assigned chemical shifts and conformations. Namely, for I. II and III, the preferred conformations are *trans*, while for IV, V and VI they are *cis*"a."

In Table III, however, all the observed values seem to be smaller than the estimated ones. This suggests a small contribution of the *cis*"a" conformer for I, II and III and/or the *trans* conformer for IV, V and VI.

As shown in the previous report,[4] the C-6 chemical shift acts as an indicator of the equilibrium state "*trans*⇌*cis*"a" " of benzo[*a*]quinolizidines and can be used to determine the population of *trans* conformer ($P_{trans}$). Based on the data[4] that the C-6 chemical shifts are 53.4 ppm and 43.2 ppm for the 100% *trans* conformation and the 100% *cis*"a" conformer, the *trans* population ($P_{trans}$) can be estimated from eq. (1), where $\delta_{C-6}$ is the C-6

$$\frac{\delta_{C-6}-43.2}{53.4-43.2} \times 100 = P_{trans} \qquad (1)$$

chemical shift. In this work, this approach has been applied to six benzo[*a*]quinolizidine derivatives and estimated $P_{trans}$ values are presented in the last column of Table I. These values show that the state of equilibrium is affected by the position and/or the kind of substituent, as might be expected.

Our approach, employing $\Delta_{C-T}$ or the C-6 chemical shift, represents a valuable empirical approach which should aid in determining the stereochemistries of new benzo[*a*]quinolizidine derivatives which may be prepared in the future.

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## Atropine-like Activities of 2-Substituted 5-Piperidinomethylfuran Derivatives

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2-Substituted 5-piperidinomethylfuran derivatives were synthesized and their atropine-like and antihistamine activities were tested. The $pA_2$ values of the tested compounds for atropine-like activity were 7.50 to 5.21, less than that for atropine. The antihistamine activities ($pA_2$ values: 6.64 to 4.31) were much less than that of chlorpheniramine. Methylation of piperidine essentially did not affect the atropine-like activities but considerably decreased both the competitive and noncompetitive antihistamine activities.

**Keywords**——atropine-like activity; antihistamine activity; papaverine-like activity; 2-substituted 5-piperidinomethylfuran; effect of methylation of piperidine

2-Furfuryltrimethylammonium (furmethide) and its 5-methylderivative were found to have potent muscarinic activities.[2,3] It is well known that in a series of cholinergic drugs agonistic activity is replaced by antagonistic activity on replacing a part of the

1) Location: *a) Kawada-cho, Shinjuku-ku, Tokyo; b) Miyama, Funabashi, Chiba; c) Sadohara-cho, Shinjuku-ku, Tokyo.*

2) E.J. Fellows and A.E. Livingston, *J. Pharmacol. Exp. Ther.*, **68**, 231 (1940).

3) H.R. Ing, P. Kordik and D.P.H.T. Williams, *Brit. J. Pharmacol.*, **7**, 103 (1952).

agonist molecule with large groups. Therefore, in the present study, compounds having large groups at the 5-position of furmethide and piperidine in place of the trimethylammonium moiety of furmethide were synthesized and assayed for antiacetylcholine (atropine-like), antihistamine and papaverine-like activities.

## Materials and Methods

The procedures used for the preparation of compounds **1**—**6** are outlined in Charts 1 and 2. 2-(α-Hydroxybenzyl)-5-piperidinomethylfuran (**5**) and 2-(α-hydroxycyclohexylmethyl)-5-piperidinomethylfuran (**6**) were obtained by the reaction of 5-piperidinomethylfurfural I with phenylmagnesium bromide and cyclohexylmagnesium bromide, respectively. The secondary alcohols **5** and **6** were oxidized with manganese dioxide or by the Oppenauer's oxidation to the corresponding ketones II, which gave 2-(α-cyclohexyl-α-hydroxybenzyl)-5-piperidinomethylfuran (**1**) and 2-(α-hydroxybenzhydryl)-5-piperidinomethylfuran (**2**), respectively.

