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Studies on Spasmolytics. I. Synthesis and Spasmolytic Activities of 4-Acyloxy-1-(1,3-dioxolan-4-ylmethyl)piperidines[1)]

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Twenty-four derivatives (**5**) of 4-acyloxy-1-(1,3-dioxolan-4-ylmethyl)piperidine were synthesized and their spasmolytic activities were examined. Some of them showed remarkable papaverine-like and/or atropine-like activities; in particular, compounds **5c**, **5d**, **5e**, **5i**, and **5p** were as active or more active than papaverine. The introduction of lipophilic substituents on the dioxolane moiety increased the papaverine-like activity.

Keywords——structure–activity relationship; drug design; 4-acyloxy-1-(1,3-dioxolan-4-ylmethyl)piperidine; papaverine-like activity; atropine-like activity

Based on the idea that chemical modification of acetylcholine or muscarine might lead to compounds possessing antagonistic activities, a large number of acyclic and cyclic acyloxyalkylamines, including arylacetoxyethylamines (**1**),[3)] arylacetoxypiperidines (**2**)[4)] and arylacetyltropines (**3**),[5)] have hitherto been synthesized and tested for antagonistic atropine-like (anticholinergic) activities. The structure–activity relationships can be summarized as follows: an essential requirement for the exhibition of cholinergic and anticholinergic activity is the presence of nitrogen (N) and oxygen (O) atoms which must be separated by a suitable distance (usually with two carbon atoms).[6)] In addition, a suitable bulkiness of R of the arylacetoxy group (RCOO) in the derivatives (**1**, **2**, and **3**) is required for potent anticholinergic activity.[3,4)]

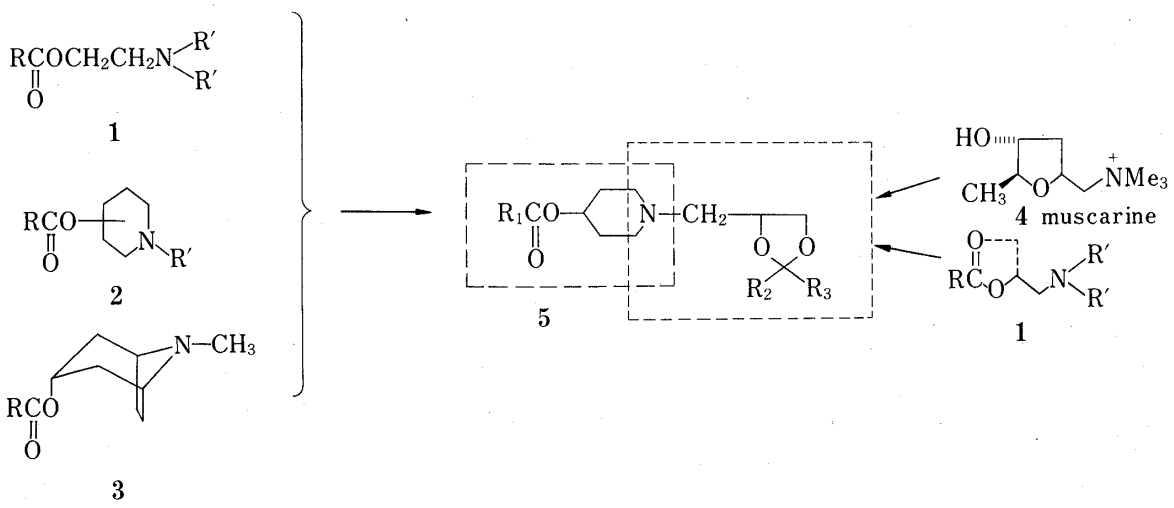
Although 4-aminomethyl-1,3-dioxolanes have been considered as muscarine isosteres and are known to have potent muscarinic activity,[7,8)] rather few studies have been carried out on their antagonistic activity.[9,10)] We therefore designed several 4-acyloxy-1-(1,3-dioxolan-4-ylmethyl)piperidines (**5**), shown in Chart 1, in order to develop potent atropine-like drugs.

These compounds were expected to exhibit potent spasmolytic activities since they have two active sites, both a dioxolane ring and an acyloxy group, on the piperidine ring, and they should provide valuable information of the structure–activity relationship, including the mechanism of the activity. The positional isomer of **5**, 3-benziloyloxy-1-(2,2-dimethyl-1,3-dioxolan-4-ylmethyl)piperidine (BDP), was also synthesized and its spasmolytic activity was compared with those of the compounds **5**.

