N, 2.70. Found: C, 59.99; H, 6.27; N, 2.43. *cis*-**2f**: ^{1}H-NMR(CD_3OD): 1.40 (3H, s, CH_3), 1.47 (3H, s, CH_3), 3.17 (3H, s, N–CH_3), 4.95 (1H, m, C_4–H of the piperidine), 5.13 (1H, s, =CHCOO), 7.20 (8H, m, aromatic). IR ν_{max}^{KBr} cm^{-1}: 1735 (C=O). *Anal.* Calcd for $C_{26}H_{32}BrNO_5$: C, 60.23; H, 6.22; N, 2.70. Found: C, 60.06; H, 6.34; N, 2.54.

4-(α-Cyclohexyl-α-phenylglycoloyloxy)-1-methyl-1-(2,2-dimethyl-1,3-dioxolan-4-ylmethyl)piperidinium Bromide (*trans*- and *cis*-2g)——*trans*-**2g**: ^{1}H-NMR (CD_3OD): 1.39 (3H, s, CH_3), 1.45 (3H, s, CH_3), 3.25 (3H, s, N–CH_3), 5.10 (1H, m, C_4–H of the piperidine), 7.25—7.80 (5H, m, Ph). IR ν_{max}^{KBr} cm^{-1}: 3350 (OH), 1725 (C=O). *Anal.* Calcd for $C_{26}H_{40}BrNO_5 \cdot H_2O$: C, 57.35; H, 7.78; N, 2.57. Found: C, 57.19; H, 7.66; N, 2.36. *cis*-**2g**: ^{1}H-NMR (CD_3OD): 1.39 (3H, s, CH_3), 1.45 (3H, s, CH_3), 3.26 (3H, s, N–CH_3), 5.08 (1H, m, C_4–H of the piperidine), 7.25—7.80 (5H, m, Ph). *Anal.* Calcd for $C_{26}H_{40}BrNO_5$: C, 59.31; H, 7.66; N, 2.66. Found: C, 59.28; H, 7.77; N, 2.63.

4-(Fluorene-9-carbonyloxy)-1-methyl-1-(2,2-dimethyl-1,3-dioxolan-4-ylmethyl)piperidinium Bromide (*trans*- and *cis*-2h)——*trans*-**2h**: ^{1}H-NMR (CD_3OD): 1.30 (3H, s, CH_3), 1.38 (3H, s, CH_3), 3.28 (3H, s, N–CH_3), 5.03 (1H, s, CHCOO), 5.05 (1H, m, C_4–CH of the piperidine), 7.27—7.86 (8H, m, aromatic). IR ν_{max}^{KBr} cm^{-1}: 1725 (C=O). *Anal.* Calcd for $C_{26}H_{32}BrNO_4$: C, 62.15; H, 6.42; N, 2.79. Found: C, 62.21; H, 6.49; N, 2.61. *cis*-**2h**: ^{1}H-NMR (CD_3OD): 1.30 (3H, s, CH_3), 1.38 (3H, s, CH_3), 3.39 (3H, s, N–CH_3), 4.98 (1H, s, CHCOO), 5.08 (1H, m, C_4–H of the piperidine), 7.28—7.85 (8H, m, aromatic). IR ν_{max}^{KBr} cm^{-1}: 1725 (C=O). *Anal.* Calcd for $C_{26}H_{32}BrNO_4$: C, 62.15; H, 6.42; N, 2.79. Found: C, 62.09; H, 6.58; N, 2.61.

4-Lactoyloxy-1-methyl-1-(2,2-diphenyl-1,3-dioxolan-4-ylmethyl)piperidinium Bromide (*trans*-2i)——^{1}H-NMR (CD_3OD): 1.36 (3H, d, J=7 Hz, C–CH_3), 3.28 (3H, s, N–CH_3), 4.32 (1H, q, J=7 Hz, CHCOO), 5.05 (1H, m, C_4–H of the piperidine), 7.40 (10H, m, Ph×2). IR ν_{max}^{KBr} cm^{-1}: 3350 (OH), 1735 (C=O). *Anal.* Calcd for $C_{25}H_{32}BrNO_5$: C, 59.29; H, 6.37; N, 2.77. Found: C, 59.51; H, 6.31; N, 2.86. Pure *cis*-**2i** could not be obtained; the product was contaminated with *trans*-**2i**.