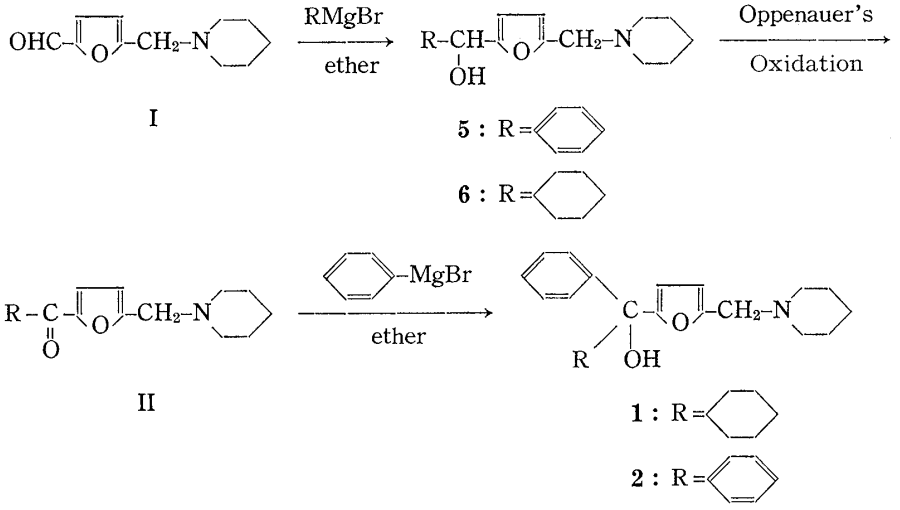



Chart 1

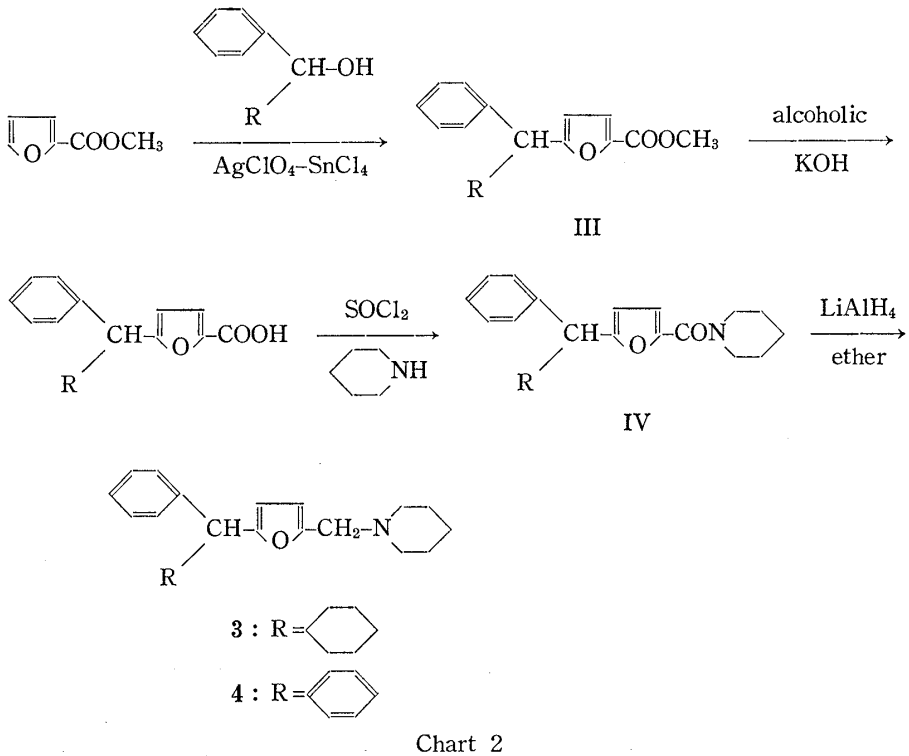



Chart 2

on Grignard reaction with phenylmagnesium bromide (Chart 1). Methyl 5-(α-cyclohexylbenzyl)-2-furoate and 5-benzhydryl-2-furoate (III) were obtained from methyl-2-furoate by the reaction with α-cyclohexylbenzyl alcohol and benzhydryl alcohol, respectively. 5-Substituted 2-furoates III were converted to the corresponding piperidides, which were reduced in ether with $LiAlH_4$ to 2-(α-cyclohexylbenzyl)-5-piperidinomethylfuran (3) and 2-benzhydryl-5-piperidinomethylfuran (4), respectively (Chart 2). Various piperidinium halides were prepared from the bases **1**—**6** in the usual way. Detail of the experimental procedures will be reported elsewhere in the near future.

