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Studies on Spasmolytics. III.[1] Synthesis and Anticholinergic Activity of 4-Acyloxy-1-(1,3-dioxolan-2-ylmethyl)piperidines and Their Quaternary Salts[2]

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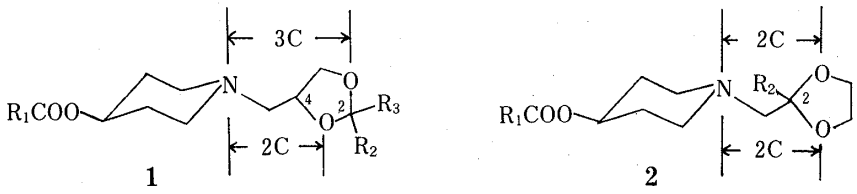
Twenty-one derivatives of 4-acyloxy-1-(1,3-dioxolan-2-ylmethyl)piperidines (**2**) and their quaternary salts (**6**) were synthesized and tested for anticholinergic activities. The piperidine derivatives (**2**) exhibit moderate activities. Among the quaternary salts (**6**), the *trans*-isomers were always more active than the corresponding *cis*-isomers.

Keywords——drug design; 4-acyloxy-1-(1,3-dioxolan-2-ylmethyl)piperidine; quaternization; 4-acyloxy-1-alkyl-1-(1,3-dioxolan-2-ylmethyl)piperidinium salt; diastereoisomer; anticholinergic activity; structure–activity relationship

In previous papers,[1,3] we showed that 4-acyloxy-1-(1,3-dioxolan-4-ylmethyl)piperidines (**1**) and their diastereoisomeric quaternary salts exhibit potent papaverine-like and atropine-like (anticholinergic) activities. Among the quaternary salts, the *trans*-isomers in which both the *N*-substituent and 4-acyloxy (RCOO) group are equatorial showed greater activity than the corresponding *cis*-isomers. In addition, the *trans*-isomer of 4-benziloyloxy-1-(2,2-dimethyl-1,3-dioxolan-4-ylmethyl)-1-methylpiperidinium bromide was more active than the *cis*-isomer of the 3-benziloyloxy derivative. These results suggest that a suitable distance between the nitrogen and oxygen atoms on the piperidine ring is required for activity.[1,4]

Kier[5] clarified that both nitrogen and oxygen in the muscarine molecule are necessary for binding with the muscarinic receptor and estimated their separation to be 3.2 Å on the basis of extended Hückel calculations. Ariëns[6] showed that similar sites exist in the acetylcholine receptor.

Thus, we sought to synthesize 4-acyloxy-1-(1,3-dioxolan-2-ylmethyl)piperidines (**2**), since these compounds each have two equal nitrogen–oxygen separations (2.5—3.5 Å)[7] in the same molecule (Chart 1). This report describes the synthesis, anticholinergic activity, and structure–activity relationship of the compounds **2** and their quaternary salts (**6**).



2C and 3C represent the numbers of carbon atoms between nitrogen and oxygen.

Chart 1. Structures of Compounds **1** and **2**

Results and Discussion

Synthesis of 4-Acyloxy-1-(1,3-dioxolan-2-ylmethyl)piperidine (2a—k)

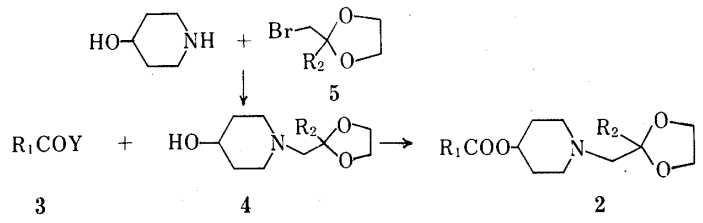
The desired compounds (**2**) were synthesized by alkylation of 4-piperidinol with 2-bromomethyl-1,3-dioxolanes (**5**)[8,9] followed by esterification in a manner similar to that described in previous papers[3,10] (Chart 2).

However, **2i** was obtained by direct acylation with 3-phenylpropionyl chloride. Since the products (**2**) were usually oily materials, they were characterized as the crystalline hydrochlorides or oxalates. The yields and melting points are listed in Table I.

TABLE I. Yields and Melting Points of 4-Acyloxy-1-(1,3-dioxolan-2-ylmethyl)piperidines (**2**)

Compd. **2**	mp (°C)	Yield[a] (%)	R_1COY (**3**) Y
2a	189—190 (HCl)	94.1	OMe
2b	Amorphous	75.5[b]	OMe
2c	159—160 (HCl)	95.4	OMe
2d	207—208 (HCl)	92.3	OMe
2e	205—206 (HCl)	90.8	OMe
2f	103—105 (Oxalate)	86.9	OEt
2g	Amorphous	82.1[b]	OEt
2h	72—73	84.1	OEt
2i	138—139 (HCl)	87.2	Cl
2j	119—121 (Oxalate)	93.1	OEt
2k	158—161 (Oxalate)	79.1	OMe

a) Isolated yield.
b) Isolated by silica-gel column chromatography.



3 **4** **2**

Y=OMe or OEt **4a** and **5a**: R_2=H
4b and **5b**: R_2=Me

Compd.	R_1	R_2
2a	$Ph_2C(OH)$	H
2b	$Ph_2C(OH)$	Me
2c	9-xanthenyl	H
2d	9-xanthenyl	Me
2e	PhC(c-Hex)(OH)	H
2f	PhC(Th)(OEt)	H
2g	$Th_2C(OH)$	H
2h	4-Cl-$PhCH_2$	H
2i	$PhCH_2CH_2$	H
2j	4-iso-BuPhCH(CH_3)	H
2k	(c-pentyl)$_2$CH	H

Chart 2

c-Hex=cyclohexyl; Th=thien-2-yl.

