

[Chem. Pharm. Bull.]  
32(3) 967-976 (1984)]

## Studies on Spasmolytics. I. Synthesis and Spasmolytic Activities of 4-Acyloxy-1-(1,3-dioxolan-4-ylmethyl)piperidines<sup>1)</sup>

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(Received March 28, 1983)

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 arylacetoxethylamines (**1**),<sup>3)</sup> arylacetoxypiperidines (**2**)<sup>4)</sup> and arylacetotropines (**3**),<sup>5)</sup> 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).<sup>6)</sup> In addition, a suitable bulkiness of R of the arylacetox group (RCOO) in the derivatives (**1**, **2**, and **3**) is required for potent anticholinergic activity.<sup>3,4)</sup>

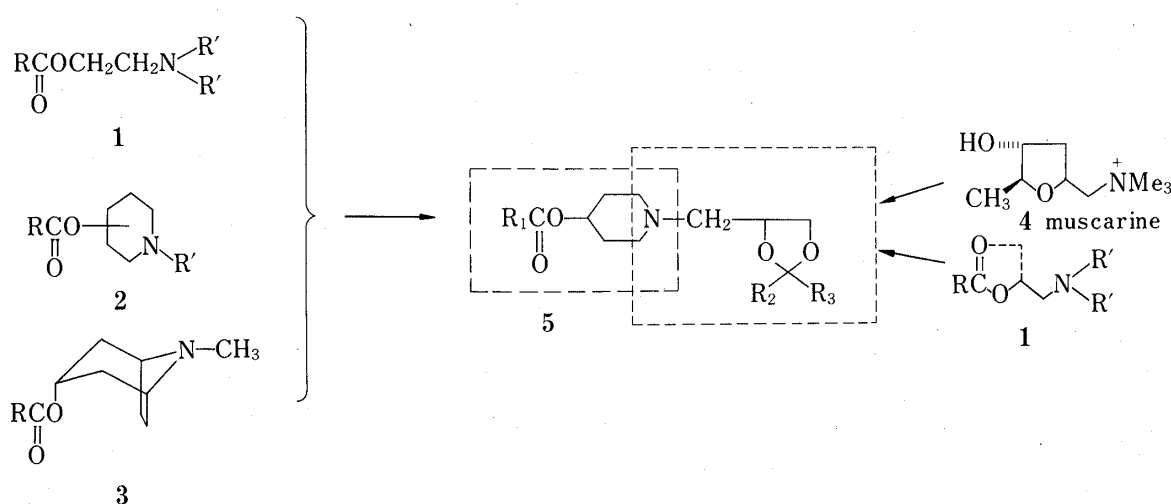
Although 4-aminomethyl-1,3-dioxolanes have been considered as muscarine isosteres and are known to have potent muscarinic activity,<sup>7,8)</sup> rather few studies have been carried out on their antagonistic activity.<sup>9,10)</sup> We therefore designed several 4-acyloxy-1-(1,3-dioxolan-4-ylmethyl)piperidines (**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.<sup>9)</sup> For example, the reaction



