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Synthesis and Selective Activity of Cholinergic Agents with Rigid Skeletons. I[1]

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A common conformation was assumed to be involved in the potent muscarinic activities of L(+)-muscarine, acetylcholine, and (+)-*trans*-2*S*-acetoxycyclopropyl-1*S*-trimethylammonium. The conformation of other muscarinic agents was also considered from this point of view; three types of quaternary salts having semi-rigid piperidine ring structures which satisfy the hypothetical requirements were synthesized, and their muscarinic activities were examined. These synthetic compounds showed selective muscarinic activity.

Keywords——cholinergic agents; muscarinic activity; design and synthesis; semi-rigid conformation; quaternary salts of piperidine derivatives; dose-response curve

Many conformational hypotheses have been presented in relation to the interaction of acetylcholine with the muscarinic receptor.[3–11] These proposals were largely based on the crystal structures of energetically favored conformations in solution of acetylcholine and its agonists. However, the conformation interacting with the receptor may or may not be similar to that in the crystals or in solution. This paper considers the conformation of cholinergic agents binding on the receptor from an alternative point of view, and describes the synthesis of some compounds with semi-rigid structures designed on the basis of our working hypothesis, together with their biological activities.

Acetylcholine (Fig. 1-**3**) has an open-chain of six atoms from the methyl carbon of the acetyl group (C^1) to the ammonium nitrogen (N^6), and most muscarinic agents commonly possess terminal methyls (C^1) and basic ammonium or tertiary nitrogen atoms (N^6). Semi-rigid moieties are found in L(+)-muscarine (Fig. 1-**1**) and (+)-*trans*-2*S*-acetoxycyclopropyl-1*S*-trimethylammonium[12] (Fig. 1-**2**), which are both well-known potent muscarinic agents. Their skeletons can be superposed on each other, as well as on that of acetylcholine, as shown in Fig. 1-**4**. Thus the six atoms from C^1 to N^6 of each compound are located in nearly the same relative positions. The approximate distances between the main atoms and the torsion angles of the bonds in this conformation of acetylcholine are also given in Fig. 1. The skeletons

1) A part of this work was reported at the 98th Annual Meeting of the pharmaceutical Society of Japan, Okayama, 1978.
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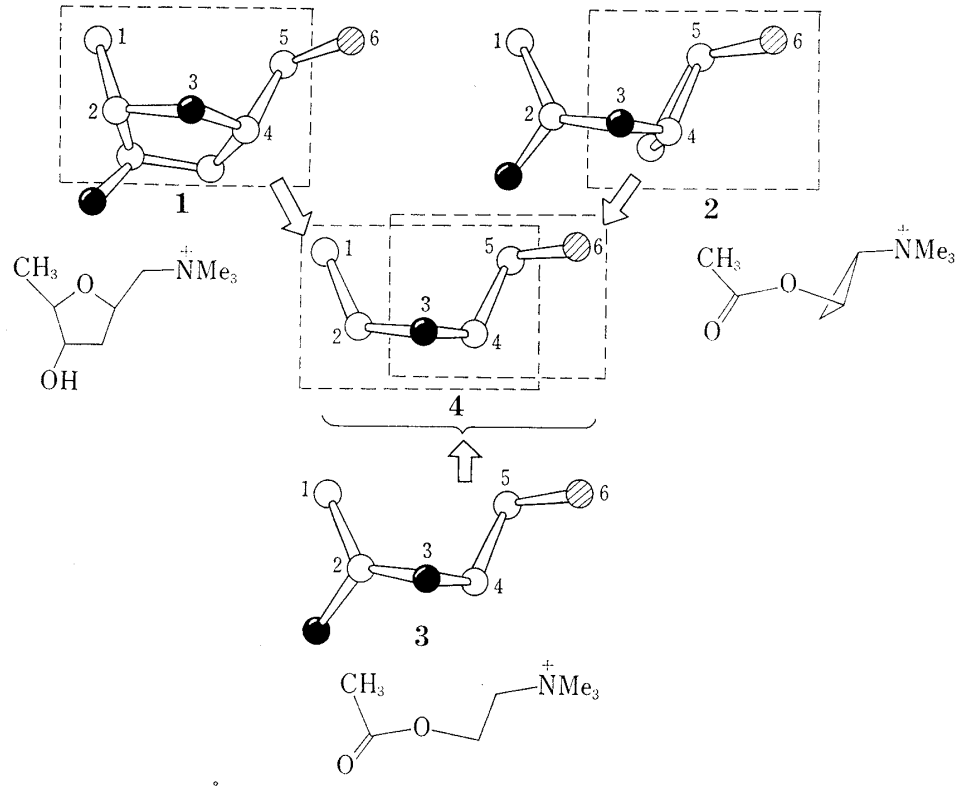
3) M. Martin-Smith, G.A. Amail, and J.B. Stenlake, *J. Pharm. Pharmacol.*, **19**, 561 (1967).
4) L.B. Kier, *Mol. Pharmacol.*, **3**, 487 (1967); *idem*, *ibid.*, **4**, 70 (1968).
5) R.W. Baker, C.H. Chothia, P. Pauling, and T.J. Petcher, *Nature* (London), **230**, 439 (1971).
6) F.G. Canepa, P. Pauling, and H. Sorm, *Nature* (London), **210**, 907 (1966).
7) A.W. Solter, *J. Pharm. Sci.*, **54**, 1755 (1965).
8) J. Durell, J.T. Garland, and R.O. Friedel, *Science*, **165**, 862 (1969).
9) B. Belleau, and J. Puranen, *J. Med. Dhem.*, **6**, 325 (1963).
10) B. Belleau, *Advan. Drug Res.*, **2**, 89 (1965).
11) S. Ehrenpreis, *Ann. N.Y. Acad. Sci.*, **144**, 720 (1967).
12) C.Y. Chiou, J.P. Long, J.G. Cannon, and P.D. Armstrong, *J. Pharmacol. Exp. Ther.*, **166**, 243 (1969).