Quaternization and Stereochemistry of 4-Acyloxy-1-alkyl-1-(1,3-dioxolan-2-ylmethyl)-piperidinium Salts (6a—g)

The quaternization of **2** was achieved by using methyl bromide in acetonitrile at room

temperature in nearly quantitative yield. As reported in the preceding paper,[1] the resulting piperidinium salts (**6**) were a mixture of two diastereoisomers due to *cis–trans* isomerism involving tetravalent nitrogen and the C-4 substituent (Chart 3). The mixture was easily separated by fractional crystallizations.

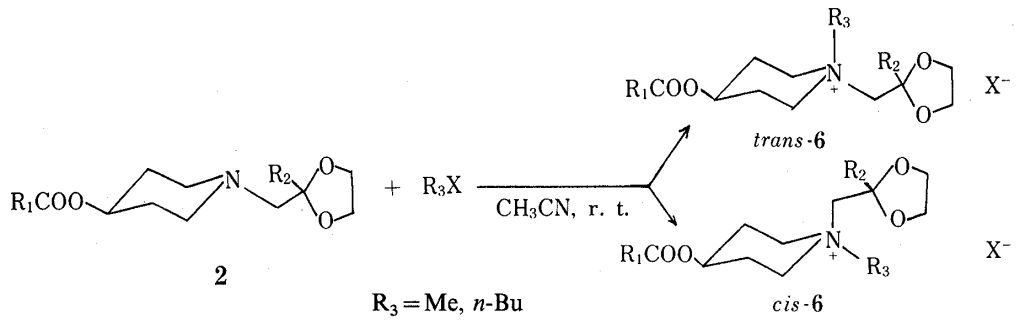


Chart 3

Compd.	R_1	R_2	R_3	X
6a1	$Ph_2C(OH)$	H	Me	Br
6a2	$Ph_2C(OH)$	H	Me	Cl[a]
6a3	$Ph_2C(OH)$	H	Me	$MeSO_4$
6a4	$Ph_2C(OH)$	H	*n*-Bu	Br
6b	$Ph_2C(OH)$	Me	Me	Br
6c	9-xanthenyl	H	Me	Br
6d	9-xanthenyl	Me	Me	Br
6e	PhC(c-Hex)(OH)	H	Me	Br
6f	PhC(Th)(OEt)	H	Me	Br
6g	$Th_2C(OH)$	H	Me	Br

a) Chloride prepared by exchange reaction of the bromide (**6a1**) with chloride anion.
c-Hex = cyclohexyl, Th = thien-2-yl.

The ratios of the two isomers (**6**) were determined to be approximately 1 : 1 by comparison of the relative intensity of N–CH_3 signals in the proton nuclear magnetic resonance (^{1}H-NMR) spectra of the crude product before separation, showing that the stereoselectivity in the quaternization of **2** is low.[1] The configuration of N–CH_3 was elucidated on the basis of the fact that axial N–CH_3 hydrogens in *N*-methylpiperidinium derivatives usually resonate at higher field than equatorial ones[11] assuming that the 4-acyloxy group always takes the equatorial orientation.[1,12] The fact that the C_4-proton in both *trans*- and *cis*-**6** appeared at 4.99—5.20 ppm as a multiplet (half-width[12a] 18—24 Hz) supported this assumption.[13] The yields, melting points and ^{1}H-NMR spectral data of **6** are summarized in Table II.

Pharmacology

The four compounds **2a**, **2c**, **2d**, and **2e** were tested for spasmolytic activities by the Magnus method using isolated ileum from guinea pigs. The competitive antagonistic activities of these compounds were expressed as the pA_2 values calculated from the shift of the concentration–action curve of acetylcholine.[14,15] As shown in Table III, they all had potent anticholinergic activities.

In contrast to compounds (**1**), which exhibited significant papaverine-like activity,[3] compounds (**2**) did not show this activity. This difference in the activities may be attributed to the difference of binding ability with the receptor. The symmetrical arrangement of two similar oxygen atoms of the dioxolane ring of **2** might assist binding to the acetylcholine receptor. In contrast, the bulky substituents on the dioxolane ring in compound (**1**) may

TABLE II. Chemical Shifts of the N-Methyl Signal in ^{1}H-NMR Spectra, Yields and Melting Points of the *trans*- and *cis*-Isomers of 4-Acyloxy-1-(1,3-dioxolan-2-ylmethyl)-1-methylpiperidinium Bromides (**6**)

Compd. **6**	Quaternization yield[a] (%)	*trans*-Isomer			*cis*-Isomer		
		Yield[b] (%)	mp (°C)	Chemical shift (δ ppm, in CD_3OD)	Yield[b] (%)	mp (°C)	Chemical shift (δ ppm, in CD_3OD)
6a1	95.6	44.0	222—223	3.12	38.5	203—204	3.20
6a2[c]			223—224	3.11	—[d]		
6a3	90.3	40.3	160—162	3.11	31.6	Amorphous	3.19
6a4[e]	75.5	35.8	194—197	—[f]	31.1	219—220	—[f]
6b	93.2	44.4	226—227	3.13	34.4	216—218	3.21
6c	91.7	40.6	206—207	3.18	35.9	199—200	3.19
6d	91.6	29.7	238—239	3.20	—[g]		3.25[h]
6e	88.4	35.6	228—229	3.22	30.0	203—205	3.28
6f	87.9	42.8	209—211	3.15	43.0	208—209	3.25
6g	95.3	39.9	220—221	3.22	—[g]		3.29[h]

a) Isolated yield as a mixture of diastereoisomers (*trans*- and *cis*-**6**).
b) Yield of pure isomer (*trans*- and *cis*-**6**).
c) Chloride prepared from the exchange reaction of the bromide of *trans*-**6a1** with chloride anion.
d) Not prepared.
e) 1-Butylpiperidinium compound.
f) The signal of N–$CH_2CH_2CH_2CH_3$ was ill-defined.
g) Not isolated.
h) The N-methyl signal of the *cis*-isomer in the diastereoisomeric mixture before separation.