Results and Discussion

Synthesis

4-Acyloxy-1-(1,3-dioxolan-4-ylmethyl)piperidines (5a—x)——The compounds (**5**) were synthesized by alkylation of 4-piperidinol (**8**) with 4-halomethyl-1,3-dioxolanes (**9**), followed by esterification. The dioxolane derivatives (**9**) were prepared from epibromohydrin and/or 1-chloro-2,3-propanediol and the appropriate carbonyl compounds.[9)] For example, the reaction



R = $Ph_2C(OH)$, 9-xanthenyl, *etc.*
R′ = alkyl

Compd. 5	R_1	R_2	R_3
5a	$Ph_2C(OH)$	H	H
5b	$Ph_2C(OH)$	Me	Me
5c	$Ph_2C(OH)$	Et	Et
5d	$Ph_2C(OH)$	*n*-Pr	*n*-Pr
5e	$Ph_2C(OH)$	iso-Pr	iso-Pr
5f	$Ph_2C(OH)$	$-(CH_2)_5-$	
5g	PhCH(OH)	Me	Me
5h	*p*-(iso-Bu)PhCH(CH_3)	Me	Me
5i	9-xanthenyl	Me	Me
5j	9-xanthenyl	H	H
5k	Ph_2CH	Me	Me
5l	9-fluorenyl	Me	Me
5m	PhC(c-Hex)(OH)	Me	Me
5n	$Ph_2C(OH)$	c-Hex	c-Hex
5o	$PhCH_2$	Ph	Ph
5p	CH_3CH_2	Ph	Ph
5q	CH_3	Ph	Ph
5r	$CH_3CH(OH)$	Ph	Ph
5s	PhCH(OH)	Ph	Ph
5t	$Ph_2C(OH)$	Ph	Ph
5u	$Ph_2C(OH)$	Ph	Ph
5v	Ph_2CH	Ph	Ph
5w	$Ph_2C(OH)$	Me	Ph
5x	$Ph_2C(OH)$	c-Hex	Ph

Chart 1

of 4-piperidinol with 4-bromomethyl-2,2-dimethyl-1,3-dioxolane (**9b**$_1$) gave 1-(2,2-dimethyl-1,3-dioxolan-4-ylmethyl)-4-piperidinol (**7b**) in 93.0% yield. The structure of the product was corroborated by the mass (MS) spectrum (M^+ *m/e* 215) and the proton nuclear magnetic resonance (^{1}H-NMR) spectrum [δ 1.35, 1.40 ($CH_3 \times 2$) and 3.57 (OH, disappeared with D_2O)]. The esterification of **7** was satisfactorily achieved by transesterification[11] with methyl esters (**6**; Y = OCH_3) (method a in Chart 2). For example, the reaction of 1-(2,2-dimethyl-1,3-dioxolan-4-ylmethyl)-4-piperidinol (**7b**) with methyl benzilate (**6**; $R_1 = Ph_2COH$, Y = OCH_3) in the presence of sodium hydride afforded 4-benziloyloxy-1-(2,2-dimethyl-1,3-dioxolan-4-ylmethyl)piperidine (**5b**) in 90.9% yield. The MS of the free base (M^+ *m/e* 425), the infrared (IR) spectrum (1730 cm^{-1} and 3475 cm^{-1}) and the ^{1}H-NMR spectrum [δ 1.32, 1.37 ($CH_3 \times 2$),

3.43 (OH, disappeared with D_2O), 5.01 (C_4–H in the piperidine), and 7.35 (Ph × 2)] were consistent with the assigned structure. Other methods of esterification (methods b and c) and an alternative synthetic route (method d) are shown in Chart 2.