1-Methyl-1-(2,2-diphenyl-1,3-dioxolan-4-ylmethyl)-4-propanoyloxypiperidinium Bromide (*trans*- and *cis*-2j)——*trans*-**2j**: ^{1}H-NMR (CD_3OD): 1.12 (3H, t, J=7.2 Hz, $CH_2C\underline{H}_3$), 2.40 (2H, q, J=7.2 Hz, C$\underline{H}_2$CH$_3$), 3.33 (3H, s, N–CH_3), 4.95 (1H, m, C_4–H of the piperidine), 7.40 (10H, m, Ph×2). IR ν_{max}^{KBr} cm^{-1}: 1725 (C=O). *Anal.* Calcd for $C_{25}H_{32}BrNO_4$: C, 61.23; H, 6.58; N, 2.86. Found: C, 61.39; H, 6.53; N, 3.05. *cis*-**2j**: ^{1}H-NMR (CD_3OD): 1.12 (3H, t, J=7.2 Hz, $CH_2C\underline{H}_3$), 2.37 (2H, q, J=7.2 Hz, C$\underline{H}_2$CH$_3$), 3.36 (3H, s, N–CH_3), 5.00 (1H, m, C_4–H of the piperidine), 7.40 (10H, m, Ph×2). IR ν_{max}^{KBr} cm^{-1}: 1728 (C=O). *Anal.* Calcd for $C_{25}H_{32}BrNO_4$: C, 61.23; H, 6.58; N, 2.86. Found: C, 61.15; H, 6.72; N, 2.91.

4-Benziloyloxy-1-methyl-1-(2-methyl-2-phenyl-1,3-dioxolan-4-ylmethyl)piperidinium Bromide (*trans*- and *cis*-2k-A; *trans*- and *cis*-2k-B)——1) *trans* and *cis*-**2k**-A: The resulting mixture was chromatographed on silica gel with a mixture of dichloromethane and acetonitrile (5:1) to give *trans*- and *cis*-**2k**-A as the first and second fractions, respectively. Each compound was crystallized from a mixture of acetone and cyclohexane and obtained as colorless needles. *trans*-**2k**-A: ^{1}H-NMR (CD_3OD): 1.59 (3H, s, CH_3), 3.11 (3H, s, N–CH_3), 5.16 (1H, m, C_4–H of the piperidine), 7.42 (15H, m, Ph×3). IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1730 (C=O). *Anal.* Calcd for $C_{31}H_{36}BrNO_5$: C, 63.92; H, 6.23; N, 2.40. Found: C, 64.01; H, 6.21; N, 2.47. *cis*-**2k**-A: ^{1}H-NMR (CD_3OD): 1.59 (3H, s, CH_3), 3.23 (3H, s, N–CH_3), 5.20 (1H, m, C_4–H of the piperidine), 7.42 (15H, m, Ph×3). IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1728 (C=O). *Anal.* Calcd for $C_{31}H_{36}BrNO_5$: C, 63.92; H, 6.23; N, 2.40. Found: C, 63.79; H, 6.51; N, 2.23.

2) *trans*- and *cis*-**2k**-B: A mixture of diastereoisomers (*trans*- and *cis*-**2k**-B) was treated according to the procedure described above and obtained as colorless needles. *trans*-**2k**-B: ^{1}H-NMR (CD_3OD): 1.63 (3H, s, CH_3),