TABLE III. Anticholinergic Activities of 4-Acyloxy-1-(1,3-dioxolan-2-ylmethyl)piperidines (**2**)

Compd. **2**	Anticholinergic activity
	pA_2
2a	8.24
2c	7.74
2d	7.48
2e	7.36
Atropine sulfate	9.26

reduce the ability of the compound to approach the acetylcholine receptor site, thus leaving only papaverine-like activity.

The *trans*- and *cis*-isomers of **6** were similarly tested for anticholinergic activities. The *trans*-isomers usually showed higher activities, as shown in Table IV.

Among them, the activities of the *trans*-isomers **6c**, **6e** and **6g** were equal to or greater than that of atropine. Their anticholinergic activities were the strongest among compounds so far synthesized. These compounds have a compact dioxolane ring and a flat conformation. Their binding to the receptor might be stronger than that of the *trans*-isomer of the quaternary salt of **1**.

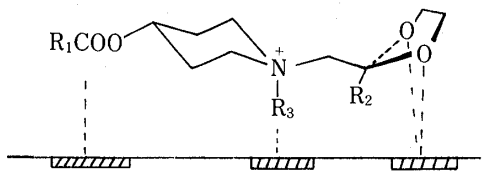
The binding sites for the quaternary nitrogen and for the acetoxy group are called the anionic site and the esteratic site, respectively.[6] Here, we tentatively designate the site at which two oxygen atoms of the dioxolane ring equally bind the receptor as the "cationic site." Therefore, a suitable conformation model for the *trans*-isomer (**6**) binding with the receptor

TABLE IV. Anticholinergic Activities of 4-Acyloxy-1-(1,3-dioxolan-2-ylmethyl)-1-methylpiperidinium Bromides (**6**)

Compd. **6**	Anticholinergic activity (pA_2)	
	trans-Isomer	*cis*-Isomer
6a1	8.80	6.98
6a2[a]	8.98	—[b]
6a3[c]	8.70	—[d]
6a4[e]	5.75	5.13
6b	8.92	6.84
6c	9.40	7.53
6d	8.69	—[f]
6e	9.15	—[d]
6f	6.18	5.34
6g	9.41	—[f]
Atropine methobromide	9.28	

a) Chloride.
b) Not prepared.
c) Methylsulfate.
d) Not tested.
e) 1-Butylpiperidinium compound.
f) Not obtained as the pure isomer.

trans-**6**



esteratic site anionic site cationic site

Chart 4

may be as illustrated in Chart 4.

The present studies on the structure–activity relationship of **6** led to the following results.

1) The *trans*-isomer of **6a4** (R_3 = *n*-Bu) showed activity approximately 10^{-3} times weaker than those of **6a1**, **6a2** and **6a3** ($R_3 = CH_3$) because of the increase of steric hindrance to binding to an anionic site of the receptor.

2) The activity of the ethyl ether (*trans*-**6f**) was low. This may be due to hindrance of the approach of the phenyl and thienyl groups to the receptor by the presence of the ethyl group.

3) The *trans*-isomers (**6**) were more active than the corresponding *cis*-isomers (**6**). For example, the *trans*-isomer of **6c** was 62 times more potent than *cis*-**6c**.[16]

4) The difference of activities between the compounds with H and CH_3 groups as R_2 was negligible.

5) Change of the çounter anions, *e.g.* Cl^- (*trans*-**6a1**), Br^- (*trans*-**6a2**) and $CH_3SO_4^-$ (*trans*-**6a3**), had no effect on the potency.

Experimental

All melting points are uncorrected. Infrared (IR) spectra were recorded with a JASCO IRA-1 spectrophotom-

eter and mass spectra (MS) were determined on a Hitachi RM-50 spectrometer. ^{1}H-NMR spectra were taken on 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; br, broad. For column chromatography, silica gel (Wako gel, C-200) was used.

2-Bromomethyl-2-methyl-1,3-dioxolane (5b)——This compound was prepared by the known procedure.[8] A colorless oil, bp_7 57—58 °C (lit.[8] bp_{18} 73—74 °C). ^{1}H-NMR ($CDCl_3$): 1.50 (3H, s, CH_3), 3.41 (2H, s, $BrCH_2$), 4.01 (4H, s, OCH_2CH_2O). MS *m/e*: 182, 180 (M^+, 1 : 1).

2-Bromomethyl-1,3-dioxolane (5a)——Compound **5a** was obtained similarly. A colorless oil, bp_{14} 67 °C (lit.,[9] bp_{15} 68—71 °C). MS *m/e* 168, 166 (M^+, 1 : 1).