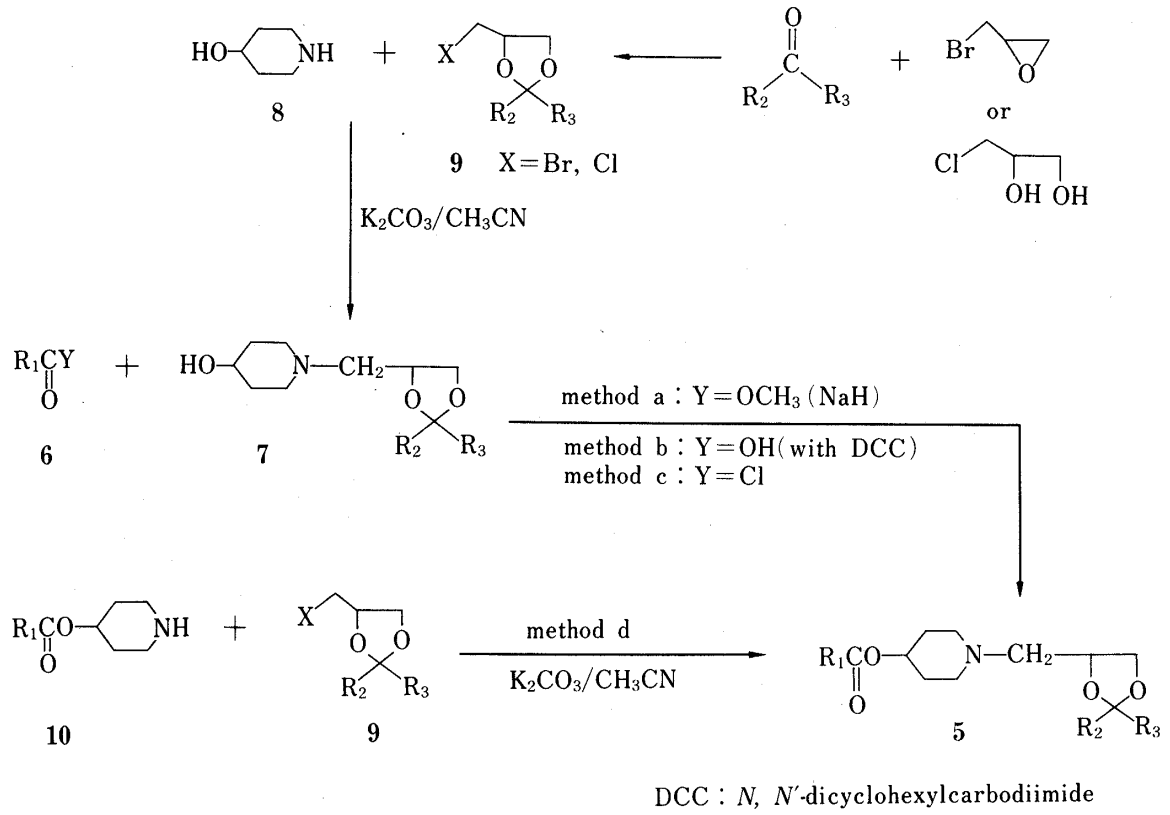


Chart 2

For compounds **9f**, **9h**, **7i**, **5w**, and **5x**, diastereoisomers are expected because R_2 is not the same as R_3. Among them, the products **9h**, **7i**, **5w**, and **5x** were separated into each isomer by repeated crystallization and/or silica-gel column chromatography, although their relative stereochemistry could not be established.

The compounds (**5**) were usually obtained as oils and were characterized as their hydrochlorides. The yields and melting points of **5** are summarized in Table I.

Pharmacology

Eleven selected 4-acyloxy-1-(1,3-dioxolan-4-ylmethyl)piperidine derivatives (**5**) were examined for spasmolytic activities by the Magnus method using ileum isolated from guinea pigs. The competitive and non-competitive antagonistic activities of the compounds were expressed as the pA_2 and pD_2' values. Both values were calculated from the shift of the concentration–action curve of acetylcholine.[11,12] The results are shown in Table II.

Most of the compounds **5** showed potent papaverine-like activities. In particular, the activities of **5c**, **5d**, **5e**, **5i**, and **5t** were equal to or greater than that of papaverine.

Brown[10] *et al.* reported that 2-aryl or 2,2-diaryl substituted acyclic and/or cyclic 4-aminomethyl-1,3-dioxolanes exhibited potent atropine-like activity together with weak or moderate papaverine-like action. On the other hand, most 4-arylacetoxypiperidines (**2**) exhibit atropine-like action, but do not possess papaverine-like activity.[3,4] Therefore, it is interesting that the compounds **5** exhibited potent papaverine-like activities.

A consideration of the chemical structure–spasmolytic activity relationship led to the

TABLE I. Yields and Melting Points of 4-Acyloxy-1-(1,3-dioxolan-4-ylmethyl)piperidines (**5**)

Compd. **5**	Method[a]	mp[b] (°C)	Yield[c] (%)
5a	a	166.1—167.5	67.2
5b	a	169.0—171.0	90.9
5c	a	157.5—159.0	86.2
5d	a	167.0—169.5	73.5
5e	d	165.5—166.5	74.0
5f	a	solid oil	92.0
5g	a	104.8—105.5[d]	83.2
5h	a	144.0—147.0	79.5
5i	c	167.5—168.0	64.2
5j	a	188.0—190.0	61.0
5k	a	155.0—156.5	70.3
5l	b	207.0—208.0	67.1
5m	a	79.0—82.0	87.2
5n	a	122.5—123.5[e]	94.4
5o	c	167.3—169.3[f]	95.1
5p	c	83.8—85.3[e]	98.9
5q	c	86.5—87.5[e]	95.2
5r	a	89.5—91.3[e]	68.1
5s	a	156.5—158.4[f]	70.4
5t	a	177.0—178.0	79.5
5u	a	204.0—207.0	91.3
5v	a	95.0—96.0[e]	83.6
5w	a	83.0—85.0[e,g] / 160.0—161.0[e,g]	90.6
5x	a	195.0—197.0[h] / solid oil[h]	93.2

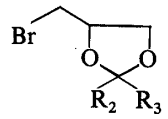
a) Method a, transesterification; method b, dehydration in the presence of DCC; method c, esterification by use of acyl chloride; method d, dioxolanylmethylation of the 4-benziloyloxypiperidine.
b) mp of HCl salt unless otherwise noted.
c) Isolated yield.
d) *p*-Nitrobenzoate.
e) Free base.
f) Oxalate.
g) Isolated by fractional crystallizations.
h) Isolated by silica-gel column chromatography.

TABLE II. Spasmolytic Activities of 4-Acyloxy-1-(1,3-dioxolan-4-ylmethyl)piperidines (**5**)

Compd. **5**	pA_2	pD_2'	Compd. **5**	pA_2	pD_2'
5b	6.08		**5m**	6.99	
5c		5.03	**5n**[a]	7.67	4.54
5d		5.37	**5p**		4.43
5e		5.45	**5t**		5.07
5i	4.98	4.98	BDP[b]		4.80
5k		4.69	Atropine	9.20	
5l		4.80	Papaverine		5.10

a) The antagonistic activity was competitive at lower ($\leqq 10^{-5}$ M) concentration, but non-competitive at higher dose (10^{-5} M<).
b) 3-Benziloyloxy-1-(2,2-dimethyl-1,3-dioxolan-4-ylmethyl)piperidine.