distances Å		torsion angles	
C^1–N^6	4.8	C^4–O^3–C^2–C^1	*ca.* −120°−anticlinal
C^1–O^3	2.4	C^5–C^4–O^3–C^2	*ca.* +87°+synclinal
O^3–N^6	3.7	N^6–C^5–C^4–O^3	*ca.* +170°−antiplanar

Fig. 1. Superposition of the Skeletons of L(+)-Muscarine (**1**), (+)-*trans*-2*S*-Acetoxycyclopropyl-1*S*-trimethylammonium (**2**), and Acetylcholine (**3**), showing the Common Conformation of the C^1 to N^6 Chain (**4**)

○, carbon; ◍, nitrogen; ●, oxygen. The distances between key atoms and the torsion angles were measued using Dreiding stereomodels.

of other known potent muscarinic agonists and antagonists are shown for comparison. Fig. 2 shows the three-dimensional projections of such compounds.[13]

All these compounds (**1**—**3**, **5**—**7**, **9** and **11**) have two oxygen atoms which probably correspond to the oxygen atoms in the ester moiety of acetylcholine. Fig. 3 shows the positions of four atoms (C^1, O_a, O_b and N^6) of each of these compounds located as close as possible to the corresponding atoms in the acetylcholine conformation **3**. The projection A (Fig. 3) shows that $O_b{}^3$ of these compounds is located to the right. This implies a corresponding arrangement of the sites in the muscarinic receptor.

On this basis, some semi-rigid compounds, types A, B, and C, were designed (Fig. 4).

Compound **17** (one of the type A compounds) was obtained by acetylation of 3-hydroxy-1-methylpiperidine (**15**) followed by quaternization with methyl iodide to yield the desired methiodide (Chart 1). The synthesis of the second type, B, was performed starting from 4-carboethoxy-1-methyl-3-oxopiperidine (**13**), which was obtained by a modification of McElain's method.[14] In the Dieckmann cyclization of the diester (**12**), the best result was obtained using sodium ethoxide in a toluene–benzene mixture. The reduction of the keto-ester (**13**) with lithium aluminum hydride was unsuccessful. Dreiding[15] reported that β-keto-

13) The matcing was done with Dreiding stereomodels. When the activities of both enantiomers were found in the literature, the more active one was chosen.
14) E.A. Prill and S.M. McElvain, *J. Am. Chem. Soc.*, **55**, 1233 (1933).
15) A.S. Dreiding, *J. Am. Chem. Soc.*, **75**, 939 (1953).

