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Structure–Activity Relationship of 3- and 4-Acyloxy-1-(1,3-dioxolan-4-ylmethyl)piperidine Derivatives[1)]

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Derivatives of 3- and 4-acyloxy-1-(1,3-dioxolan-4-ylmethyl)piperidine were synthesized and tested for atropine-like activities on the ileum from guinea pigs. The structure–activity relationship was assessed. Features favoring potent atropine-like action were considered to be as follows: (1) both the acyloxy group and the dioxolane ring should be diequatorial on the piperidine ring, (2) the acyloxy group should be moderately bulky, and (3) a substituent on the dioxolane ring is unnecessary. The highest activity (pA_2) determined was 8.64 which is about 50 times that of scopolamine *N*-butyl bromide.

Keywords——stereochemistry; structure–activity relationship; 3- and 4-acyloxy-1-(1,3-dioxolan-4-ylmethyl)piperidine derivative; spasmolytic activity; atropine-like action; acetylcholine receptor; stereoisomer

In order to study the relationship between stereochemical structure and spasmolytic activity, we synthesized about fifty derivatives of 3- and 4-acyloxy-1-(1,3-dioxolan-4-ylmethyl)piperidine and tested them for atropine-like activities on the ileum from guinea pigs.[3)] Their basal molecular structure consists of two parts, acyloxypiperidine (**a**)[4)] and dioxolanylmethylpiperidine (**b**)[5)] known to have spasmolytic activities (Chart 1).

In this work, we studied not only the synergistic effect caused by a combination of these two compounds but also the relationship between stereochemical structure and biological activity. By quaternization of piperidine in the basal molecular structure, two stereoisomers

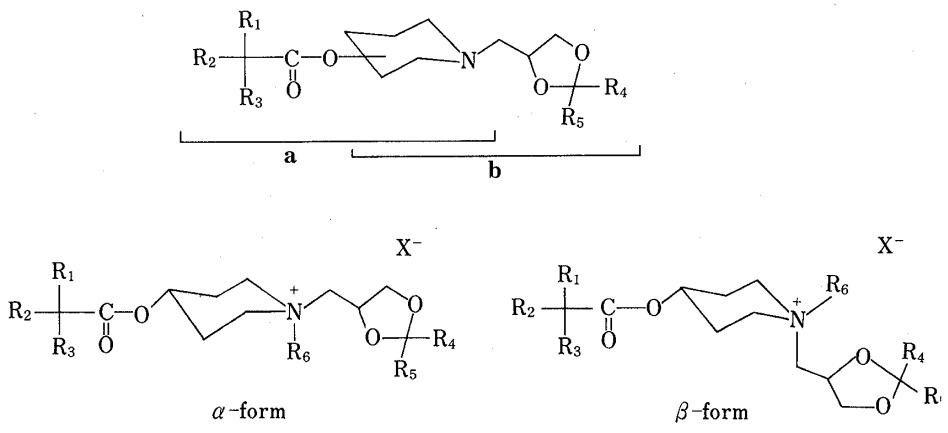

Chart 1

are obtained as epimers on the piperidine ring. For convenience, they are termed α- and β-forms. Their syntheses and stereochemistry have been described.[3b] The optical resolution of the asymmetric dioxolane ring on each epimer was so difficult that each compound was studied as a racemate.

The present investigation examined the influence of stereoisomerism, the structure of the acyloxy group, the substituent on the dioxolane ring, *etc.*, in these derivatives on spasmolytic activity.

Materials and Methods

Assay of Spasmolytic Activity——Male guinea pigs, 200 to 300 g, were starved overnight then killed by a blow on the head and the ileum was isolated. A piece (1.5 to 2.0 cm) of the middle ileum was suspended in a 10 ml organ bath filled with Locke–Ringer solution kept at 32 °C and bubbled through with air. Responses of the ileum to drugs were recorded isotonically. Competitive antiacetylcholine activities were expressed as pA_2 values.[6] After the control dose-response curves of acetylcholine had been obtained cumulatively, the curve for acetylcholine in the presence of an antagonist was obtained with ileum which had been treated beforehand with the antagonist for 5 min. Water-insoluble compounds were dissolved in a mixture of propylene glycol, ethanol and water (7 : 1 : 2) and a 0.1 to 0.3 ml aliquot was added to the organ bath.