Compd. 5	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>
<b>5a</b>	Ph <sub>2</sub> C(OH)	H	H
<b>5b</b>	Ph <sub>2</sub> C(OH)	Me	Me
<b>5c</b>	Ph <sub>2</sub> C(OH)	Et	Et
<b>5d</b>	Ph <sub>2</sub> C(OH)	<i>n</i> -Pr	<i>n</i> -Pr
<b>5e</b>	Ph <sub>2</sub> C(OH)	iso-Pr	iso-Pr
<b>5f</b>	Ph <sub>2</sub> C(OH)	-(CH <sub>2</sub> ) <sub>5</sub> -	
<b>5g</b>	PhCH(OH)	Me	Me
<b>5h</b>	<i>p</i> -(iso-Bu)PhCH(CH <sub>3</sub> )	Me	Me
<b>5i</b>	9-xanthenyl	Me	Me
<b>5j</b>	9-xanthenyl	H	H
<b>5k</b>	Ph <sub>2</sub> CH	Me	Me
<b>5l</b>	9-fluorenyl	Me	Me
<b>5m</b>	PhC( <i>c</i> -Hex)(OH)	Me	Me
<b>5n</b>	Ph <sub>2</sub> C(OH)	<i>c</i> -Hex	<i>c</i> -Hex
<b>5o</b>	PhCH <sub>2</sub>	Ph	Ph
<b>5p</b>	CH <sub>3</sub> CH <sub>2</sub>	Ph	Ph
<b>5q</b>	CH <sub>3</sub>	Ph	Ph
<b>5r</b>	CH <sub>3</sub> CH(OH)	Ph	Ph
<b>5s</b>	PhCH(OH)	Ph	Ph
<b>5t</b>	Ph <sub>2</sub> C(OH)	Ph	Ph
<b>5u</b>	Ph <sub>2</sub> C(OH)	Ph	Ph
<b>5v</b>	Ph <sub>2</sub> CH	Ph	Ph
<b>5w</b>	Ph <sub>2</sub> C(OH)	Me	Ph
<b>5x</b>	Ph <sub>2</sub> C(OH)	<i>c</i> -Hex	Ph

R = Ph<sub>2</sub>C(OH),  
9-xanthenyl, etc.  
R' = alkyl

Chart 1

of 4-piperidinol with 4-bromomethyl-2,2-dimethyl-1,3-dioxolane (**9b<sub>1</sub>**) 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 (<sup>1</sup>H-NMR) spectrum [ $\delta$  1.35, 1.40 (CH<sub>3</sub> × 2) and 3.57 (OH, disappeared with D<sub>2</sub>O)]. The esterification of **7** was satisfactorily achieved by transesterification<sup>11)</sup> with methyl esters (**6**; Y = OCH<sub>3</sub>) (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<sub>1</sub> = Ph<sub>2</sub>COH, Y = OCH<sub>3</sub>) 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<sup>-1</sup> and 3475 cm<sup>-1</sup>) and the <sup>1</sup>H-NMR spectrum [ $\delta$  1.32, 1.37 (CH<sub>3</sub> × 2),

3.43 (OH, disappeared with D<sub>2</sub>O), 5.01 (C<sub>4</sub>-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.