TABLE III. 4-Bromomethyl-1,3-dioxolanes (**9**)



Compd. **9**	R_2	R_3	bp °C/Torr (mp, °C)	Yield[a] (%)	MS (*m/e*)
9a[b]	H	H	142.0—143.0/760[c]	73.0[d]	123/121 (M^+-H)=1/3
9b$_1$	Me	Me	78.5/24	90.2	181/179 (M^+-Me)=1/1
9b$_2$[b]	Me	Me	93.0/113	75.8	137/135 (M^+-Me)=1/3
9c	Et	Et	78.5/8	73.4	195/193 (M^+-Et)=1/1
9d	*n*-Pr	*n*-Pr	105.0/8	85.7	209/207 (M^+-n-Pr)=1/1
9e	iso-Pr	iso-Pr	98.0/10	24.0	252/250 (M^+)=1/1
9f	Me	Ph	143.0—145.7/7	80.0	243/241 (M^+-Me)=1/1
9g	$-(CH_2)_5-$		115.0/10	87.0	236/234 (M^+)=1/1
9h	c-Hex	Ph	124.0/0.03	83.8	326/324 (M^+)=1/1
9i	$PhCH_2$	$PhCH_2$	193.0—195.0/4	76.3	257/255 (M^+-PhCH_2)=1/1
9j	Ph	Ph	(74.0)[e]	91.2	243/241 (M^+-Ph)=1/1
9k	c-Hex	c-Hex	(58.5—59.5)	86.8	249/247 (M^+-c-Hex)=1/1

a) Isolated yield.
b) 4-Chloromethyl compound.
c) Lit.[9]; bp 146—147 °C/745 Torr.
d) Prepared by the reaction of 1-chloro-2,3-propanediol and paraformaldehyde.
e) Lit.[9]; mp 71—73 °C.

TABLE IV. 1-(1,3-Dioxolan-4-ylmethyl)-4-piperidinols (**7**) Synthesized from 4-Bromomethyl-1,3-dioxolane Derivatives (**9**)

Compd. **7**	R_2	R_3	bp °C/Torr (mp °C)	Yield[a] (%)	MS (*m/e*)
7a	H	H	Oil	56.4[d]	187 (M^+)
7b	Me	Me	159.0/11	93.0	215 (M^+)
	Me	Me		99.8[c]	215 (M^+)
	Me	Me	166.0—167.5/15	41.8[d]	215 (M^+)
7c	Et	Et	158.0—159.0/4	86.7	243 (M^+)
7d	*n*-Pr	*n*-Pr	170.0—170.5/4	95.5	271 (M^+)
7e	$-(CH_2)_5-$		Oil	87.1[e]	255 (M^+)
7f	Ph	Ph	(101.2—101.7)	75.1	339 (M^+)
7g	c-Hex	c-Hex	197.0/0.2	95.4	351 (M^+)
7h	$PhCH_2$	$PhCH_2$	Oil	60.3[e]	367 (M^+)
7i	Me	Ph	Oil[f]	68.3[e]	277 (M^+)
7j	c-Hex	Ph	(110.0—111.6)[g]	75.8	345 (M^+)
			Oil[g]	84.2	345 (M^+)

a) Isolated yield.
b) The 4-chloromethyl compound (**9a**) was used and the product was isolated by silica-gel column chromatography.
c) *N*,*N*-Dimethylformamide was used as a solvent.
d) The 4-chloromethyl compound (**9b**$_2$) was used in the presence of pyridine as a base and solvent.
e) Isolated by silica-gel column chromatography.
f) A mixture of two diastereoisomers.
g) One of two diastereoisomers.

following results: 1) when both R_2 and R_3 are methyl groups, 3- and 4-benziloyloxy compounds (BDP and **5b**) showed papaverine- and atropine-like activities, respectively; 2) when R_2 and R_3 are larger than a methyl group, 4-benziloyloxy compounds (**5c**, **5d**, **5e**, **5n**,

TABLE V. ^{1}H-NMR and IR Spectral Data for 4-Acyloxy-1-(1,3-dioxolan-4-ylmethyl)piperidines (**5**)