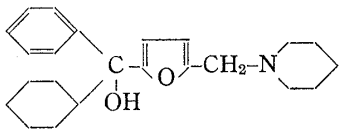
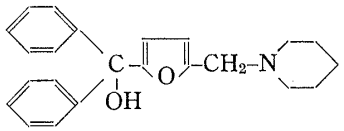
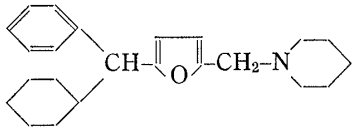
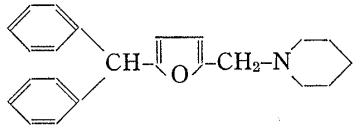
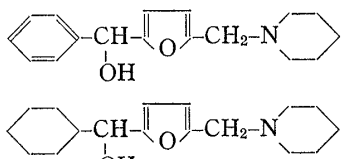
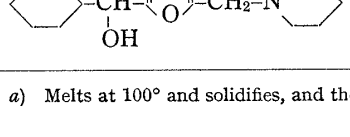
Male guinea pigs, weighing 250 to 350 g were killed and a piece (4 to 5 cm) taken from the middle ileum was suspended in a 50 ml organ bath filled with Tyrode's solution (NaCl 137, KCl 2.7, $CaCl_2$ 1.8, $MgCl_2$ 1.1, $NaH_2PO_4$ 5.6, $NaHCO_3$ 11.9 and glucose 5.6 mM) at 32° and bubbled through with air. The responses of the ileum to drugs were recorded isotonically. Competitive and noncompetitive antagonistic activities (papaverine-like activity) were expressed as $pA_2$[4] and $pD_2'$[5] values, respectively. The control concentration action curve of an agonist was first obtained, then the curve for the agonist in the presence of an antagonist was obtained using ileum which had been treated for 5 min beforehand with the antagoinst. The values were calculated according to the tables of van Rossum.[6]

*Rectus abdominis* muscles isolated from female frogs (*R. nigromaculata*) weighing 25 to 40 g were used in some experiments.[7] The isolated skeletal muscle was suspended in Ringer's solution (NaCl 115, KCl 2.5, $CaCl_2$ 1.8, $Na_2HPO_4$ 2.15 and $NaH_2PO_4$ 0.43 mM) at 20° and bubbled through with air. The responses to acetylcholine were also recorded isotonically.

## Results and Discussion

Chemical structures and properties of the synthesized compounds are listed in Table I. The test compounds had atropine-like and antihistamine activities, as summarized in

Table I. Chemical Structures and Properties of 2-Substituted 5-Piperidinomethylfuran Derivatives

| No. | Compound | | mp (°C) | Appearance | Recryst. solvent |
|---|---|---|---|---|---|
| **1a** |  | ·HCl | 161 (dec.) | Colorless prisms | Methanol–acetone–ether |
| **1b** | | ·$CH_3I$ | 178 (dec.) | Colorless needles | Acetone–petroleum ether |
| **1c** | | ·$C_2H_5I$ | 161—162 | Colorless prisms | Acetone–petroleum ether |
| **1d** | | ·$n$-$C_4H_9I$ | 164—165 | Colorless prisms | Acetone–petroleum ether |
| **2a** |  | ·HCl | 170 (dec.) | Colorless prisms | Methanol–acetone–ether |
| **2b** | | ·$CH_3I$ | 185 (dec.) | Colorless needles | Methanol–ether |
| **3a** |  | ·HCl·$H_2O$ | 100—128[a] | Colorless needles | Methanol–acetone–ether |
| **3b** | | ·$CH_3I$ | 134—138 | Colorless needles | Acetone–ether |
| **4a** |  | ·HCl | 182—184 (dec.) | Colorless scales | Acetone–ether |
| **4b** | | ·$CH_3I$ | 171 (dec.) | Colorless needles | Methanol–ether |
| **5a** |  | ·HCl | 158—160 (dec.) | Colorless prisms | Methanol–acetone–ether |
| **5b** | | ·$CH_3I$ | 127—129 | Colorless needles | Methanol–acetone–ether |
| **6a** |  | ·HCl | 192 (dec.) | Colorless needles | Methanol–ether |

a) Melts at 100° and solidifies, and then remelts at about 128°.