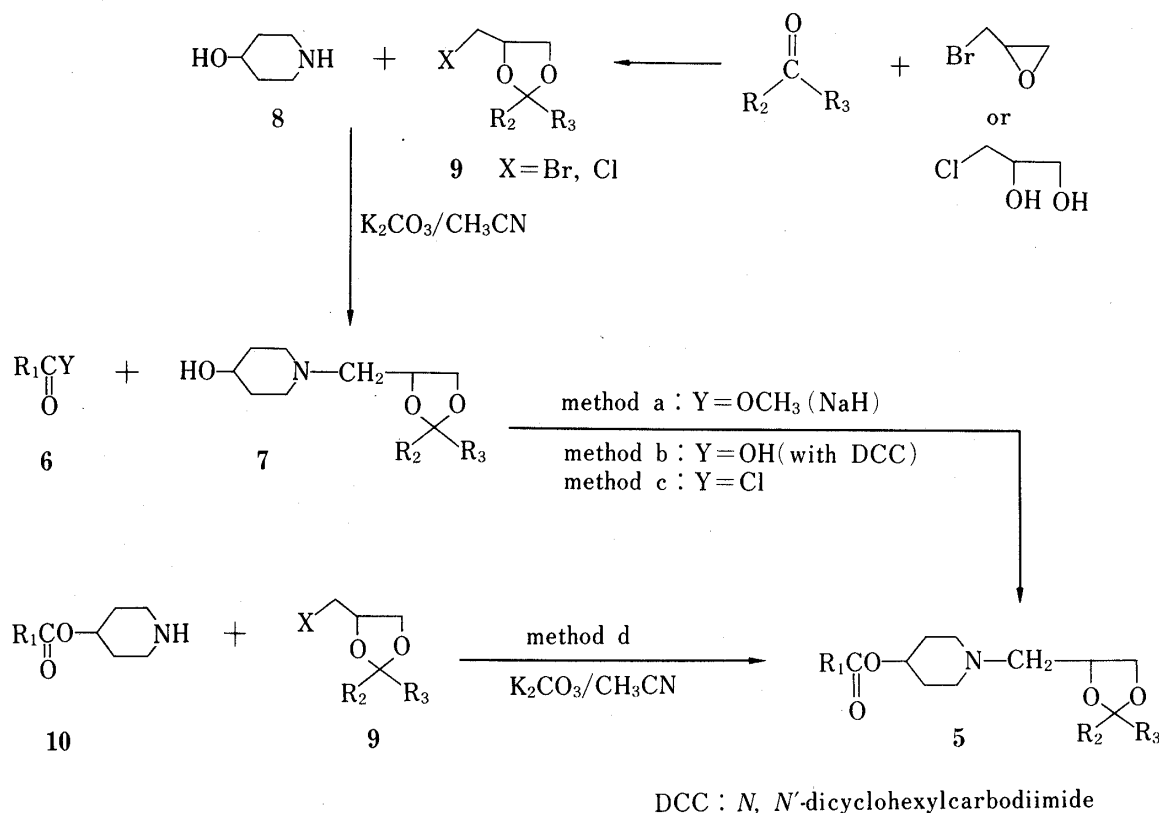


Chart 2

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.<sup>11,12)</sup> 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<sup>10)</sup> *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.<sup>3,4)</sup> 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 <sup>a)</sup>	mp <sup>b)</sup> (°C)	Yield <sup>c)</sup> (%)
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 <sup>d)</sup>	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 <sup>e)</sup>	94.4
5o	c	167.3—169.3 <sup>f)</sup>	95.1
5p	c	83.8—85.3 <sup>e)</sup>	98.9
5q	c	86.5—87.5 <sup>e)</sup>	95.2
5r	a	89.5—91.3 <sup>e)</sup>	68.1
5s	a	156.5—158.4 <sup>f)</sup>	70.4
5t	a	177.0—178.0	79.5
5u	a	204.0—207.0	91.3
5v	a	95.0—96.0 <sup>e)</sup>	83.6
5w	a	83.0—85.0 <sup>e, g)</sup>	90.6
		160.0—161.0 <sup>e, g)</sup>	
5x	a	195.0—197.0 <sup>h)</sup>	93.2
		solid oil <sup>h)</sup>	

a) Method a, transesterification; method b, dehydration in the presence of DCC; method c, esterification by use of acyl chloride; method d, dioxolanymethylation 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.

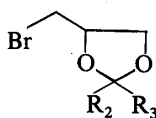
TABLE II. Spasmolytic Activities of 4-Acyloxy-1-(1,3-dioxolan-4-ylmethyl)piperidines (5)

Compd. 5	pA <sub>2</sub>	pD <sub>2</sub> '	Compd. 5	pA <sub>2</sub>	pD <sub>2</sub> '
5b	6.08		5m	6.99	
5c		5.03	5n <sup>a)</sup>	7.67	4.54
5d		5.37	5p		4.43
5e		5.45	5t		5.07
5i	4.98	4.98	BDP <sup>b)</sup>		4.80
5k		4.69	Atropine	9.20	
5l		4.80	Papaverine		5.10