Drugs——The following drugs were used: Acetylcholine chloride (Tokyo Kasei Kogyo Co.), atropine sulfate (Tokyo Kasei Kogyo Co.), scopolamine *N*-butyl bromide (Hata Pharmaceutical Co.).

Results and Discussion

1) Comparison of α- and β-Forms; Stereochemical Aspects

As shown in Table I, the α-forms of compounds **1** to **4** were obviously more potent than their β-forms. In the case of compound **2**, for example, the α-form was about 80 times as active as the β-form. On the other hand, in the case of compound **5**, the activity of the α-form was equal to or slightly weaker than that of the β-form.

These results suggest that the activities of α-forms are generally much higher than those of β-forms in derivatives with relatively large acyloxy groups on the piperidine ring and small substituents on the dioxolane ring, whereas derivatives with larger acyloxy goups on the piperidine ring and larger substituents on the dioxolane ring show lower activities and the difference in activities between α- and β-forms is not marked.

Both electronic and steric interactions involving the oxygen atoms of the acyloxy group or dioxolane ring and the receptor should be concerned in the pharmacological activity.

TABLE I. Spasmolytic Activities of α- and β-Forms

Compd. No.	R_1	R_2	R_3	R_4	R_5	R_6	X	Position of acyloxy	Epimer	pA_2	Activity[a] ratio
1	C_6H_5	C_6H_5	OH	CH_3	CH_3	CH_3	Br	4	α	7.76	6.17
									β	6.17	0.16
2	$C_{12}H_8$[b]		H	CH_3	CH_3	CH_3	Br	4	α	7.96	9.77
									β	6.06	0.12
3	C_6H_5	C_6H_5	H	CH_3	CH_3	CH_3	Cl	4	α	7.43	2.88
									β	5.80	0.07
4	C_6H_5	C_6H_5	OH	C_2H_5	C_2H_5	CH_3	Br	4	α	7.38	2.57
									β	6.12	0.14
5	C_6H_5	C_6H_5	OH	C_6H_5	C_6H_5	CH_3	Br	4	α	6.43	0.29
									β	6.62	0.45
6	C_6H_5	C_6H_5	OH	CH_3	CH_3	C_2H_5	Br	4	α	6.88	0.81
7	C_6H_5	C_6H_5	OH	H	H	CH_3	Br	4	α	8.08	12.88

a) Activity ratio: scopolamine *N*-butyl bromide = 1. *b*) 2,2′-Biphenylene.