4) O. Arunlakshana and H.O. Schild, *Brit. J. Pharmacol.*, **14**, 48 (1959).
5) E.J. Ariens and J.M. van Rossum, *Arch. Int. Pharmacodyn.*, **110**, 275 (1957).
6) J.M. van Rossum, *Arch. Int. Pharmacodyn.*, **143**, 299 (1963).
7) K. Takagi and I. Takayanagi, *Pharm. Bull.* (Tokyo), **5**, 248 (1957).

Table II. Antiacetylcholine and Antihistamine Activities (Values are presented as Mean of 5 to 10 Experiments with S. E. in Parentheses)

| Compd. No. | Atropine-like $pA_2$ | Antihistamine | |
|---|---|---|---|
| | | $pA_2$ | $pD_2'$ |
| **1a** | 7.50(0.17) | 6.64(0.13) | 5.08(0.26) |
| **1b** | 7.31(0.11) | 5.91(0.18) | |
| **1c** | 7.41(0.08) | | 5.11(0.14) |
| **1d** | 5.76(0.09) | | 5.23(0.20) |
| **2a** | 6.51(0.14) | 6.12(0.16) | 4.52(0.22) |
| **2b** | 6.86(0.08) | 5.74(0.17) | |
| **3a** | 6.82(0.13) | 6.44(0.13) | 5.27(0.21) |
| **3b** | 6.77(0.07) | 6.28(0.15) | 4.18(0.19) |
| **4a** | 6.77(0.07) | 6.28(0.17) | 5.51(0.30) |
| **4b** | 6.94(0.09) | 5.75(0.14) | 4.22(0.23) |
| **5a** | 5.21(0.13) | 5.57(0.11) | 4.22(0.29) |
| **5b** | 5.58(0.16) | 4.31(0.16) | |
| **6a** | 5.36(0.11) | 5.62(0.21) | 4.33(0.22) |
| Atropine $1/2H_2SO_4$ | 8.68(0.10) | | |
| Chrorpheniramine maleate | | 8.25(0.12) | |
| Papaverine HCl | | | 5.13(0.21) |

Table II. Compound **1a** was the most potent antiacetylcholine drug among the compounds synthesized, but was weaker than atropine. The equipotent molar ratio relative to atropine was about 10 (the difference between the two $pA_2$ values was 1.18). The atropine-like activities of compounds **2a**, **3a** and **4a**, the tertiary compounds, were practically the same. Replacement of one benzene in a benzhydryl group by cyclohexane increased the atropine-like activity in this series but no other clear relation between structure and activity was found among compounds **1a**, **2a**, **3a** and **4a**. The dose-response curve of acetylcholine on the frog skeletal muscle was not influenced by $10^{-5}$ M **1a** or **1b**, which were highly active compounds in this series. Therefore, these compounds are considered not to have curare-like activity at the concentrations required for atropine-like activity.

The antihistamine activities of all the compounds synthesized were much less than that of chlorpheniramine: $pA_2$ values for the test compounds were 6.64 to 4.31. Methylation of piperidine essentially did not influence the atropine-like activities but considerably decreased the antihistamine activities. Therefore, the differences between atropine-like activities and competitive antihistamine activities were larger in the quaternary compounds. In compound **1**, quaternization with *n*-butyl reduced the ability to block postganglionic cholinergic receptors. The effects of quaternization on atropine-like activities in the series of **1** were similar to those observed when similar changes were made to hyoscine.[8] Noncompetitive antihistamine (papaverine-like) activities of tertiary compounds were greatly reduced by methylation (Table II).

8) R.B. Barlow, "Introduction to Chemical Pharmacology," Methuen, London, 1964, p. 216.