a) The antagonistic activity was competitive at lower ( $\leq 10^{-5}$  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 <sub>2</sub>	R <sub>3</sub>	bp °C/Torr (mp, °C)	Yield <sup>a)</sup> (%)	MS (m/e)
9a <sup>b)</sup>	H	H	142.0—143.0/760 <sup>c)</sup>	73.0 <sup>d)</sup>	123/121 (M <sup>+</sup> - H) = 1/3
9b <sub>1</sub>	Me	Me	78.5/24	90.2	181/179 (M <sup>+</sup> - Me) = 1/1
9b <sub>2</sub> <sup>b)</sup>	Me	Me	93.0/113	75.8	137/135 (M <sup>+</sup> - Me) = 1/3
9c	Et	Et	78.5/8	73.4	195/193 (M <sup>+</sup> - Et) = 1/1
9d	<i>n</i> -Pr	<i>n</i> -Pr	105.0/8	85.7	209/207 (M <sup>+</sup> - <i>n</i> -Pr) = 1/1
9e	iso-Pr	iso-Pr	98.0/10	24.0	252/250 (M <sup>+</sup> ) = 1/1
9f	Me	Ph	143.0—145.7/7	80.0	243/241 (M <sup>+</sup> - Me) = 1/1
9g	-(CH <sub>2</sub> ) <sub>5</sub> -		115.0/10	87.0	236/234 (M <sup>+</sup> ) = 1/1
9h	<i>c</i> -Hex	Ph	124.0/0.03	83.8	326/324 (M <sup>+</sup> ) = 1/1
9i	PhCH <sub>2</sub>	PhCH <sub>2</sub>	193.0—195.0/4	76.3	257/255 (M <sup>+</sup> - PhCH <sub>2</sub> ) = 1/1
9j	Ph	Ph	(74.0) <sup>e)</sup>	91.2	243/241 (M <sup>+</sup> - Ph) = 1/1
9k	<i>c</i> -Hex	<i>c</i> -Hex	(58.5—59.5)	86.8	249/247 (M <sup>+</sup> - <i>c</i> -Hex) = 1/1

a) Isolated yield.

b) 4-Chloromethyl compound.

c) Lit.<sup>9)</sup>; bp 146—147 °C/745 Torr.

d) Prepared by the reaction of 1-chloro-2,3-propanediol and paraformaldehyde.

e) Lit.<sup>9)</sup>; 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 <sub>2</sub>	R <sub>3</sub>	bp °C/Torr (mp °C)	Yield <sup>a)</sup> (%)	MS (m/e)
7a	H	H	Oil	56.4 <sup>d)</sup>	187 (M <sup>+</sup> )
7b	Me	Me	159.0/11	93.0	215 (M <sup>+</sup> )
	Me	Me		99.8 <sup>c)</sup>	215 (M <sup>+</sup> )
	Me	Me	166.0—167.5/15	41.8 <sup>d)</sup>	215 (M <sup>+</sup> )
7c	Et	Et	158.0—159.0/4	86.7	243 (M <sup>+</sup> )
7d	<i>n</i> -Pr	<i>n</i> -Pr	170.0—170.5/4	95.5	271 (M <sup>+</sup> )
7e	-(CH <sub>2</sub> ) <sub>5</sub> -		Oil	87.1 <sup>e)</sup>	255 (M <sup>+</sup> )
7f	Ph	Ph	(101.2—101.7)	75.1	339 (M <sup>+</sup> )
7g	<i>c</i> -Hex	<i>c</i> -Hex	197.0/0.2	95.4	351 (M <sup>+</sup> )
7h	PhCH <sub>2</sub>	PhCH <sub>2</sub>	Oil	60.3 <sup>e)</sup>	367 (M <sup>+</sup> )
7i	Me	Ph	Oil <sup>f)</sup>	68.3 <sup>e)</sup>	277 (M <sup>+</sup> )
7j	<i>c</i> -Hex	Ph	(110.0—111.6) <sup>g)</sup>	75.8	345 (M <sup>+</sup> )
			Oil <sup>g)</sup>	84.2	345 (M <sup>+</sup> )

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<sub>2</sub>) 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<sub>2</sub> and R<sub>3</sub> are methyl groups, 3- and 4-benzoyloxy compounds (BDP and 5b) showed papaverine- and atropine-like activities, respectively; 2) when R<sub>2</sub> and R<sub>3</sub> are larger than a methyl group, 4-benzoyloxy compounds (5c, 5d, 5e, 5n,

TABLE V. <sup>1</sup>H-NMR and IR Spectral Data for 4-Acyloxy-1-(1,3-dioxolan-4-ylmethyl)piperidines (5)

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

TABLE V. (continued)