Compd.[a]	^{1}H-NMR[b] Solvent[c]	^{1}H-NMR[b] δ ppm	IR cm^{-1}
5a	A	4.65, 5.10 (2H, dd, J=24 Hz, C_2–H in the dioxolane), 4.90 (1H, m, C_4–H), 7.30 (10H, m, Ph)	3500 (OH)
5b	A	1.32 (3H, s, CH_3), 1.37 (3H, s, CH_3), 5.01 (1H, m, C_4–H), 7.35 (10H, m, Ph)	3475 (OH) 1730 (C=O)
5c[d]	B	0.90 (6H, t, J=7.0 Hz, 2×CH_3), 1.63 (4H, q, J=7.0 Hz, 2×$C\underline{H}_2CH_3$), 5.10 (1H, m, C_4–H), 7.31 (10H, m, Ph)	3370 (OH) 1730 (C=O)
5d[d]	B	0.90 (6H, m, 2×CH_3), 1.50 (8H, m, 2×$C\underline{H}_2C\underline{H}_2CH_3$), 5.10 (1H, m, C_4–H), 7.32 (10H, m, Ph)	3380 (OH) 1730 (C=O)
5e[d]	B	0.91 (12H, d, J=7.0 Hz, CH_3), 5.17 (1H, m, C_4–H), 7.39 (10H, m, Ph)	3400 (OH) 1735 (C=O)
5f	A	1.55 (10H, m, pentamethylene), 5.20 (1H, C_4–H), 7.35 (10H, m, Ph)	3400 (OH) 1735 (C=O)
5g	A	1.31 (3H, s, CH_3), 1.36 (3H, s, CH_3), 5.15 (1H, s, $C\underline{H}$Ph), 7.15—7.50 (5H, m, Ph)	3420 (OH) 1740 (C=O)
5h	A	0.89 (6H, d, J=6.5 Hz, 2×CH_3, in isobutyl), 1.31 (3H, d, J=8.0 Hz, –CH($C\underline{H}_3$)COO–), 1.33, 1.39 (6H, s, s, 2×CH_3, in the dioxolane), 4.80 (1H, m, C_4–H), 7.17 (4H, m, aromatic)	1735 (C=O)
5i	A	1.32 (3H, s, CH_3), 1.38 (3H, s, CH_3), 1.63 (4H, m, $C_{3,5}$–H), 4.71 (1H, m, C_4–H), 4.93 (1H, s, =CHCOO), 7.15 (8H, m, aromatic)	1735 (C=O)
5j[d]	B	4.82 (1H, s, C_2–H, in the dioxolane), 5.00 (1H, s, C_2–H, in the dioxolane), 5.01 (1H, s, =CHCOO), 6.90—7.45 (8H, m, aromatic)	1730 (C=O)
5k[d]	B	1.32 (3H, s, CH_3), 1.40 (3H, s, CH_3), 5.10 (1H, m, C_4–H), 5.12 (1H, s, =CHCOO), 7.30 (10H, m, Ph)	1730 (C=O)
5l[d]	B	1.35 (3H, s, CH_3), 1.45 (3H, s, CH_3), 4.80 (1H, m, C_4–H), 4.80 (1H, s, =CHCOO), 7.20—7.90 (8H, m, aromatic)	1730 (C=O)
5m[d]	A	1.38 (3H, s, CH_3), 1.45 (3H, s, CH_3), 5.10 (1H, m, C_4–H), 7.25—7.75 (5H, m, Ph)	3400 (OH) 1720 (C=O)
5n	A	1.10—1.76 (22H, m, 2× c-Hex), 5.00 (1H, m, C_4–H), 7.38 (10H, m, 2×Ph)	3250 (OH) 1730 (C=O)
5o	A	1.75 (4H, m, $C_{3,5}$–H), 3.55 (2H, s, $C\underline{H}_2$Ph), 4.75 (1H, m, C_4–H), 7.25 (15H, m, 3×Ph)	1725 (C=O)
5p	A	1.09 (4H, t, J=7.5 Hz, CH_3), 1.80 (4H, m, $C_{3,5}$–H), 2.30 (2H, q, J=7.5 Hz, $C\underline{H}_2CH_3$), 4.75 (1H, m, C_4–H), 7.28 (10H, m, Ph)	3250 (OH) 1730 (C=O)
5q	A	1.96 (3H, s, CH_3), 4.70 (1H, m, C_4–H), 7.30 (10H, m, 2×Ph)	1730 (C=O)
5r	A	1.36 (3H, d, J=7.5 Hz, CH_3), 1.80 (4H, m, $C_{3,5}$–H), 4.21 (1H, q, J=7.5 Hz, $C\underline{H}_2CH_3$), 4.81 (1H, m, C_4–H), 7.30 (10H, m, 2×Ph)	3480 (OH) 1735 (C=O)
5s	A	1.65 (4H, m, $C_{3,5}$–H), 4.75 (1H, m, C_4–H), 5.10 (1H, s, $C\underline{H}$Ph), 7.28 (15H, m, 3×Ph)	3460 (OH) 1730 (C=O)
5t[d]	B	2.91 (4H, s, 2×$C\underline{H}_2$Ph), 5.10 (1H, m, C_4–H), 7.20—7.36 (20H, m, 4×Ph)	3360 (OH) 1730 (C=O)
5u	A	1.72 (4H, m, $C_{3,5}$–H), 4.95 (1H, m, C_4–H), 7.30 (20H, m, 4×Ph)	3475 (OH) 1728 (C=O)
5v	A	4.95 (1H, m, C_4–H), 5.03 (1H, s, =CHCOO), 7.30 (20H, m, 4×Ph)	1710 (C=O)

TABLE V. (continued)

Compd.[a]	^{1}H-NMR[b] Solvent[c]	^{1}H-NMR[b] δ ppm	IR cm^{-1}
5w[e]	A	1.62 (3H, s, CH_3), 3.60—4.00 (3H, m, C_4–H and C_5–H, in the dioxolane), 4.95 (1H, m, C_4–H), 7.32 (15H, m, 3 × Ph)	3450 (OH) 1728 (C=O)
	A	1.59 (3H, s, CH_3), 3.35 (1H, m, C_5–H, in the dioxolane), 4.00—4.30 (2H, m, C_4–H and C_5–H, in the dioxolane), 4.92 (1H, m, C_4–H), 7.30 (15H, m, 3 × Ph)	3440 (OH) 1730 (C=O)
5x[e]	A	1.05 (11H, m, c-Hex), 1.70 (4H, m, $C_{3,5}$–H), 3.50—4.15 (3H, m, C_4–H and C_5–H, in the dioxolane), 4.90 (1H, m, C_4–H), 7.30 (15H, m, 3 × Ph)	3488 (OH) 1730 (C=O)
	A	1.05 (11H, m, c-Hex), 3.21 (1H, m, C_5–H, in the dioxolane), 3.90—4.45 (2H, m, C_4–H and C_5–H, in the dioxolane), 4.90 (1H, m, C_4–H), 7.30 (15H, m, 3 × Ph)	3495 (OH) 1730 (C=O)

a) Free base unless otherwise noted.
b) Spectral data for C_3-, C_4-, and C_5-protons are those of the corresponding piperidine unless otherwise mentioned.
c) A, $CDCl_3$; B, CD_3OD.
d) Hydrochloride.
e) The diastereoisomers were separated.