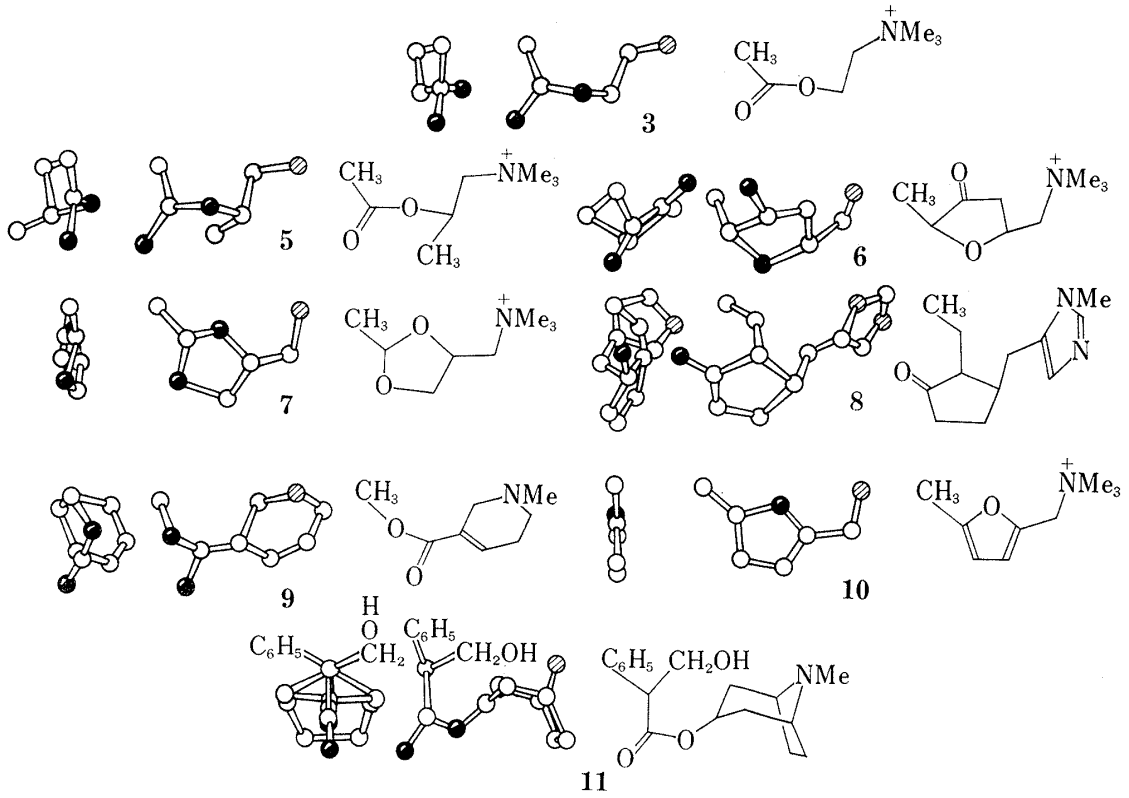


Fig. 2. Three-dimensional Representations of known Muscarinic Agonists and Antagonists

3, acetylcholine; 5, L(+)-*S*-acetyl-β-methylcholine; 6, D(−)-muscarone; 7, (+)-*cis*-2*S*-methyl-4*R*-trimethylammoniummethyl-1,3-dioxolan; 8, pilocarpine; 9, arecoline; 10, 5-methylfurmethide; 11, atropine. ○, carbon, ●, oxygen; ◍, nitrogen.

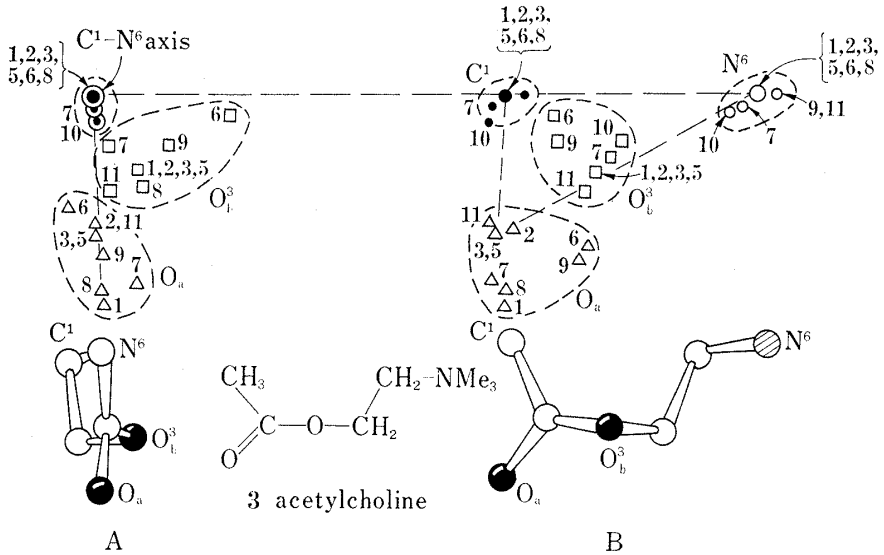
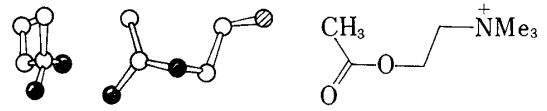


Fig. 3. Three-dimensional Projections of C^1, N^6, O_a, and O_b of Compounds **1**—**3**, **5**—**11**

esters were generally not reduced to diols by lithium aluminum hydride, but gave complex mixtures. Since a large excess of sodium borohydride often successfully reduces caroxy-esters to hydroxymethyl groups,[16] the reduction was carried out by refluxing the hydrochloride of

16) H.C. Brown and H. Rapoport, *J. Org. Chem.*, **29**, 3261 (1963).