Compd. <sup>a)</sup>	<sup>1</sup> H-NMR <sup>b)</sup>		IR cm <sup>-1</sup>
	Solvent <sup>c)</sup>	$\delta$ ppm	
<b>5w</b> <sup>e)</sup>	A	1.62 (3H, s, CH <sub>3</sub> ), 3.60—4.00 (3H, m, C <sub>4</sub> -H and C <sub>5</sub> -H, in the dioxolane), 4.95 (1H, m, C <sub>4</sub> -H), 7.32 (15H, m, 3 × Ph)	3450 (OH) 1728 (C=O)
	A	1.59 (3H, s, CH <sub>3</sub> ), 3.35 (1H, m, C <sub>5</sub> -H, in the dioxolane), 4.00—4.30 (2H, m, C <sub>4</sub> -H and C <sub>5</sub> -H, in the dioxolane), 4.92 (1H, m, C <sub>4</sub> -H), 7.30 (15H, m, 3 × Ph)	3440 (OH) 1730 (C=O)
<b>5x</b> <sup>e)</sup>	A	1.05 (11H, m, c-Hex), 1.70 (4H, m, C <sub>3,5</sub> -H), 3.50—4.15 (3H, m, C <sub>4</sub> -H and C <sub>5</sub> -H, in the dioxolane), 4.90 (1H, m, C <sub>4</sub> -H), 7.30 (15H, m, 3 × Ph)	3488 (OH) 1730 (C=O)
	A	1.05 (11H, m, c-Hex), 3.21 (1H, m, C <sub>5</sub> -H, in the dioxolane), 3.90—4.45 (2H, m, C <sub>4</sub> -H and C <sub>5</sub> -H, in the dioxolane), 4.90 (1H, m, C <sub>4</sub> -H), 7.30 (15H, m, 3 × Ph)	3495 (OH) 1730 (C=O)

a) Free base unless otherwise noted.

b) Spectral data for C<sub>3</sub>-, C<sub>4</sub>-, and C<sub>5</sub>-protons are those of the corresponding piperidine unless otherwise mentioned.

c) A, CDCl<sub>3</sub>; B, CD<sub>3</sub>OD.

d) Hydrochloride.

e) The diastereoisomers were separated.

and **5t**) exhibited papaverine-like activities; 3) when R<sub>2</sub> and R<sub>3</sub> 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<sub>2</sub> and R<sub>3</sub>) 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. <sup>1</sup>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  $\delta$  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<sub>1</sub>)**—Stannic chloride (1.3 g, 0.005 mol) in CCl<sub>4</sub> (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<sub>2</sub>CO<sub>3</sub> 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<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The residual oil was distilled under reduced pressure to yield 17.6 g (90.2%) of **11b<sub>1</sub>** as a colorless oil. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 1.35 (3H, s, CH<sub>3</sub>), 1.44 (3H, s, CH<sub>3</sub>), 3.35 (2H, m, BrCH<sub>2</sub>), 3.80—4.30 (3H, m, C<sub>4,5</sub>-H). MS *m/e*: 181, 179 (M<sup>+</sup> - CH<sub>3</sub>, 1:1). The other derivatives, 4-halomethyl-1,3-dioxolanes (**11a**, **11b<sub>2</sub>**—**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<sub>1</sub>** (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<sub>2</sub>CO<sub>3</sub> (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<sub>2</sub>SO<sub>4</sub>