3.13 (3H, s, N–CH_3), 5.20 (1H, m, C_4–H of the piperidine), 7.48 (15H, m, Ph×3). IR ν_{max}^{KBr} cm^{-1}: 3360 (OH), 1740 (C=O). *Anal.* Calcd for $C_{31}H_{36}BrNO_5$: C, 63.92; H, 6.23; N, 2.40. Found: C, 63.88; H, 6.50; N, 2.31. *cis*-**2k**-B: ^{1}H-NMR (CD_3OD): 1.63 (3H, s, CH_3), 3.23 (3H, s, N–CH_3), 5.18 (1H, m, C_4–H of the piperidine), 7.48 (15H, m, Ph×3). IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1740 (C=O). *Anal.* Calcd for $C_{31}H_{36}BrNO_5$: C, 63.92; H, 6.23; N, 2.40. Found: C, 63.75; H, 6.48; N, 2.27. Each diastereoisomer (*trans*- and *cis*-**2k**-A, *trans*- and *cis*-**2k**-B) could be obtained separately by means of crystallization.

General Procedure for the Preparation of 4-Acyloxy-1-(1,3-dioxolan-4-ylmethyl)-1-methylpiperidinium Chloride (2l—n)——After quaternization of 4-acyloxy-1-(1,3-dioxolan-4-ylmethyl)piperidine (0.01 mol) with methyl bromide (1.5 ml) in acetonitrile (30 ml), the reaction mixture was worked up according to the procedure described above. The mixture of the diastereoisomers of the bromide obtained was treated with AgCl (0.012 mol) in EtOH, affording the corresponding chloride quantitatively. Then, the mixture was separated into each diastereoisomer (*trans* and *cis*) in the same manner as mentioned above.

4-Benziloyloxy-1-(2,2-diethyl-1,3-dioxolan-4-ylmethyl)-1-methylpiperidinium Chloride (*trans*- and *cis*-2l)——*trans*-**2l**: ^{1}H-NMR (CD_3OD): 0.87 (6H, t, J=8 Hz, CH_3×2), 1.65 (2H, q, J=8 Hz, $C\underline{H}_2CH_3$), 1.68 (2H, q, J=8 Hz, $C\underline{H}_2CH_3$), 3.08 (3H, s, N–CH_3), 5.15 (1H, m, C_4–H of the piperidine), 7.39 (10H, m, Ph×2). IR ν_{max}^{KBr} cm^{-1}: 3380 (OH), 1730 (C=O). *Anal.* Calcd for $C_{28}H_{38}ClNO_5 \cdot H_2O$: C, 64.42; H, 7.72; N, 2.68. Found: C, 65.31; H, 7.98; N, 2.77.

cis-**2l**: ^{1}H-NMR (CD_3OD): 0.87 (6H, t, J=8 Hz, CH_3×2), 1.63 (2H, q, J=8 Hz, $C\underline{H}_2CH_3$), 1.66 (2H, q, J=8 Hz, $C\underline{H}_2CH_3$), 3.20 (3H, s, N–CH_3), 5.18 (1H, m, C_4–H of the piperidine), 7.39 (10H, m, Ph×2). IR ν_{max}^{KBr} cm^{-1}: 3205 (OH), 1730 (C=O). *Anal.* Calcd for $C_{28}H_{38}ClNO_5$: C, 66.72; H, 7.60; N, 2.78. Found: C, 66.68; H, 7.71; N, 2.60.

4-Benziloyloxy-1-(2,2-diisopropyl-1,3-dioxolan-4-ylmethyl)-1-methylpiperidinium Chloride (*trans*- and *cis*-2m)——*trans*-**2m**: ^{1}H-NMR (CD_3OD): 0.93 (12H, d, J=7 Hz, CH_3×4), 2.08 (2H, m, $C\underline{H}(CH_3)_2$×2), 3.12 (3H, s, N–CH_3), 5.16 (1H, m, C_4–H of the piperidine), 7.38 (10H, m, Ph×2). IR ν_{max}^{KBr} cm^{-1}: 3380 (OH), 1725 (C=O). *Anal.* Calcd for $C_{30}H_{42}ClNO_5 \cdot H_2O$: C, 65.50; H, 8.06; N, 2.55. Found: C, 65.37; H, 8.21; N, 2.48. *cis*-**2m**: ^{1}H-NMR (CD_3OD): 0.93 (12H, d, J=7 Hz, CH_3×4), 2.08 (2H, m, $C\underline{H}(CH_3)_2$×2), 3.23 (3H, s, N–CH_3), 5.20 (1H, m, C_4–H of the piperidine), 7.37 (10H, m, Ph×2). IR ν_{max}^{KBr} cm^{-1}: 3250 (OH), 1725 (C=O). *Anal.* Calcd for $C_{30}H_{42}ClNO_5$: C, 67.72; H, 7.96; N, 2.63. Found: C, 67.70; H, 8.01; N, 2.68.