3 acetylcholine

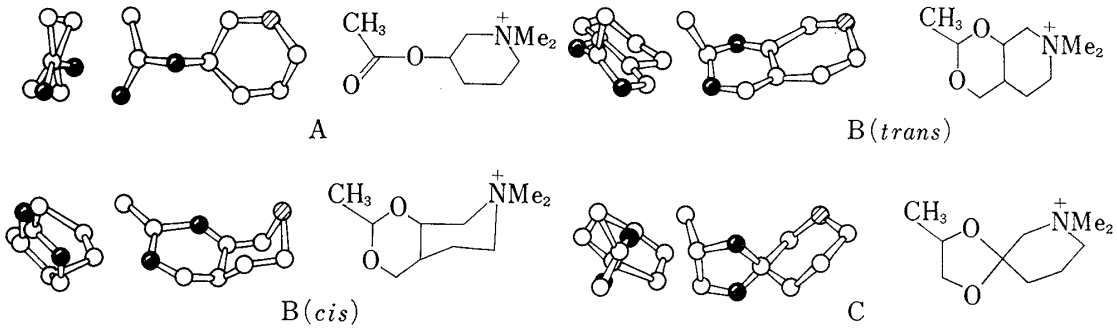


Fig. 4. Three-dimensional Projections of the Designed Compounds having Semi-rigid Skeletons

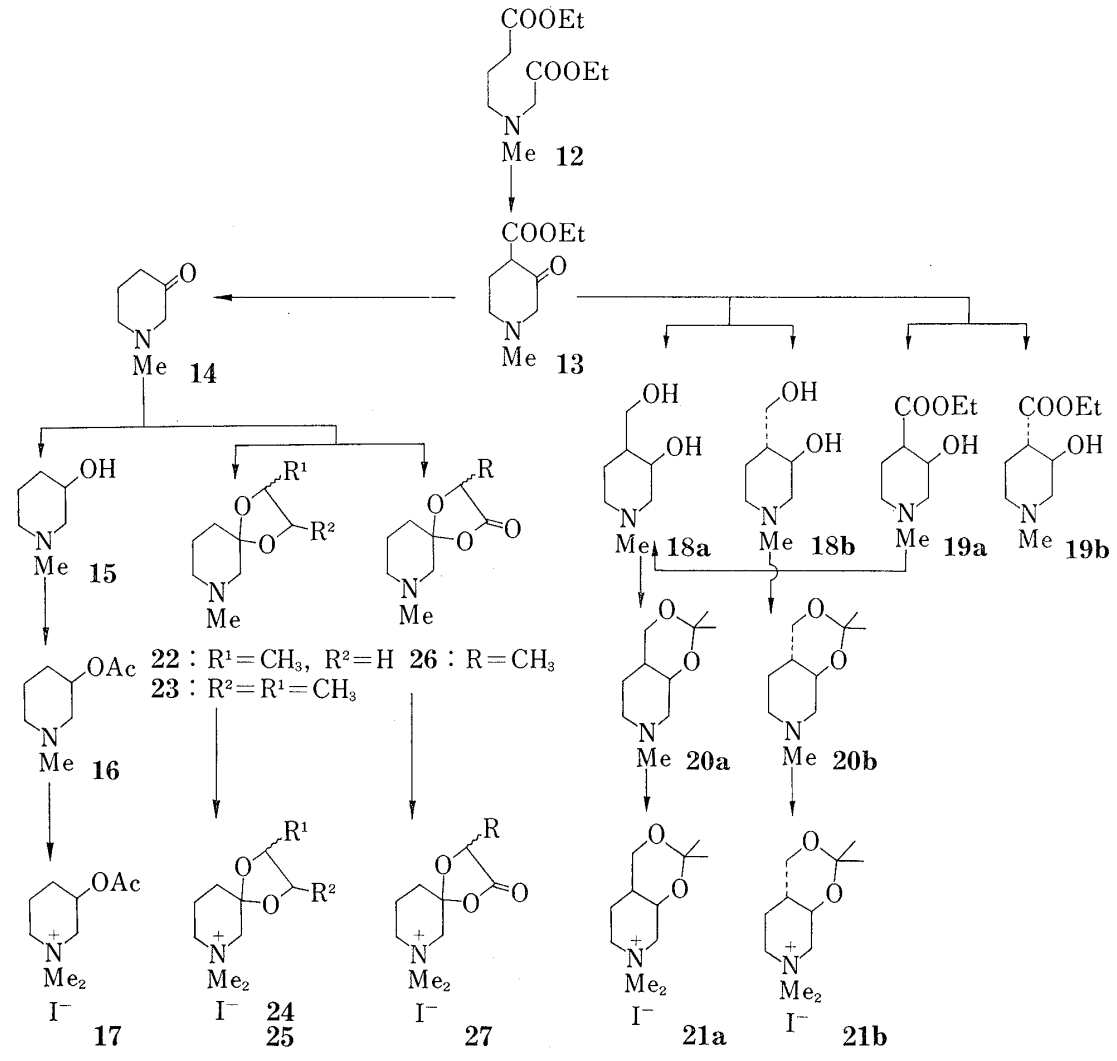


Chart 1

13 with a large excess of sodium borohydride and sodium hydroxide in methanol, yielding a mixture of *cis* and *trans* diols, **18a** and **18b**, in a ratio of approximately 4:1. A milder reduction of **13** with sodium borohydride gave a mixture of hydroxy-esters, **19a** and **19b**. The isomer **19a** was converted to **18a** by reduction with a large amount of sodium borohydride. The diols, **18a** and **18b**, gave the ketals, **20a** and **20b**, on reaction with acetone, in the presence of a molecular sieve and *p*-toluenesulfonic acid, respectively. Each ketal was then quaternized with methyl iodide to yield methiodide (**21a** and **21b**).