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

Compd. 5	MS <sup>a)</sup> <i>m/e</i>	Formula	Analysis (%)		
			Found (Calcd)		
			C	H	N
5a	397 (M <sup>+</sup> ), 396 (M <sup>+</sup> - H),	C <sub>23</sub> H <sub>27</sub> NO <sub>5</sub> · HCl	63.51	6.77	3.08
	324 (base peak)		(63.66)	6.51	3.23)
5b	425 (M <sup>+</sup> ), 410 (M <sup>+</sup> - Me),	C <sub>25</sub> H <sub>31</sub> NO <sub>5</sub> · HCl	65.11	6.72	3.12
	324 (base peak)		(64.99)	6.98	3.03)
5c	453 (M <sup>+</sup> ), 424 (M <sup>+</sup> - Et),	C <sub>27</sub> H <sub>35</sub> NO <sub>5</sub> · HCl	66.45	7.25	3.12
	324 (base peak)		(66.18)	7.41	2.86)
5d	481 (M <sup>+</sup> ), 438 (M <sup>+</sup> - <i>n</i> -Pr),	C <sub>29</sub> H <sub>39</sub> NO <sub>5</sub> · HCl	67.18	7.28	2.96
	324 (base peak)		(67.23)	7.59	2.70)
5e	481 (M <sup>+</sup> ), 438 (M <sup>+</sup> - iso-Pr),	C <sub>29</sub> H <sub>39</sub> NO <sub>5</sub> · HCl	67.35	7.43	2.81
	324 (base peak)		(67.23)	7.59	2.70)
5f	465 (M <sup>+</sup> ), 324 (base peak)	C <sub>28</sub> H <sub>35</sub> NO <sub>5</sub>		— <sup>b)</sup>	
5g	349 (M <sup>+</sup> ), 334 (M <sup>+</sup> - Me),	C <sub>19</sub> H <sub>27</sub> NO <sub>5</sub> · <i>p</i> -nitrobenzoate	60.22	6.35	5.20
	248 (base peak)		(60.46)	6.24	5.42)
5h	403 (M <sup>+</sup> ), 388 (M <sup>+</sup> - Me),	C <sub>24</sub> H <sub>37</sub> NO <sub>4</sub> · HCl	65.63	8.59	3.24
	302 (base peak)		(65.51)	8.71	3.18)
5i	423 (M <sup>+</sup> ), 408 (M <sup>+</sup> - Me),	C <sub>25</sub> H <sub>29</sub> NO <sub>5</sub> · HCl	65.47	6.38	3.16
	322 (base peak)		(65.28)	6.57	3.05)
5j	395 (M <sup>+</sup> ), 394 (M <sup>+</sup> - H),	C <sub>23</sub> H <sub>35</sub> NO <sub>5</sub> · HCl	63.67	6.29	3.01
	322 (base peak)		(63.96)	6.07	3.24)
5k	409 (M <sup>+</sup> ), 394 (M <sup>+</sup> - Me),	C <sub>25</sub> H <sub>31</sub> NO <sub>4</sub> · HCl	67.12	7.45	2.89
	308 (base peak)		(67.33)	7.23	3.14)
5l	407 (M <sup>+</sup> ), 392 (M <sup>+</sup> - Me),	C <sub>25</sub> H <sub>29</sub> NO <sub>4</sub> · HCl	67.57	6.97	3.08
	306 (base peak)		(67.63)	6.81	3.15)
5m	431 (M <sup>+</sup> ), 416 (M <sup>+</sup> - Me),	C <sub>25</sub> H <sub>37</sub> NO <sub>5</sub> · HCl · H <sub>2</sub> O	61.97	8.11	2.75
	330 (base peak)		(61.78)	7.88	2.88)
5n	561 (M <sup>+</sup> ), 478 (M <sup>+</sup> - <i>c</i> -Hex),	C <sub>35</sub> H <sub>47</sub> NO <sub>5</sub>	74.75	8.72	2.36
	324 (base peak)		(74.83)	8.43	2.49)
5o	457 (M <sup>+</sup> ), 380 (M <sup>+</sup> - Ph),	C <sub>29</sub> H <sub>31</sub> NO <sub>4</sub> · oxalate	67.96	6.21	2.48
	232 (base peak)		(68.00)	6.07	2.56)
5p	395 (M <sup>+</sup> ), 318 (M <sup>+</sup> - Ph),	C <sub>24</sub> H <sub>29</sub> NO <sub>4</sub>	72.77	7.55	3.42
	170 (base peak)		(72.89)	7.39	3.54)
5q	381 (M <sup>+</sup> ), 304 (M <sup>+</sup> - Ph),	C <sub>23</sub> H <sub>27</sub> NO <sub>4</sub>	72.40	7.36	3.59
	156 (base peak)		(72.42)	7.14	3.67)
5r	411 (M <sup>+</sup> ), 334 (M <sup>+</sup> - Ph),	C <sub>24</sub> H <sub>29</sub> NO <sub>5</sub>	70.21	7.37	3.27
	186 (base peak)		(70.05)	7.10	3.40)
5s	473 (M <sup>+</sup> ), 397 (M <sup>+</sup> - Ph),	C <sub>29</sub> H <sub>31</sub> NO <sub>5</sub> · oxalate	66.12	7.31	2.40
	248 (base peak)		(66.06)	7.03	2.49)
5t	577 (M <sup>+</sup> ), 486 (M <sup>+</sup> - CH <sub>2</sub> Ph),	C <sub>37</sub> H <sub>39</sub> NO <sub>5</sub> · HCl	72.28	6.76	2.19
	324 (base peak)		(72.36)	6.56	2.28)
5u	549 (M <sup>+</sup> ), 472 (M <sup>+</sup> - Ph),	C <sub>35</sub> H <sub>35</sub> NO <sub>5</sub> · HCl	71.58	6.31	2.27
	324 (base peak)		(71.71)	6.19	2.39)
5v	533 (M <sup>+</sup> ), 456 (M <sup>+</sup> - Ph),	C <sub>35</sub> H <sub>35</sub> NO <sub>4</sub>	78.52	6.88	2.50
	308 (base peak)		(78.77)	6.61	2.62)
5w <sup>c)</sup>	487 (M <sup>+</sup> ), 472 (M <sup>+</sup> - Me),	C <sub>30</sub> H <sub>33</sub> NO <sub>5</sub>	73.81	6.96	2.68
	410 (M <sup>+</sup> - Ph), 324 (base peak)		(73.90)	6.82	2.87)
	487 (M <sup>+</sup> ), 472 (M <sup>+</sup> - Me),	C <sub>30</sub> H <sub>33</sub> NO <sub>5</sub>	73.74	6.99	2.76
	410 (M <sup>+</sup> - Ph), 324 (base peak)		(73.90)	6.82	2.87)
5x <sup>c)</sup>	555 (M <sup>+</sup> ), 478 (M <sup>+</sup> - Ph),	C <sub>35</sub> H <sub>41</sub> NO <sub>5</sub> · HCl	70.78	7.31	2.45
	472 (M <sup>+</sup> - <i>c</i> -Hex), 324 (base peak)		(70.99)	7.15	2.37)
	555 (M <sup>+</sup> ), 478 (M <sup>+</sup> - Ph),	C <sub>35</sub> H <sub>41</sub> NO <sub>5</sub>		— <sup>b)</sup>	
	472 (M <sup>+</sup> - <i>c</i> -Hex), 324 (base peak)				