and **5t**) exhibited papaverine-like activities; 3) when R_2 and R_3 are methyl groups and a hydroxy group is absent in the 4-arylacetoxy group, the compounds (**5i**, **5k**, and **5l**) exhibited papaverine-like activities.

From the above results, we consider that the structure–activity relationship for the atropine- and papaverine-like activities is closely correlated to the physical properties of the dioxolane ring, such as lipophilic character. For example, increase of the bulkiness of the substituents (R_2 and R_3) on the dioxolane ring increased the papaverine-like activities.

In conclusion, it was found that most of the compounds (**5**) exhibited potent papaverine-like activities rather than atropine-like activities.

Experimental

All melting points were measured with a Mettler FP-5 apparatus and are uncorrected. IR spectra were recorded on a JASCO IRA-1 spectrophotometer and mass spectra (MS) were determined on a Hitachi RM-50 spectrometer. ^{1}H-NMR spectra were taken with a Hitachi R-24 (60 MHz) spectrometer using tetramethylsilane as an internal standard, and chemical shifts are given in 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.

4-Bromomethyl-2,2-dimethyl-1,3-dioxolane (9b$_1$)——Stannic chloride (1.3 g, 0.005 mol) in CCl_4 (20 ml) was added slowly to a solution of epibromohydrin (13.7 g, 0.1 mol) in acetone (40 ml) with stirring in an ice-bath. The reaction mixture was stirred at room temperature for 2.5 h, then neutralized by the addition of K_2CO_3 powder and concentrated *in vacuo*. Ether (70 ml) was added to the residue and the ethereal extract was washed with water (10 ml × 2), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residual oil was distilled under reduced pressure to yield 17.6 g (90.2%) of **11b$_1$** as a colorless oil. ^{1}H-NMR ($CDCl_3$): 1.35 (3H, s, CH_3), 1.44 (3H, s, CH_3), 3.35 (2H, m, $BrCH_2$), 3.80—4.30 (3H, m, $C_{4,5}$–H). MS *m/e*: 181, 179 ($M^+ - CH_3$, 1 : 1). The other derivatives, 4-halomethyl-1,3-dioxolanes (**11a**, **11b$_2$**—**k**), listed in Table III were prepared by a similar procedure.

1-(2,2-Dimethyl-1,3-dioxolan-4-ylmethyl)-4-piperidinol (7b)——A solution of **9b$_1$** (19.5 g, 0.1 mol) and 4-piperidinol (10.1 g, 0.1 mol) in acetonitrile (100 ml) was refluxed for 16 h in the presence of K_2CO_3 (13.8 g, 0.1 mol). After cooling, the reaction mixture was filtered and concentrated *in vacuo*. The residue was dissolved in dichloromethane (100 ml) and the mixture was washed with water (50 ml × 2). The organic layer was dried over anhydrous Na_2SO_4

TABLE VI. Mass Spectral and Analytical Data for 4-Acyloxy-1-(1,3-dioxolan-4-ylmethyl)piperidines (**5**)