1-(1,3-Dioxolan-2-ylmethyl)-4-piperidinol (4a)——A solution of **5a** (5 g, 0.04 mol) and 4-piperidinol (4.1 g, 0.04 mol) in acetonitrile (50 ml) was refluxed for 15 h in the presence of potassium carbonate (5.5 g, 0.04 mol). After cooling, the reaction mixture was filtered and concentrated *in vacuo*. The residue was dissolved in dichloromethane (50 ml) and the solution was washed with water (20 ml × 2), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The product was distilled under reduced pressure to yield 6.3 g (83.5%) of **4a** as a colorless oil, bp_8 143 °C. ^{1}H-NMR ($CDCl_3$): 3.62 (1H, m, C_4–H of the piperidine), 3.86 (4H, d-like, OCH_2CH_2O), 4.95 (1H, t, J=4.5 Hz, C_2–H of the dioxolane). IR ν_{max}^{film} cm^{-1}: 3350 (OH), 1130, 1070. MS *m/e*: 186 ($M^+ - H$), 114 (base peak), 72. The oxalate formed colorless needles from acetone, mp 126 °C. *Anal.* Calcd for $C_{11}H_{19}NO_7$: C, 47.65; H, 6.91; N, 5.05. Found: C, 47.53; H, 6.75; N, 5.21.

1-(2-Methyl-1,3-dioxolan-2-ylmethyl)-4-piperidinol (4b)——Compound **4b** was prepared in the same manner as described for **4a** in 47% yield as a colorless oil, bp_7 148—149 °C. ^{1}H-NMR ($CDCl_3$): 1.35 (3H, s, CH_3), 2.40 (2H, s, $N\text{–}CH_2\underset{CH_3}{\overset{}{C}}<$), 3.60 (1H, m, C_4–H of the piperidine), 3.94 (4H, s, OCH_2CH_2O). IR ν_{max}^{film} cm^{-1}: 3350 (OH), 1070, 1045.

MS *m/e*: 201 (M^+), 186 ($M^+ - CH_3$), 114 (base peak), 72.

General Procedure for the Preparation of 4-Acyloxy-1-(1,3-dioxolan-2-ylmethyl)piperidines (2a—h, 2j and 2k)

Sodium hydride (50% oil suspension, 830 mg, 0.017 mol) was added to 1-(1,3-dioxolan-2-ylmethyl)-4-piperidinol (**4a**; 0.173 mol) or 1-(2-methyl-1,3-dioxolan-2-ylmethyl)-4-piperidinol (**4b**; 0.173 mol) with stirring, and the reaction mixture was heated at 80 °C for 30 min *in vacuo*. Then, methyl or ethyl ester (**3**; 0.19 mol) was added to the reaction mixture, and MeOH generated was removed *in vacuo* for 3 h. Dichloromethane (300 ml) was added to the residue and the solution was washed with water (80 ml × 2), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The resulting product was usually converted into the oxalate or hydrochloride using oxalic acid or pyridine hydrochloride (0.164 mol) in EtOH. Thus, the salts of **2a**, **2c—f**, **2j** and **2k** were obtained in 79.1—95.4% yields as colorless needles. The other compounds (**2b** and **2g**) were chromatographed on silica-gel (CH_2Cl_2 : MeOH = 9 : 1) to afford colorless oils in 75.5 and 82.1% yields, respectively, while the free base of **2h** was directly crystallized from cyclohexane, giving colorless needles in 84.1% yield.

4-Benziloyloxy-1-(1,3-dioxolan-2-ylmethyl)piperidine (2a)——^{1}H-NMR (CD_3OD): 4.00 (4H, m, OCH_2CH_2O), 5.20 (1H, m, C_4–H of the piperidine), 5.25 (1H, t, J=4.5 Hz, C_2–H of the dioxolane), 7.10—7.60 (10H, m, Ph × 2). IR ν_{max}^{KBr} cm^{-1}: 3300 (OH), 1730 (C=O). MS *m/e*: 397 (M^+), 324 (base peak), 183, 114, 105, 98, 77. *Anal.* Calcd for $C_{23}H_{27}NO_5 \cdot HCl$: C, 63.66; H, 6.50; N, 3.23. Found: C, 63.39; H, 6.42; N, 3.37.

4-Benziloyloxy-1-(2-methyl-1,3-dioxolan-2-ylmethyl)piperidine (2b)——Free base. ^{1}H-NMR ($CDCl_3$): 1.28 (3H, s, CH_3), 2.21 (1H, s, OH, disappeared with D_2O), 3.80 (4H, m, OCH_2CH_2O), 4.90 (1H, m, C_4–H of the piperidine), 7.10—7.55 (10H, m, Ph × 2). IR ν_{max}^{film} cm^{-1}: 3350 (OH), 1725 (C=O). MS *m/e*: 411 (M^+), 396 ($M^+ - CH_3$), 324 (base peak), 183, 114, 105, 77.

1-(1,3-Dioxolan-2-ylmethyl)-4-(xanthene-9-carbonyloxy)piperidine (2c)——^{1}H-NMR ($CDCl_3$): 3.93 (4H, m, OCH_2CH_2O), 4.89 (1H, m, C_4–H of the piperidine), 4.92 (1H, s, =CHCOO), 5.40 (1H, t, J=4.5 Hz, C_2–H of the dioxolane), 7.00—7.40 (8H, m, aromatic). IR ν_{max}^{KBr} cm^{-1}: 1725 (C=O). MS *m/e*: 395 (M^+), 322 (base peak), 181. *Anal.* Calcd for $C_{23}H_{25}NO_5 \cdot HCl$: C, 63.96; H, 6.07; N, 3.24. Found: C, 64.07; H, 6.01; N, 3.39.

1-(2-Methyl-1,3-dioxolan-2-ylmethyl)-4-(xanthene-9-carbonyloxy)piperidine (2d)——^{1}H-NMR (CD_3OD): 1.35 (3H, s, CH_3), 1.80—2.18 (4H, m, $C_{3,5}$–H of the piperidine), 3.35 (6H, m, N–CH_2 × 3), 4.05 (4H, s, OCH_2CH_2O), 4.74 (1H, m, C_4–H of the piperidine), 5.08 (1H, s, =CHCOO), 7.00—7.50 (8H, m, aromatic). IR ν_{max}^{KBr} cm^{-1}: 1730 (C=O). MS *m/e*: 409 (M^+), 322 (base peak), 181. *Anal.* Calcd for $C_{24}H_{27}NO_5 \cdot HCl$: C, 64.64; H, 6.33; N, 3.14. Found: C, 64.59; H, 6.48; N, 3.01.