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. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 1.35 (3H, s, CH<sub>3</sub>), 1.40 (3H, s, CH<sub>3</sub>), 1.76 (4H, m, C<sub>3,5</sub>-H in the piperidine), 2.30 (1H, br s, OH, disappeared with D<sub>2</sub>O), 2.50 (6H, m, N-CH<sub>2</sub> × 3), 4.20 (1H, m, C<sub>4</sub>-H in the piperidine). IR  $\nu_{\max}^{\text{film}}$  cm<sup>-1</sup>: 3380 (OH). MS *m/e*: 215 (M<sup>+</sup>), 200 (M<sup>+</sup> - CH<sub>3</sub>). 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<sub>3</sub>, 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<sub>2</sub>SO<sub>4</sub> 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<sub>2</sub>O to afford colorless needles.

Method b: 4-(Fluorene-9-carboxyloxy)-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<sub>2</sub>SO<sub>4</sub>, 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-Benzoyloxy-1-(2,2-diisopropyl-1,3-dioxolan-4-ylmethyl)piperidine (**5e**): A mixture of 4-benzoyloxy-piperidine (**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<sub>2</sub>CO<sub>3</sub> (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 <sup>1</sup>H-NMR and IR spectral data for **5a-x** are summarized in Table V, and MS and analytical data in Table VI.