Compd. **5**	MS[a] *m/e*	Formula	Analysis (%) Found (Calcd)		
			C	H	N
5a	397 (M^+), 396 (M^+-H), 324 (base peak)	$C_{23}H_{27}NO_5 \cdot HCl$	63.51 (63.66	6.77 6.51	3.08 3.23)
5b	425 (M^+), 410 (M^+-Me), 324 (base peak)	$C_{25}H_{31}NO_5 \cdot HCl$	65.11 (64.99	6.72 6.98	3.12 3.03)
5c	453 (M^+), 424 (M^+-Et), 324 (base peak)	$C_{27}H_{35}NO_5 \cdot HCl$	66.45 (66.18	7.25 7.41	3.12 2.86)
5d	481 (M^+), 438 (M^+-n-Pr), 324 (base peak)	$C_{29}H_{39}NO_5 \cdot HCl$	67.18 (67.23	7.28 7.59	2.96 2.70)
5e	481 (M^+), 438 (M^+-iso-Pr), 324 (base peak)	$C_{29}H_{39}NO_5 \cdot HCl$	67.35 (67.23	7.43 7.59	2.81 2.70)
5f	465 (M^+), 324 (base peak)	$C_{28}H_{35}NO_5$		—[b]	
5g	349 (M^+), 334 (M^+-Me), 248 (base peak)	$C_{19}H_{27}NO_5 \cdot$ *p*-nitrobenzoate	60.22 (60.46	6.35 6.24	5.20 5.42)
5h	403 (M^+), 388 (M^+-Me), 302 (base peak)	$C_{24}H_{37}NO_4 \cdot HCl$	65.63 (65.51	8.59 8.71	3.24 3.18)
5i	423 (M^+), 408 (M^+-Me), 322 (base peak)	$C_{25}H_{29}NO_5 \cdot HCl$	65.47 (65.28	6.38 6.57	3.16 3.05)
5j	395 (M^+), 394 (M^+-H), 322 (base peak)	$C_{23}H_{35}NO_5 \cdot HCl$	63.67 (63.96	6.29 6.07	3.01 3.24)
5k	409 (M^+), 394 (M^+-Me), 308 (base peak)	$C_{25}H_{31}NO_4 \cdot HCl$	67.12 (67.33	7.45 7.23	2.89 3.14)
5l	407 (M^+), 392 (M^+-Me), 306 (base peak)	$C_{25}H_{29}NO_4 \cdot HCl$	67.57 (67.63	6.97 6.81	3.08 3.15)
5m	431 (M^+), 416 (M^+-Me), 330 (base peak)	$C_{25}H_{37}NO_5 \cdot HCl \cdot H_2O$	61.97 (61.78	8.11 7.88	2.75 2.88)
5n	561 (M^+), 478 (M^+-c-Hex), 324 (base peak)	$C_{35}H_{47}NO_5$	74.75 (74.83	8.72 8.43	2.36 2.49)
5o	457 (M^+), 380 (M^+-Ph), 232 (base peak)	$C_{29}H_{31}NO_4 \cdot$ oxalate	67.96 (68.00	6.21 6.07	2.48 2.56)
5p	395 (M^+), 318 (M^+-Ph), 170 (base peak)	$C_{24}H_{29}NO_4$	72.77 (72.89	7.55 7.39	3.42 3.54)
5q	381 (M^+), 304 (M^+-Ph), 156 (base peak)	$C_{23}H_{27}NO_4$	72.40 (72.42	7.36 7.14	3.59 3.67)
5r	411 (M^+), 334 (M^+-Ph), 186 (base peak)	$C_{24}H_{29}NO_5$	70.21 (70.05	7.37 7.10	3.27 3.40)
5s	473 (M^+), 397 (M^+-Ph), 248 (base peak)	$C_{29}H_{31}NO_5 \cdot$ oxalate	66.12 (66.06	7.31 7.03	2.40 2.49)
5t	577 (M^+), 486 (M^+-CH_2Ph), 324 (base peak)	$C_{37}H_{39}NO_5 \cdot HCl$	72.28 (72.36	6.76 6.56	2.19 2.28)
5u	549 (M^+), 472 (M^+-Ph), 324 (base peak)	$C_{35}H_{35}NO_5 \cdot HCl$	71.58 (71.71	6.31 6.19	2.27 2.39)
5v	533 (M^+), 456 (M^+-Ph), 308 (base peak)	$C_{35}H_{35}NO_4$	78.52 (78.77	6.88 6.61	2.50 2.62)
5w[c]	487 (M^+), 472 (M^+-Me), 410 (M^+-Ph), 324 (base peak)	$C_{30}H_{33}NO_5$	73.81 (73.90	6.96 6.82	2.68 2.87)
	487 (M^+), 472 (M^+-Me), 410 (M^+-Ph), 324 (base peak)	$C_{30}H_{33}NO_5$	73.74 (73.90	6.99 6.82	2.76 2.87)
5x[c]	555 (M^+), 478 (M^+-Ph), 472 (M^+-c-Hex), 324 (base peak)	$C_{35}H_{41}NO_5 \cdot HCl$	70.78 (70.99	7.31 7.15	2.45 2.37)
	555 (M^+), 478 (M^+-Ph), 472 (M^+-c-Hex), 324 (base peak)	$C_{35}H_{41}NO_5$		—[b]	

a) The base peak is due to the 1-methylidene-4-acyloxypiperidinium ion fragment.
b) Elementary analysis was not done.
c) Two diastereoisomers.

and concentrated *in vacuo*. The residue was distilled under reduced pressure to yield 19.9 g (93.0%) of **7b** as a colorless oil. ^{1}H-NMR ($CDCl_3$): 1.35 (3H, s, CH_3), 1.40 (3H, s, CH_3), 1.76 (4H, m, $C_{3,5}$–H in the piperidine), 2.30 (1H, br s, OH, disappeared with D_2O), 2.50 (6H, m, N–CH_2 × 3), 4.20 (1H, m, C_4–H in the piperidine). IR ν_{max}^{film} cm^{-1}: 3380 (OH). MS *m/e*: 215 (M^+), 200 ($M^+ - CH_3$). The other compounds, 1-(1,3-dioxolan-4-ylmethyl)-4-piperidinols (**8a**, **8c**—**j**), were prepared similarly and are listed in Table IV.

Syntheses of 4-Acyloxy-1-(1,3-dioxolan-4-ylmethyl)piperidines (5a—x)——Method a: Sodium hydride (50% oil suspension, 0.003 mol) was added to **7** (0.03 mol) and the mixture was heated at 80 °C for 0.5—2 h *in vacuo*. A methyl ester (**6**; Y = OCH_3, 0.03 mol) was added to the mixture and the MeOH produced was removed for 1—5 h *in vacuo*. Dichloromethane (100 ml) was added to the residue and the organic layer was washed with water (50 ml × 2), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was converted directly or after column chromatography into the corresponding hydrochloride using pyridine–HCl. The crude salt of **5** was crystallized from MeOH–Et_2O to afford colorless needles.