In compounds **18** to **21**, the "a" series was concluded to have *cis*-configuration, and the "b" to be *trans* on the basis of the nuclear magnetic resonance spectra (NMR) of **19** and the hydrogenation of **13** with rhodium-aluminum oxide. In the NMR of the hydroxy-ester, **19a**, the proton signal of C-3 appeared at 4.3 ppm (m, $W_{1/2}$=7.5 Hz), and its coupling constant with the C-4 proton was estimated to be not larger than 5 Hz, while in compound **19b**, the C-4 proton with a somewhat larger coupling constant, 11 Hz. These observations suggest that compounds of the series "a" have *cis* configuration and those of "b" are *trans*. It is known that the hydrogenation of *β*-keto-esters in the presence of a rhodium-aluminum oxide catalyst gives *cis* adducts selectively.[17,18] Therefore, the keto-ester, **13**, was hydrogenated with 5% rhodium on alumina at 50—60° under pressure. The product was identified as **19a** by thin-layer chromatography. The series "a" is thus confirmed to have *cis* configuration.

The synthesis of the compounds of type C, **24**, **25**, and **27**, was started from 1-methyl-3-piperidone, **14**.[19] The reactions of **14** with *dl*-1,2-propanediol and 2,3-butanediol in the presence of sulfuric acid gave the corresponding ketals, **22**, and **23**, respectively. Each spiroketal was converted to the quaternary salt (**24** and **25**) with methyl iodide. The reaction of **14** with *dl*-lactic acid in the presence of sulfuric acid gave a lactone, **26**, which was quaternized with methyl iodide to give **27**. The ketal-amine, **22**, was found to be a mixture of two isomers (**22a** and **22b**) on the basis of its NMR spectrum. The proton signals of C–CH_3 appeared as two doublets at 1.13 ppm (6.0 Hz) and 1.28 ppm (5.5 Hz). The ratio of the components was estimated from the integral values of the signals to be 3:2. One of the isomers (**22a**) was obtained by stirring the mixture with aluminum oxide in ether. This product showed only one doublet of C–CH_3 signal at 1.13 ppm. The other isomer (**22b**) could not be isolated in a pure state. The conversion of **22** to **24** was carried out using the isomer "a". Similarly, the ketal, **23**, was also a mixture of two isomers (**23a** and **23b**) which exhibited two doublets of C–CH_3 signals at 1.24 ppm (6H, 5.5 Hz) and 1.14 ppm (6H, 6.5 Hz). The ratio of the components was estimated to be 4:1 by comparison of the integral values. Treatment of the mixture with aluminum oxide gave one component (**23a**) which exhibited a C–CH_3 signal at 1.24 ppm. The other isomer (**23b**) could not be isolated. The stereochemistries of **22a** and **23a** were not established. Compound **25** was obtained from **23a**.

The lactone, **26**, gave one spot on thin-layer chromatography, exhibited one doublet corresponding to C–CH_3 in NMR, and appeared to be a single component on distillation under reduced pressure, but no definitive evidence was obtained on its stereochemistry.

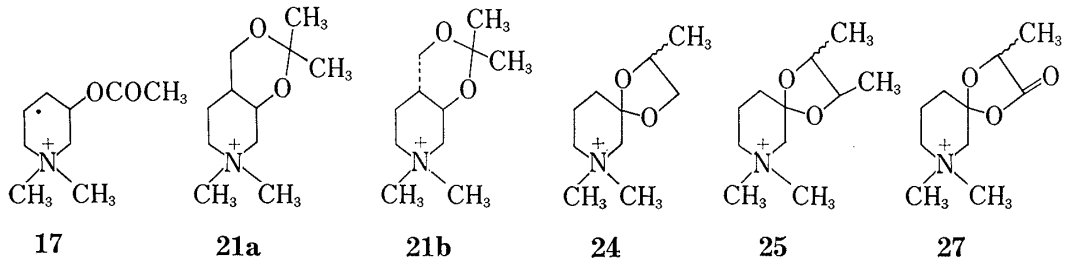
Pharmacology and Discussion[20]

The cholinomimetic activities of the compounds **17**, **21a**, **21b**, **24**, **25** and **27** were examined. The compounds tested, except for compound **25**, produced contraction; compound **25** showed relaxation. The contractions produced by these compounds were inhibited by the selective ganglion blocking agent atropine, but were not inhibited by the selective ganglion blocking

17) S. Siegel, *Advan. Catal.*, **16**, 131 (1966).
18) D.O. Spry and H.S. Aaron, *J. Org. Chem.*, **34**, 3674 (1969).
19) R.E. Lyle, R.E. Adel and G.G. Lyle, *J. Org. Chem.*, **24**, 342 (1956).
20) The details of the pharmacological studies will be presented shortly.

agent hexamethonium. These results suggest that the compounds **17**, **21a**, **21b**, **24** and **27** act on muscarinic receptors, but not on nicotinic receptors. The contractions produced by these compounds were not potentiated by the selective cholinesterase inhibitor, eserine, unlike those by ACh. This suggests that the compounds tested may be not destroyed by cholinesterase.