**3-Benzoyloxy-1-(2,2-dimethyl-1,3-dioxolan-4-ylmethyl)piperidine (BDP)**—A solution of **9b<sub>1</sub>** (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<sub>2</sub>CO<sub>3</sub> (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<sub>6</sub> 163.0 °C. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 1.32 (3H, s, CH<sub>3</sub>), 1.40 (3H, s, CH<sub>3</sub>), 1.76 (4H, m, C<sub>4,5</sub>-H in the piperidine), 2.45 (6H, m, N-CH<sub>2</sub> × 3), 3.60 (1H, br s, OH, disappeared with D<sub>2</sub>O). IR  $\nu_{\max}^{\text{film}}$  cm<sup>-1</sup>: 3380 (OH). MS *m/e*: 215 (M<sup>+</sup>), 200 (M<sup>+</sup> - CH<sub>3</sub>).

*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<sub>2</sub>SO<sub>4</sub> 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<sub>2</sub>O to afford colorless needles. mp 189.0–191.0 °C. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 1.30 (3H, s, CH<sub>3</sub>), 1.35 (3H, s, CH<sub>3</sub>), 1.60 (4H, m, C<sub>4,5</sub>-H in the piperidine), 2.45 (6H, m, N-CH<sub>2</sub> × 3), 4.95 (1H, m, C<sub>3</sub>-H), 7.30 (10H, m, Ph × 2). IR  $\nu_{\max}^{\text{film}}$  cm<sup>-1</sup>: 3440 (OH), 1730 (C=O). MS *m/e*: 425 (M<sup>+</sup>), 410 (M<sup>+</sup> - CH<sub>3</sub>), 324 (base peak). *Anal.* Calcd for C<sub>25</sub>H<sub>31</sub>NO<sub>5</sub>·HCl: C, 64.99; H, 6.98; N, 3.03. Found: C, 65.07; H, 6.81; N, 3.14.

**Acknowledgements** The authors wish to express their gratitude to Prof. Issei Takayanagi, School of Pharmaceutical Sciences, Toho University, and Prof. Shiro Ikegami, Faculty of Pharmaceutical Sciences, Teikyo University, for helpful advice and encouragement throughout this work. Thanks are also due to the members of the Pharmacological Laboratory, Ohta Pharmaceutical Co., Ltd., for pharmacological tests.

#### References and Notes

- 1) a) A part of this work was presented at the 11th Congress of Heterocyclic Chemistry, Kanazawa, October 1978; b) T. Kutsuma, S. Sugai, H. Ikawa, and Y. Hasegawa, Japan. Patent Kokai Koho 77-83763 (1977) [*Chem. Abstr.*, **88**, 6859a (1978)].
- 2) Present address: Research Laboratories, Fuji Zoki Seiyaku K. K., Komiyacho, Hachioji, Tokyo 192, Japan.

- 3) R. R. Burtner and J. W. Cusic, *J. Am. Chem. Soc.*, **65**, 262 (1943).
- 4) J. H. Biel, H. L. Friedman, H. A. Leiser, and E. P. Sprengeler, *J. Am. Chem. Soc.*, **74**, 1485 (1952).
- 5) O. Hromatka, C. Csoklich, and I. Hofbauer, *Monatsh. Chem.*, **83**, 1321 (1952).
- 6) a) H. R. Ing, *Science*, **109**, 264 (1949); b) H. R. Ing, P. Kordik, and D. P. H. Tudor Williams, *Br. J. Pharmacol.*, **7**, 103 (1952).
- 7) L. Gyermek and K. R. Unna, *Proc. Soc. Exp. Biol. Med.*, **98**, 882 (1958).
- 8) E. Fourneau, D. Bovet, F. Bovet, and G. Montezin, *Bull. Soc. Chim. Biol.*, **26**, 134 (1944).
- 9) F. F. Blicke and F. E. Anderson, *J. Am. Chem. Soc.*, **74**, 1377 (1952).
- 10) B. B. Brown and H. W. Werner, *J. Pharmacol. Exp. Ther.*, **97**, 157 (1949).
- 11) Y. Wu and R. F. Feldkamp, *J. Org. Chem.*, **26**, 1519 (1961).
- 12) J. M. van Rossum, *Arch. Int. Pharmacodyn. Ther.*, **143**, 299 (1963).
- 13) I. Takayanagi, *Pharmacometrics*, **2**, 131 (1968).