4-(α-Cyclohexyl-α-phenylglycoloyloxy)-1-(1,3-dioxolan-2-ylmethyl)piperidine (2e)——^{1}H-NMR (CD_3OD): 0.95—1.70 (11H, m, c-Hex), 1.85—2.30 (4H, m, $C_{3,5}$–H of the piperidine), 3.35 (6H, m, N–CH_2 × 3), 4.00 (4H, m, OCH_2CH_2O), 5.05 (1H, m, C_4–H of the piperidine), 5.28 (1H, t, J=4.5 Hz, C_2–H of the dioxolane), 7.15—7.80 (5H, m, Ph). IR ν_{max}^{KBr} cm^{-1}: 3360 (OH), 1720 (C=O). MS *m/e*: 403 (M^+), 330 (base peak), 189, 114, 98, 96, 77. *Anal.* Calcd for $C_{23}H_{33}NO_5 \cdot HCl$: C, 62.79; H, 7.79; N, 3.18. Found: C, 62.71; H, 7.95; N, 3.06.

1-(1,3-Dioxolan-2-ylmethyl)-4-[α-ethoxy-α-phenyl-α-(thien-2-yl)acetoxy]piperidine (2f)——Free base. ^{1}H-NMR ($CDCl_3$): 1.22 (3H, t, J=7 Hz, CH_3), 3.39 (2H, q, J=7 Hz, CH_2CH_3), 3.82 (4H, m, OCH_2CH_2O), 4.85 (1H, m, C_4–H of the piperidine), 4.88 (1H, t, J=4.5 Hz, C_2–H of the dioxolane), 6.80—7.60 (8H, m, aromatic). IR ν_{max}^{film} cm^{-1}: 1725 (C=O). MS *m/e*: 431 (M^+), 430, 358 (base peak), 217, 188, 114, 98, 96, 77. *Anal.* Calcd for $C_{23}H_{29}NO_5S \cdot$oxalate: C,

57.57; H, 5.99; N, 2.69. Found: C, 57.49; H, 6.11; N, 2.72.

1-(1,3-Dioxolan-2-ylmethyl)-4-[α,α-di(thien-2-yl)glycoloyloxy]piperidine (2g)——Free base. ^{1}H-NMR ($CDCl_3$): 3.86 (4H, m, OCH_2CH_2O), 4.78 (1H, m, C_4–H of the piperidine), 4.95 (1H, t, J=4.5 Hz, C_2–H of the dioxolane), 6.80—7.30 (6H, m, aromatic). IR ν_{max}^{film} cm^{-1}: 3400 (OH), 1730 (C=O). MS *m/e*: 409 (M^+), 336 (base peak), 195, 194, 96, 83.

4-(4-Chlorophenylacetoxy)-1-(1,3-dioxolan-2-ylmethyl)piperidine (2h)——Free base. ^{1}H-NMR ($CDCl_3$): 3.58 (2H, s, CH_2COO), 3.90 (4H, m, OCH_2CH_2O), 4.80 (1H, m, C_4–H of the piperidine), 4.98 (1H, t, J=4.5 Hz, C_2–H of the dioxolane), 7.25 (4H, s, aromatic). IR ν_{max}^{KBr} cm^{-1}: 1725 (C=O). MS *m/e*: 340, 338 (M^+, 1 : 3), 267, 265 (base peak), 126, 124, 114, 96. *Anal.* Calcd for $C_{17}H_{22}ClNO_4$: C, 60.09; H, 6.53; N, 4.12. Found: C, 59.83; H, 6.71; N, 4.01.

1-(1,3-Dioxolan-2-ylmethyl)-4-[2-(4-isobutylphenyl)propionyloxy]piperidine (2j)——Free base. ^{1}H-NMR ($CDCl_3$): 0.85 (6H, d, J=6 Hz, $CH(CH_3)_2$), 1.45 (3H, d, J=7 Hz, $CHCH_3$), 2.20 (1H, m, $CHCH_2C_6H_4$), 2.42 (2H, d, J=6 Hz, $CH_2C_6H_4$), 3.83 (4H, m, OCH_2CH_2O), 4.71 (1H, m, C_4–H of the piperidine), 4.88 (1H, t, J=4.5 Hz, C_2–H of the dioxolane), 6.87—7.28 (4H, m, aromatic). IR ν_{max}^{film} cm^{-1}: 1725 (C=O). MS *m/e*: 375 (M^+), 302 (base peak), 161, 114, 98, 96. *Anal.* Calcd for $C_{22}H_{33}NO_4$·oxalate: C, 61.92; H, 7.58; N, 3.01. Found: C, 62.06; H, 7.69; N, 2.89.

4-Dicyclopentylacetoxy-1-(1,3-dioxolan-2-ylmethyl)piperidine (2k)——^{1}H-NMR (CD_3OD): 1.52 (18H, br s, dicyclopentyl), 3.92 (4H, m, OCH_2CH_2O), 4.92 (1H, m, C_4–H of the piperidine), 5.18 (1H, t, J=4.5 Hz, C_2–H of the dioxolane). IR ν_{max}^{KBr} cm^{-1}: 1720 (C=O). MS *m/e*: 365 (M^+), 292 (base peak), 151, 114, 96. *Anal.* Calcd for $C_{21}H_{35}NO_4$·oxalate: C, 60.64; H, 8.19; N, 3.07. Found: C, 60.49; H, 8.32; N, 3.01.