The intrinsic activities of those compounds on ACh receptors were examined. The maximum contraction produced by compound **17** was similar to that produced by ACh. That is, the intrinsic activity of compound **17** is the same as that of **1**. However, the dose-response curve was shifted to the right compared with that of ACh. This suggests that the affinity of this compound for ACh receptors may be lower than that of ACh. The *cis*-ketal, **21a**, showed the same type of dose-response curve as ACh but at a much higher concentration region, while the intrinsic activity of the *trans*-isomer, **21b** was smaller than that of **21a** (about 0.6). This suggests that some structural requirement for binding is not satisfied in **21b**. The affinities of the compounds **24** and **27** were almost the same as that of **21b**, whereas their intrinsic activities were smaller. It is interesting that the addition of one methyl group in **24** (compound **25**) gave an exceptional compound, causing relaxation. This suggests the presence of strict steric requirements near the methyl group in the ACh receptor.



17 **21a** **21b** **24** **25** **27**

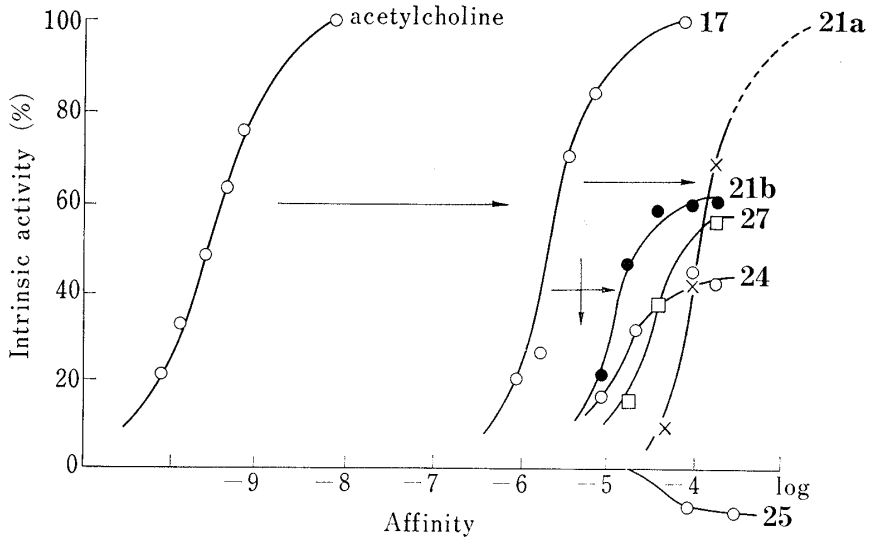


Fig. 5. Dose-response Curves (guinea-pig ileum)

Experimental

3-Acetoxy-1-methylpiperidine (16)——A mixture of 3-hydroxy-1-methylpiperidine[21] (**15**, 780 mg), pyridine (1 ml) and Ac_2O (1 ml) was refluxed for 5 min. The solvent was removed by distillation in *vacuo*, and H_2O was added to the residue. The mixture was neutralized with K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over Na_2SO_4 and the solvent was evaporated off. The residue was distilled to give

21) J.H. Biel, H.L. Friedman, H.A. Leiser, and E.P. Sprengeler, *J. Am. Chem. Soc.*, **74**, 1485 (1952).

an oil, 110—115° (bath temperature, 980 mg, 77%). This was directly converted to the methiodide (**17**). IR ν_{max}^{liq} cm^{-1}: 1720 (CH_3COO).

3-Acetoxy-1-methylpiperidine Methiodide (17)——Compound **16** (500 mg) in acetone with an excess of MeI (500 mg) was allowed to stand for 2 hr with occasional stirring. The separated crystals were collected by filtration and recrystallized from iso-PrOH, mp 148—149.5° (1.29 g, 82%). *Anal.* Calcd. for $C_9H_{18}INO_2$: C, 36.14; H, 6.07; N, 4.68. Found: C, 36.04; H, 6.11; N, 4.65. IR ν_{max}^{KCl} cm^{-1}: 1725 (CH_3COO). NMR (DMSO-d_6) δ: 1.5—2.0 (m, 4H, 4-CH_2, 5-CH_2), 2.07 (s, 3H, CH_3COO), 3.22 (d, 6H, $N^+(CH_3)_2$), 3.3—3.7 (m, 4H, 2-CH_2, 6-CH_2), 5.1 (m, 1H, 3-CH).