1-Methyl-1-(2,2-dimethyl-1,3-dioxolan-4-ylmethyl)-4-(diphenylacetoxy)piperidinium Chloride (*trans*- and *cis*-2n)——*trans*-**2n**: ^{1}H-NMR (CD_3OD): 1.37 (3H, s, CH_3), 1.43 (3H, s, CH_3), 3.13 (3H, s, N–CH_3), 5.11 (1H, m, C_4–H of the piperidine), 5.21 (1H, s, CHCOO), 7.31 (10H, s, Ph×2). IR ν_{max}^{KBr} cm^{-1}: 1725 (C=O). *Anal.* Calcd for $C_{26}H_{34}ClNO_4$: C, 67.79; H, 7.45; N, 3.04. Found: C, 67.54; H, 7.53; N, 3.10.

cis-**2n**: ^{1}H-NMR (CD_3OD): 1.37 (3H, s, CH_3), 1.43 (3H, s, CH_3), 3.22 (3H, s, N–CH_3), 5.15 (1H, m, C_4–H of the piperidine), 5.20 (1H, s, CHCOO), 7.35 (10H, s, Ph×2). IR ν_{max}^{KBr} cm^{-1}: 1725 (C=O). *Anal.* Calcd for $C_{26}H_{34}ClNO_4$: C, 67.79; H, 7.45; N, 3.04. Found: C, 67.81; H, 7.39; N, 3.16.

A Diastereoisomeric Mixture of 4-Acyloxy-1-(1,3-dioxolan-4-ylmethyl)-1-methylpiperidinium Chloride (2o) and Bromide (2p—t)——In the manner described for the general procedure, each compound (**2o—t**) was obtained as a diastereoisomeric mixture, in nearly 1:1 ratio. Since clear separation into each diastereoisomer (*trans* and *cis*) by means of crystallization was not successful, the mixture of the isomers was used in each case to test for anticholinergic activity.

3-Benziloyloxy-1-methyl-1-(2,2-dimethyl-1,3-dioxolan-4-ylmethyl)piperidinium Bromide (*trans*-BMP)——In the manner described for the general procedure, the *trans* and *cis* isomers of BMP were obtained in a ratio of 83 (δ 3.03, s, N–CH_3): 17 (δ 3.15, s, N–CH_3). *trans*-BMP was obtained in 73.5% yield. mp 228.8—229.6 °C. IR ν_{max}^{KBr} cm^{-1}: 3350 (OH), 1745 (C=O). *Anal.* Calcd for $C_{26}H_{34}BrNO_5$: C, 60.00; H, 6.58; N, 2.69. Found: C, 60.21; H, 6.31; N, 2.61.

Synthesis of 4-Benziloyloxy-1-trideuteriomethyl-1-methylpiperidinium Bromide (*trans*- and *cis*-3)——A solution of 4-benziloyloxy-1-methylpiperidine (325 mg, 1 mmol) and trideuteriomethyl bromide (0.5 ml) in acetonitrile (5 ml) was allowed to stand at room temperature for 15 h, then concentrated *in vacuo*. The residue was washed with dry ether (10 ml×2) to give a mixture of *trans*- and *cis*-**3** (402 mg) in 95.7% yield. From the relative intensity of the N-methyl signals in the ^{1}H-NMR spectrum, its composition was determined to be approximately *trans*-**3** (60%) and *cis*-**3** (40%).

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