1-(1,3-Dioxolan-2-ylmethyl)-4-(3-phenylpropionyloxy)piperidine (2i)——3-Phenylpropionyl chloride (843 mg, 0.005 mol) dissolved in dichloromethane (10 ml) was added to a solution of **4a** (950 mg, 0.005 mol) in dichloromethane (20 ml) at room temperature and the mixture was stirred for 30 min. Then 10% K_2CO_3 (10 ml) was added, and the reaction mixture was washed with water (10 ml × 2), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The resulting product was purified by silica-gel column chromatography to afford 1.39 g (87.2%) of **2i** as a colorless oil. Free base. ^{1}H-NMR ($CDCl_3$): 2.54 (2H, t, J=5 Hz, $PhCH_2$), 2.79 (2H, t, J=5 Hz, CH_2COO), 3.78 (4H, m, OCH_2CH_2O), 4.68 (1H, m, C_4–H of the piperidine), 4.88 (1H, t, J=4.5 Hz, C_2–H of the dioxolane), 7.10 (5H, s, Ph). IR ν_{max}^{film} cm^{-1}: 1720 (C=O). MS *m/e*: 319 (M^+), 246 (base peak), 114, 91, 77. *Anal.* Calcd for $C_{18}H_{25}NO_4$·HCl: C, 60.76; H, 7.37; N, 3.94. Found: C, 60.71; H, 7.53, N, 4.02.

General Procedure for the Preparation of 4-Acyloxy-1-(1,3-dioxolan-2-ylmethyl)-1-methylpiperidinium Bromides (6a1 and 6b—g)

A mixture of **2** (0.0018 mol) and methyl bromide (1 ml) in acetonitrile (20 ml) was allowed to stand at room temperature for 12 h followed by concentration *in vacuo*. Then, the mixture of diastereoisomers (*trans* and *cis*) obtained was washed with dry ether (30 ml × 2) and solidified by adding acetonitrile–ether or acetone–ether to give *trans*- and *cis*-**6** in nearly 1 : 1 ratio in 75.5—95.6% yield. The *trans*-isomer of **6** was initially separated by crystallization from acetonitrile or acetone in 29.7—44.4% yield as colorless needles. The *cis*-isomer was then obtained in 30.0—43.0% yield as colorless needles by crystallization of the mother liquor.

4-Benziloyloxy-1-(1,3-dioxolan-2-ylmethyl)-1-methylpiperidinium Bromide (*trans*- and *cis*-6a1)——*trans*-**6a1**: ^{1}H-NMR (CD_3OD): 3.12 (3H, s, N–CH_3), 3.94 (4H, m, OCH_2CH_2O), 5.15 (1H, m, C_4–H of the piperidine), 5.35 (1H, t, J=4.5 Hz, C_2–H of the dioxolane), 7.15—7.50 (10H, m, Ph × 2). IR ν_{max}^{KBr} cm^{-1}: 3240 (OH), 1720 (C=O). *Anal.* Calcd for $C_{24}H_{30}BrNO_4$: C, 58.54; H, 6.14; N, 2.84. Found: C, 58.51; H, 6.23; N, 2.71. *cis*-**6a1**: ^{1}H-NMR (CD_3OD): 3.20 (3H, s, N–CH_3), 3.90 (4H, m, OCH_2CH_2O), 5.20 (1H, m, C_4–H of the piperidine), 5.28 (1H, t, J=4.5 Hz, C_2–H of the dioxolane), 7.10—7.45 (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, 6.23; N, 2.58.

4-Benziloyloxy-1-(2-methyl-1,3-dioxolan-2-ylmethyl)-1-methylpiperidinium Bromide (*trans*- and *cis*-6b)——*trans*-**6b**: ^{1}H-NMR(CD_3OD): 1.35 (3H, s, C–CH_3), 3.13 (3H, s, N–CH_3), 3.77 (2H, s, N–CH_2–$\underset{CH_3}{C}$<), 4.05 (4H, s, OCH_2CH_2O), 5.18 (1H, m, C_4–H of the piperidine), 7.20—7.50 (10H, m, Ph × 2). IR ν_{max}^{KBr} cm^{-1}: 3270 (OH), 1720 (C=O). *Anal.* Calcd for $C_{25}H_{32}BrNO_5$: C, 59.29; H, 6.37; N, 2.77. Found: C, 59.26; H, 6.42; N, 2.55. *cis*-**6b**: ^{1}H-NMR (CD_3OD): 1.35 (3H, s, C–CH_3), 3.21 (3H, s, N–CH_3), 3.51 (2H, N–CH_2–$\underset{CH_3}{C}$<), 3.99 (4H, m, OCH_2CH_2O), 5.14 (1H, m, C_4–H of the piperidine), 7.20—7.50 (10H, m, Ph × 2). IR ν_{max}^{KBr} cm^{-1}: 3280 (OH), 1720 (C=O). *Anal.* Calcd for $C_{25}H_{32}BrNO_5$: C, 59.29; H, 6.37; N, 2.77. Found: C, 59.41; H, 6.18; N, 2.73.