4-Ethoxycarbonyl-1-methyl-3-oxopiperidine (13)——Benzene (135 ml) was added to a mixture of toluene (24 ml), EtOH (68 ml), and Na (4.73 g) and was azeotropically distilled with excess EtOH under stirring. Ethyl 1-ethoxycarbonylmethyl-1-methyl-γ-aminobutylate (**12**, 45.2 g) was added to the stirred residue and the EtOH formed was distilled with C_6H_6. After heating for 1 hr at 110—120°, H_2O was added and the mixture was washed with ether, made alkaline by saturating it with K_2CO_3 and extracted with ether. The ether extract was dried (K_2CO_3) and treated with dry HCl, giving the hydrochloride of **13**, mp 171—173° dec.) (33.8 g, 78%[13]).

***cis*- and *trans*-4-Ethoxycarbonyl-3-hydroxy-1-methylpiperidine (18a and 18b)**——i) Direct Reduction of **13** with Excess $NaBH_4$: $NaBH_4$ (8.54 g) was added in portions to a mixture of NaOH (0.99 g) in MeOH (30 ml) and the hydrochloride, **13** (5.0 g) at room temperature. After reflux for 3 hr, H_2O (10 ml) was added to the mixture and the MeOH was distilled off *in vacuo*. The residue in water was continuously extracted with $CHCl_3$, dried (K_2CO_3) and separated by preparative TLC to give **18a** and **18b** in an ratio estimated of 4:1. The overall yield (**18a**+**18b**) was 58%. **18a** was obtained as crystals, mp 116—117°. *Anal.* Calcd. for $C_7H_{15}NO_2$: C, 57.90; H, 10.41; N, 9.65. Found: C, 57.63; H, 10.41; N, 9.55. The *trans* isomer (**18b**) was obtained as an oil. As it seemed to be unstable, the crude substance was used for the next step.

ii) Reduction of **19a** to **18a**: $NaBH_4$ (170 mg) was added in small portions to the solution of the *cis*-hydroxy-ester **19a** (109 mg) in MeOH (5 ml). After decomposing excess $NaBH_4$ with H_2O, the reaction mixture was condensed *in vacuo*. The residue was dissolved in H_2O, saturated with K_2CO_3, and continuously extracted with $CHCl_3$. Evaporation of the dried (K_2CO_3) $CHCl_3$ extract yielded crystals, mp 116° (274 mg, 28.3%). This product was identical with the sample obtained by method "i" as regards spectral data and by mixed melting point determination.

Ethyl *cis*- and *trans*-3-Hydroxy-1-methyl-piperidine-4-carboxylate (19a and 19b)——A solution of the hydrochloride of **13** (1 g) in MeOH (6 ml) was stirred with solid K_2CO_3 (0.63 g) for 1 hr, adding $NaBH_4$ (90 mg) portionwise with stirring. After removal of the solvent *in vacuo*, the solution was diluted with H_2O and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over K_2CO_3 and condensed to give a mixture of **19a** and **19b** (0.43 g, 58%), which was separated by preparative TLC. **19a**: *Anal.* Calcd. for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48. Found: C, 57.77; H, 9.15; N, 7.55. NMR ($CDCl_3$) δ: 1.29 (3H, t, $CH_2C\underline{H}_3$), 1.6—3.2 (7H, m, 2, 5, 6-CH_2, and 4-CH), 2.28 (3H, s, N-CH_3), 4.17 (2H, q, $C\underline{H}_2CH_3$), 4.30 (1H, m, 3-CH). **19b**: *Anal.* Calcd. for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48. Found: C, 57.93; H, 9.32; N, 7.67. NMR ($CDCl_3$) δ: 1.26 (3H, t, $CH_2C\underline{H}_3$), 1.60—3.20 (7H, m, 2,5,6-CH_2, 4-CH), 2.27 (3H, s, N-CH_3), 3.7—4.1 (1H, d-t, J=11 Hz, 3-CH), 4.17 (2H, q, CH_2CH_3).

***cis*-3-Hydroxy-4-hydroxymethyl-1-methylpiperidine Acetonide (20a)**——A mixture of the diol **18a** (101.8 mg), acetone (5 ml), TsOH (147 mg), and molecular sieve (type 4Å) (500 mg) was refluxed for 9 hr, then filtered, and the filtrate was made alkaline with saturated aqueous K_2CO_3. The solution was distilled *in vacuo* to remove acetone extracted with $CHCl_3$, dried (K_2CO_3), and passed through a short column of Al_2O_3. The eluate with $CHCl_3$ was distilled to give an oil, bp_{13} 127° (bath temperature) (95 mg, 72%). The acetonide was converted to the methiodide (**21a**) without further purification.

***trans*-3-Hydroxy-4-hydroxymethyl-1-methylpiperidine Acetonide (20b)**——Compound **18b** (50 mg) was treated with acetone as described for **20a** to give the desired ketal, **20b** (46 mg, 71%), bp_{13} 105—110° (bath temperature). This was used to prepare methiodide, **21b**, without further purification.