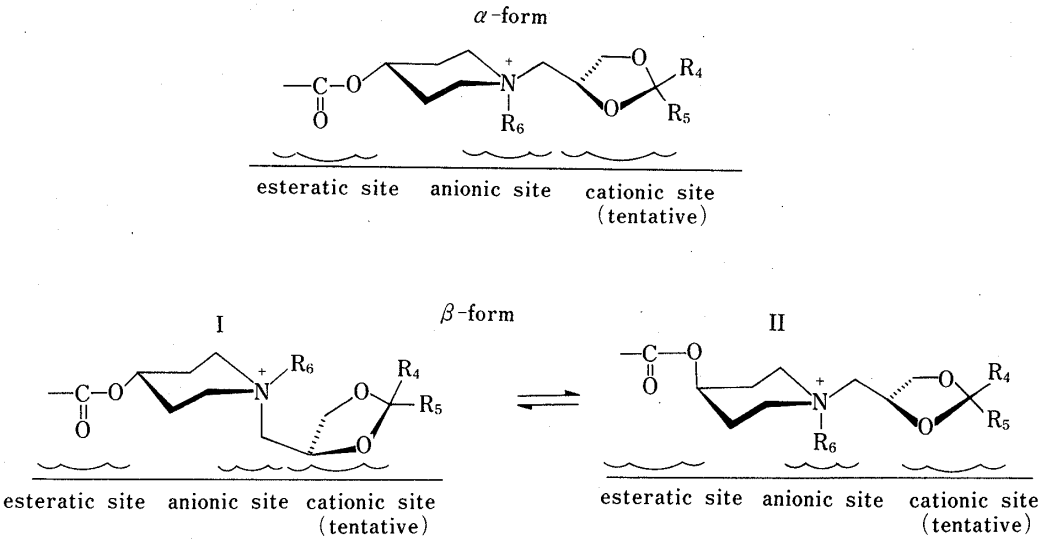

Fig. 1. Postulated Modes of Interaction of the Compounds with the Receptor

However, from the previous results[5] and our observations,[3b] we consider that the steric factor predominates over the electronic factor in the interaction with the receptor.

Figure 1 illustrates postulated modes of interaction of the drugs used with the receptor. In the α-form, the acyloxy group and dioxolanylmethyl group will take a diequatorial configuration in the piperidine chair form, the molecular conformation appears to be flattened and could be spread over the receptor.[7] On the other hand, in the β-form, the conformation is not confirmed and an equilibrium state must be considered: (1) the acyloxy group is equatorial and the dioxolanylmethyl is axial I, and (2) *vice versa* II (Fig. 1). Such conformational conversion might make the binding to the receptor less efficient. In addition, in both I and II, the acyloxy group and the dioxolane ring cannot take up the same plane, possibly hindering the combination with the receptor. Furthermore, in I, there appears to be steric hindrance of the anionic site of the receptor, whereas in II, the acyloxy group may be distant from the esteratic site of the receptor.

These stereochemical findings suggest that lower activity of the β-form is to be expected. The influence of the steric hindrance on the anionic site is also suggested by the fact that the replacement of an N-methyl group by an N-ethyl group markedly decreased the activity (activity ratio, compd. **1**: compd. **6** = 8 : 1).

When a larger substituent was introduced into the dioxolane ring, the activity of the β-form was equal to or higher than that of the α-form (compd. **5**). From a stereochemical viewpoint, this may be explained as follows: in the α-form, a larger substituent seems to interfere with the combination of the dioxolane ring with the "cationic site," whereas in conformation I of the β-form, the dioxolane ring itself appears to be quite distant from the receptor, and not parallel to it.

These results suggest that the substituent of the dioxolane ring of these compounds is of less importance in relation to the drug effect than the two oxygen atoms of the dioxolane ring. It is possible that the receptor site which we tentatively termed the "cationic site" might be equivalent to the esteratic site, and these compounds might combine with two vicinal receptor units to show biological action.

2) Comparison of Derivatives Having an Acyloxy Group at Position 3 or 4 of the Piperidine Ring

Figure 2 shows two derivatives, the upper having the acyloxy group at position 3 and the

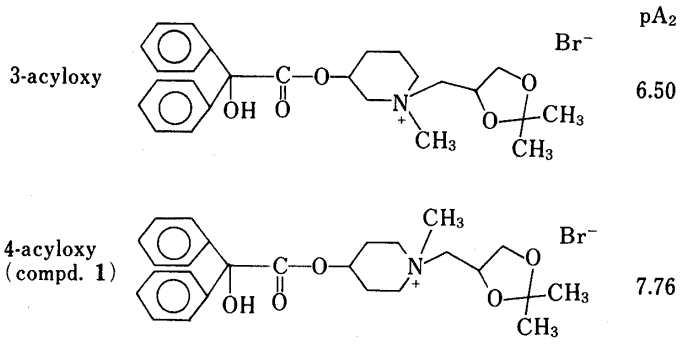

Fig. 2. Influence of the Position of the Acyloxy Group on the Piperidine Ring upon Spasmolytic Activity