1-(1,3-Dioxolan-2-ylmethyl)-1-methyl-4-(xanthene-9-carbonyloxy)piperidinium Bromide (*trans*- and *cis*-6c)——*trans*-**6c**: ^{1}H-NMR (CD_3OD): 3.18 (3H, s, N–CH_3), 3.95 (4H, m, OCH_2CH_2O), 5.13 (1H, s, =CHCOO), 5.33 (1H, t, J=4.5 Hz, C_2–H of the dioxolane), 6.90—7.55 (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, 5.75; N, 2.86. Found: C, 59.02; H, 5.54; N, 2.79. *cis*-**6c**: ^{1}H-NMR (CD_3OD): 3.19 (3H, s, N–CH_3), 4.00 (4H, m, OCH_2CH_2O), 5.12 (1H, s, =CHCOO), 5.36 (1H, t, J=4.5 Hz, C_2–H of the dioxolane), 6.90—7.55 (8H, m, aromatic). IR ν_{max}^{KBr} cm^{-1}: 1720 (C=O). *Anal.* Calcd for $C_{24}H_{28}BrNO_5$: C, 58.78; H, 5.75; N, 2.86. Found: C, 58.63; H, 5.91; N, 2.82.

1-Methyl-1-(2-methyl-1,3-dioxolan-2-ylmethyl)-4-(xanthene-9-carbonyloxy)piperidinium Bromide (*trans*-6d)——

^{1}H-NMR (CD_3OD): 3.20 (3H, s, N–CH_3), 3.68 (2H, s, N–$C\underline{H}_2$–$\overset{CH_3}{\overset{|}{C}}<$), 4.00 (4H, s, OCH_2CH_2O), 5.10 (1H, s, =CHCOO), 6.95—7.55 (8H, m, aromatic). IR ν_{max}^{KBr} cm^{-1}: 1730 (C=O). *Anal.* Calcd for $C_{25}H_{30}BrNO_5$: C, 59.53; H, 6.00; N, 2.78. Found: C, 59.69; H, 5.87; N, 2.82. The other diastereoisomer (*cis*-**6d**) was not cleanly separated.

4-(α-Cyclohexyl-α-phenylglycoloyloxy)-1-(1,3-dioxolan-2-ylmethyl)-1-methylpiperidinium Bromide (*trans*- and *cis*-6e)——*trans*-**6e**: ^{1}H-NMR (CD_3OD): 3.22 (3H, s, N–CH_3), 3.93 (4H, m, OCH_2CH_2O), 4.99 (1H, m, C_4–H of the piperidine), 5.34 (1H, t, J=4.5 Hz, C_2–H of the dioxolane), 7.20—7.80 (5H, m, Ph). IR ν_{max}^{KBr} cm^{-1}: 3300 (OH), 1720 (C=O). *Anal.* Calcd for $C_{24}H_{36}BrNO_5$: C, 57.83; H, 7.28; N, 2.81. Found: C, 57.58; H, 7.24; N, 2.57. *cis*-**6e**: ^{1}H-NMR (CD_3OD): 3.28 (3H, s, N–CH_3), 4.00 (4H, m, OCH_2CH_2O), 5.03 (1H, m, C_4–H of the piperidine), 5.40 (1H, t, J= 4.5 Hz, C_2–H of the dioxolane), 7.20—7.75 (5H, m, Ph). IR ν_{max}^{KBr} cm^{-1}: 3350 (OH), 1720 (C=O). *Anal.* Calcd for $C_{24}H_{36}BrNO_5$: C, 57.83; H, 7.28; N, 2.81. Found: C, 57.77; H, 7.51; N, 2.79.

1-(1,3-Dioxolan-2-ylmethyl)-4-[α-ethoxy-α-phenyl-α-(thien-2-yl)acetoxy]-1-methylpiperidinium Bromide (*trans*- and *cis*-6f)——*trans*-**6f**: ^{1}H-NMR (CD_3OD): 1.20 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 3.15 (3H, s, N–CH_3), 3.60 (2H, d, J= 4.5 Hz, N–$C\underline{H}_2CH<\overset{O}{\underset{O}{}}$), 3.94 (4H, m, OCH_2CH_2O), 5.14 (1H, m, C_4–H of the piperidine), 5.35 (1H, t, J=4.5 Hz, C_2–H of the dioxolane), 6.90—7.55 (8H, m, aromatic). IR ν_{max}^{KBr} cm^{-1}: 1730 (C=O). *Anal.* Calcd for $C_{24}H_{32}BrNO_5S$: C, 54.75; H, 6.13; N, 2.66. Found: C, 54.91; H, 6.08; N, 2.73. *cis*-**6f**: ^{1}H-NMR (CD_3OD): 1.20 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 3.25 (3H, s, N–CH_3), 3.98 (4H, m, OCH_2CH_2O), 5.17 (1H, m, C_4–H of the piperidine), 5.34 (1H, t, J= 4.5 Hz, C_2–H of the dioxolane), 6.90—7.60 (8H, m, aromatic). IR ν_{max}^{KBr} cm^{-1}: 1720 (C=O). *Anal.* Calcd for $C_{24}H_{32}BrNO_5S$: C, 54.75; H, 6.13; N, 2.66. Found: C, 54.81; H, 6.22; N, 2.39.

1-(1,3-Dioxolan-2-ylmethyl)-4-[α,α-di(thien-2-yl)glycoloyloxy]-1-methylpiperidinium Bromide (*trans*-6g)——^{1}H-NMR (CD_3OD): 3.22 (3H, s, N–CH_3), 4.01 (4H, m, OCH_2CH_2O), 5.20 (1H, m, C_4–H of the piperidine), 5.43 (1H, t, J=4.5 Hz, C_2–H of the dioxolane), 6.95—7.55 (6H, m, aromatic). IR ν_{max}^{KBr} cm^{-1}: 3180 (OH), 1720 (C=O). *Anal.* Calcd for $C_{20}H_{26}BrNO_5S_2$: C, 47.62; H, 5.19; N, 2.78. Found: C, 47.59; H, 5.32; N, 2.53. The other isomer (*cis*-**6g**) was not cleanly separated.