Method b: 4-(Fluorene-9-carbonyloxy)-1-(2,2-dimethyl-1,3-dioxolan-4-ylmethyl)piperidine (**5l**): *N,N'*-Dicyclohexylcarbodiimide (8.85 g, 0.043 mol) was added to a solution of **7b** (8.36 g, 0.039 mol) and fluorene-9-carboxylic acid (**6**; Y = OH, 9.0 g, 0.043 mol) in dichloromethane (50 ml), and the reaction mixture was stirred at room temperature for 15 h. After filtration of the urea compound, the filtrate was concentrated *in vacuo*. Ether (50 ml) was added to the residual oil, and the solution was filtered and concentrated *in vacuo* to give 16.7 g of **5l** as a colorless oil. The hydrochloride of **5l** was obtained as colorless needles, as described for method a, to afford 10.7 g (67.1%) of product.

Method c: A mixture of **7** (0.05 mol) and an acyl chloride (**6**; Y = Cl, 0.05 mol) was heated at 80 °C for 1 h, then cooled. Dichloromethane (50 ml) and 10% NaOH (30 ml) were added to the reaction mixture at room temperature, and the mixture was stirred for 1 h. The dichloromethane layer was washed with water (30 ml × 2), dried over dehydrated Na_2SO_4, and concentrated *in vacuo*. The residual product was treated according to the procedure described for method a to afford the hydrochloride as colorless needles.

Method d: 4-Benziloyloxy-1-(2,2-diisopropyl-1,3-dioxolan-4-ylmethyl)piperidine (**5e**): A mixture of 4-benziloyloxypiperidine (**10**; 6.66 g, 0.021 mol) and 4-bromomethyl-2,2-diisopropyl-1,3-dioxolane (**9f**; 6.45 g, 0.026 mol) in acetonitrile (50 ml) was refluxed for 124 h in the presence of K_2CO_3 (2.95 g, 0.021 mol). After cooling, the reaction mixture was concentrated *in vacuo*, and treated according to the procedure described under method a to afford the hydrochloride (8.19 g, 74.0%) of **5e** as colorless needles.

The ^{1}H-NMR and IR spectral data for **5a**—**x** are summarized in Table V, and MS and analytical data in Table VI.

3-Benziloyloxy-1-(2,2-dimethyl-1,3-dioxolan-4-ylmethyl)piperidine (BDP)——A solution of **9b**$_1$ (19.5 g, 0.1 mol) and 3-piperidinol (10.1 g, 0.1 mol) in acetonitrile (100 ml) was refluxed for 12 h in the presence of K_2CO_3 (13.8 g, 0.1 mol). Work-up of the reaction mixture as described for **7b** yielded 1-(2,2-dimethyl-1,3-dioxolan-4-ylmethyl)-3-piperidinol (17.2 g, 79.8%) as a colorless oil. bp_6 163.0 °C. ^{1}H-NMR ($CDCl_3$): 1.32 (3H, s, CH_3), 1.40 (3H, s, CH_3), 1.76 (4H, m, $C_{4,5}$–H in the piperidine), 2.45 (6H, m, N–CH_2 × 3), 3.60 (1H, br s, OH, disappeared with D_2O). IR ν_{max}^{film} cm^{-1}: 3380 (OH). MS *m/e*: 215 (M^+), 200 ($M^+ - CH_3$).

n-Butyl lithium (1.2 ml, 20% *n*-hexane solution) was added to a solution of 1-(2,2-dimethyl-1,3-dioxolan-4-ylmethyl)-3-piperidinol (1.08 g, 0.005 mol) in anhydrous toluene (20 ml) and the reaction mixture was refluxed for 30 min. Then, a solution of methyl benzilate (1.45 g, 0.006 mol) in anhydrous toluene (30 ml) was added dropwise over a period of 45 min under azeotropic removal of generated MeOH with toluene. After cooling, the solution was concentrated *in vacuo* and dichloromethane (30 ml) was added to the residue. The dichloromethane solution was washed with water (20 ml × 2), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The resulting product was chromatographed on silica gel (100 g, dichloromethane) to give 1.90 g (89.5%) of BDP as a colorless oil. The hydrochloride was crystallized from MeOH–Et_2O to afford colorless needles. mp 189.0—191.0 °C. ^{1}H-NMR ($CDCl_3$): 1.30 (3H, s, CH_3), 1.35 (3H, s, CH_3), 1.60 (4H, m, $C_{4,5}$–H in the piperidine), 2.45 (6H, m, N–CH_2 × 3), 4.95 (1H, m, C_3–H), 7.30 (10H, m, Ph × 2). IR ν_{max}^{film} cm^{-1}: 3440 (OH), 1730 (C=O). MS *m/e*: 425 (M^+), 410 ($M^+ - CH_3$), 324 (base peak). *Anal.* Calcd for $C_{25}H_{31}NO_5 \cdot HCl$: C, 64.99; H, 6.98; N, 3.03. Found: C, 65.07; H, 6.81; N, 3.14.

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References and Notes

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