TABLE II. Spasmolytic Activities of α-Forms and Mixtures

Compd. No.	R_1	R_2	R_3	R_4	R_5	R_6	X	Position of acyloxy	Epimer	pA_2	Activity ratio
8	$C_{12}H_8O$[a]		H	CH_3	CH_3	CH_3	Br	4	α	8.64	46.77
9	C_6H_5	C_6H_{11}[b]	OH	CH_3	CH_3	CH_3	Br	4	α	8.28	20.42
10	C_6H_5	C_6H_5	OH	C_6H_5	C_6H_{11}[b]	CH_3	Br	4	α	6.42	0.28
11	C_6H_5	C_6H_5	OH	C_6H_{11}[b]	C_6H_{11}[b]	CH_3	Br	4	m[c]	6.94	0.93
12	C_6H_5	C_6H_5	OH	CH_2–C_6H_5	CH_2–C_6H_5	CH_3	Br	4	m	6.51	0.35
13	C_6H_5	H	H	C_6H_5	C_6H_5	CH_3	Br	4	m	6.64	0.47
14	C_6H_5	H	OH	C_6H_5	C_6H_5	CH_3	Br	4	m	6.69	0.52
15	CH_3	H	OH	C_6H_5	C_6H_5	CH_3	Br	4	α	5.78	0.07
16	CH_3	H	H	C_6H_5	C_6H_5	CH_3	Br	4	m	5.92	0.09

a) 2,2′-Oxabiphenylene. *b*) Cyclohexyl. *c*) Nearly 1 : 1 mixture of α- and β-forms.

lower having it at position 4 of the piperidine ring. The latter showed about 19 times more activity than the former. In the acetylcholine molecule, when the molecule is maximally extended, the distance between the nitrogen atom and the oxygen atom of the acyloxy group was estimated to be 5.3 Å.[10] In the actual molecular conformation, however, the distance should be shorter. We estimated[11] that the separation might be 3.7 to 4.0 Å for atropine or scopolamine, and 3.6 to 3.8 Å and 4.0 to 4.3 Å for the 3-position and the 4-position derivatives of the α-form, respectively.

Hence, such activity difference between the 3-position and 4-position derivatives can probably not be explained merely by differences in the nitrogen-oxygen separation. The reduction of the activity of the 3-position derivatives appears to be related to a steric hindrance to receptor binding due to the proximity of the acyloxy group and the dioxolane ring.

3) Structures of the Acyloxy Group and the Substituent on the Dioxolane Ring (Tables I and II)

It has been reported that compounds **a** and **b** (Chart 1) having a larger acyloxy group or a larger substituent on the dioxolane ring show higher pharmacological activity.[4,5] We therefore studied the relationship between the structure and the activity of our compound, which is composed of **a** and **b**. Compounds **1**, **2**, **3**, **8** and **9** have a large acyloxy group and small substituent R_4, R_5 and R_6 such as a methyl group. The pA_2 values of their α-forms were relatively large. That of compound **8** was 8.64, the highest activity of all derivatives tested. Thus, higher activity was seen with the compounds having a large acyloxy group, as in the

case of acetylcholine derivatives.[10,11] On the other hand, it is clear from the results with **6**, **10**, **11** and **12** that compounds having larger structure in both the acyloxy group and the substituent on the dioxolane ring showed lower activity, and a further decrease in activity was seen with compounds having a smaller acyloxy group and a larger substituent on the dioxolane ring (**13** to **16**).

Therefore, in these derivatives, the acyloxy group is obviously of great importance for the spasmolytic activity, while the dioxolane ring seems to play some role; however, if the acyloxy group is very small, the dioxolane ring appears to be more important (**15** and **16**).[5c] It is clear from a comparison of compounds **1**, **4** and **7** that when the acyloxy group is bulky such as benziloyloxy, a substituent on the dioxolane ring is apparently unnecessary. It has been reported that the introduction of phenyl and cyclohexyl groups into the acyloxy group[12] or the dioxolane ring[13] increases the activity as compared with the corresponding diphenyl compound. In the present study, the introduction of phenyl and cyclohexyl groups into the acyloxy group (compd. **9**) gave a markedly higher activity than that of the benziloyloxy compound (compd. **1**), but their introduction into the dioxolane ring (compd. **10**) gave activity almost equal to that of the benziloyloxy compound (compd. **5**).

In conclusion, potent atropine-like action appears to require the following features in these derivatives: (1) the acyloxy group and the dioxolane ring on the piperidine ring should be diequatorial (*i.e.* α-form conformation), (2) the acyloxy group should be moderately bulky, and (3) a substituent on the dioxolane ring is unnecessary.

References and Notes

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