4-Benziloyloxy-1-(1,3-dioxolan-2-ylmethyl)-1-methylpiperidinium Chloride (*trans*-6a2)——Silver chloride (150 mg) was added to a solution of the *trans*-isomer (**6a1**; 100 mg) in EtOH (10 ml) at room temperature and the reaction mixture was stirred for 1 h. The ethanolic suspension was filtered and the filtrate was concentrated *in vacuo*. The residue was recrystallized from methyl ethyl ketone to afford the *trans*-isomer (**6a2**; 57 mg) as colorless needles. ^{1}H-NMR (CD_3OD): 3.11 (3H, s, N–CH_3), 3.94 (4H, m, OCH_2CH_2O), 5.13 (1H, m, C_4–H of the piperidine), 5.32 (1H, t, J=4.5 Hz, C_2–H of the dioxolane), 7.15—7.50 (10H, m, Ph×2). IR ν_{max}^{KBr} cm^{-1}: 3290 (OH), 1720 (C=O). *Anal.* Calcd for $C_{24}H_{30}ClNO_5$: C, 64.35; H, 6.75; N, 3.13. Found: C, 64.29; H, 6.82; N, 2.91. The title compound (*trans*-**6a2**) was also obtained quantitatively by treatment of **6a1** in MeOH with Amberlite IRA-400 at room temperature.

4-Benziloyloxy-1-(1,3-dioxolan-2-ylmethyl)-1-methylpiperidinium Methylsulfate (*trans*- and *cis*-6a3)——A 95% dimethyl sulfate (318 mg, 0.0024 mol) solution in acetonitrile (10 ml) was added to a solution of **2a** (625 mg, 0.0016 mol) in acetonitrile (10 ml) at room temperature with stirring. Then, according to the procedure described for the preparation of **6a1** and **6b**—**g**, a mixture of *trans*- and *cis*-**6a3** was obtained in nearly 1 : 1 ratio (756 mg, 90.3%). The mixture was recrystallized from acetone to give *trans*-**6a3** (337 mg, 40.3%) as colorless prisms. ^{1}H-NMR (CD_3OD): 3.11 (3H, s, N–CH_3), 3.62 (3H, s, OCH_3), 3.96 (4H, m, OCH_2CH_2O), 5.20 (1H, m, C_4–H of the piperidine), 5.34 (1H, t, J=4.5 Hz, C_2–H of the dioxolane), 7.20—7.55 (10H, m, Ph×2). IR ν_{max}^{KBr} cm^{-1}: 3380 (OH), 1720 (C=O). *Anal.* Calcd for $C_{25}H_{33}NO_9S$: C, 57.35; H, 6.35; N, 2.68. Found: C, 57.41; H, 6.31; N, 2.74. From the mother liquor, 264 mg of the other diastereoisomer (*cis*-**6a3**) was obtained similarly as hygroscopic amorphous crystals by treatment with acetone (31.6%). ^{1}H-NMR (CD_3OD): 3.19 (3H, s, N–CH_3), 3.62 (3H, s, OCH_3), 3.92 (4H, m, OCH_2CH_2O), 5.28 (1H, t, J=4.5 Hz, C_2–H of the dioxolane), 7.20—7.55 (10H, m, Ph×2).

4-Benziloyloxy-1-*n*-butyl-1-(1,3-dioxolan-2-ylmethyl)piperidinium Bromide (*trans*- and *cis*-6a4)——A solution of **2a** (516 mg, 0.0013 mol) and *n*-butyl bromide (712 mg, 0.0052 mol) in acetonitrile (20 ml) was heated at 60 °C with stirring for 72 h. After cooling, the reaction mixture was treated according to the procedure described for the preparation of **6a1** and **6b**—**g** to afford *trans*-**6a4** (249 mg, 35.8%) as colorless needles. ^{1}H-NMR (CD_3OD): 1.00 (3H, t, J=6 Hz, $CH_2CH_2CH_2C\underline{H}_3$), 1.48 (4H, m, N–$CH_2C\underline{H}_2C\underline{H}_2CH_3$), 3.58 (2H, d, J=4.5 Hz, N–$C\underline{H}_2CH<\overset{O}{\underset{O}{}}$), 3.95 (4H, m, OCH_2CH_2O), 5.20 (1H, m, C_4–H of the piperidine), 5.28 (1H, d, J=4.5 Hz, C_2–H of the dioxolane), 7.15—7.50 (10H, m, Ph×2). IR ν_{max}^{KBr} cm^{-1}: 3250 (OH), 1730 (C=O). *Anal.* Calcd for $C_{27}H_{36}BrNO_5$: C, 60.67; H, 6.79; N, 2.62. Found: C, 60.51; H, 6.91; N, 2.48. From the mother liquor, the other isomer (*cis*-**6a4**) was obtained as colorless needles by similar crystallization (216 mg, 31.1%). ^{1}H-NMR (CD_3OD): 1.04 (3H, t, J=6 Hz, $CH_2CH_2CH_2C\underline{H}_3$), 1.55 (4H, m, N–$CH_2C\underline{H}_2C\underline{H}_2CH_3$), 3.50 (2H, d, J=4.5 Hz, N–$C\underline{H}_2CH<\overset{O}{\underset{O}{}}$), 3.92 (4H, m, OCH_2CH_2O), 5.15 (1H, m, C_4–H of the piperidine), 5.19 (1H, d, J=4.5 Hz, C_2–H of the dioxolane), 7.15—7.55 (10H, m, Ph×2). IR ν_{max}^{KBr} cm^{-1}: 3260 (OH), 1725 (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, 2.43.

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