***cis*-3-Hydroxy-4-hydroxymethyl-1-methylpiperidine Acetonide Methiodide (21a)**——A mixture of the ketal **20a** (750 mg) in acetone (10 ml) and MeI (5 ml) was allowed to stand overnight. The resulting crystals were filtered off and washed with acetone (935 mg, 71%). The crude **21a** was recrystallized from iso-PrOH, mp 191—192°. *Anal.* Calcd. for $C_{11}H_{22}INO_2$: C, 40.38; H, 6.78; N, 4.28. Found: C, 40.50; H, 6.80; N, 4.29.

***trans*-3-Hydroxy-4-hydroxymethyl-1-methylpiperidine Acetonide Methiodide (21b)**——The ketal **20b** (40 mg) was treated as described for the preparation of **21a** to give crystals of **21b** (64 mg, 94%) which were recrystallized from iso-PrOH, mp 252—253°. *Anal.* Calcd. for $C_{11}H_{22}INO_2$: C, 40.38; H, 6.78; N, 4.28. Found: C, 40.17; H, 6.82; N, 4.25.

1-Methylpiperidine-3-spiro-2′-(4′-methyldioxolane) (22)——i) A mixture of 1-methyl-3-piperidone hydrobromide (**14**) (1.0 g) in propylene glycol (1 ml) and H_2SO_4 (0.1 ml) was heated at 80° for 2 hr. A cold solution of K_2CO_3 was added, and the mixture was extracted with ether. The extract was dried (K_2CO_3) and the solvent removed *in vacuo* to leave an oil (0.42 g, 28%) which appeared to be a mixture of **22a** and **22b**, as discussed previously.

ii) The hydrobromide (**14**) (1.0 g) in $CHCl_3$ (20 ml) was bubbled through with dry HCl gas (309 mg) under cooling. Propylene glycol (2 ml) and a molecular sieve (type 4Å, 1 g) were added and the mixture

was stirred at room temperature for 4.5 hr. Ice and a saturated solution of K_2CO_3 were added to the mixture, which was then extracted with ether and dried (K_2CO_3). The solvent was removed to give an oily residue (0.71 g, 40.5%) which was shown to be a mixture of **22a** and **22b**.

iii) Isolation of One Isomer (**22a**): The mixture (0.25 g) in ether (2 ml) was stirred with Al_2O_3 (Merck neutral Art 1077, 3 g) for 3 hr at room temperature, then filtered, and the filtrate was condensed to leave an oily residue (0.09 g, 36%). This was confirmed to be a single component of **22**, as described previously, and was converted to the methiodide (**24**) without further purification.

1-Methylpiperidine-3-spiro-2′-(4′-methyldioxolane) Methiodide (**24**)——One isomer of **22** (**22a**) (100 mg) in acetone (2 ml) and MeI (1 ml) was allowed to stand at room temperature, yielding crystals. These were dissolved in $CHCl_3$ and ether was added to precipitate pure crystals, mp 179—180°. *Anal.* Calcd. for $C_{10}H_{20}INO_2$: C, 38.35; H, 6.44; N, 4.47. Found: C, 38.19; H, 6.44; N, 4.51.

1-Methylpiperidine-3-spiro-2′-(4′,5′-dimethyldioxolane) (**23**)——i) A mixture of the hydrobromide (**14**) (1.0 g) in 2,3-butanediol (1 ml) and H_2SO_4 (0.1 ml) was heated at 80° for 3 hr. A cold saturated solution of K_2CO_3 was added, and the mixture was extracted with ether. The extract was dried (K_2CO_3), and the solvent removed to leave a mixture of **23a** and **23b**, as described previously.

ii) Isolation of One Isomer (**23a**): The mixture of **23a** and **23b** (275 mg) in ether (2 ml) was stirred with Al_2O_3 (Merck neutral Art 1077,3 g) for 5 hr at room temperature and filtered. The filtrate was condensed to leave an oil which gave a single spot on TLC; it was confirmed to be a single component of **23** by NMR as described previously, and was used to prepare the methiodide (**25**).

1-Methylpiperidine-3-spiro-2′-(4′,5′-dimethyldioxolane) Methiodide (**25**)——A mixture of the ketal (**23a**) in acetone (2 ml) and MeI was allowed to stand overnight. The resulting crystals were collected by filtration and recrystallized from EtOH; mp 239—240° (80 mg, 63%). *Anal.* Calcd. for $C_{11}H_{22}INO_2$: C, 40.38; H, 6.78; N, 4.28.

1-Methylpiperidine-3-spiro-2′-(4′-methyl-5′-oxodioxolane) (**26**)——H_2SO_4 (4 g) was dropped into a mixture of 1-methyl-3-piperidone (**14**) hydrobromide (1 g) and *dl*-lactic acid (1 ml) under ice-cooling with stirring. The mixture was made alkaline with K_2CO_3 under cooling after adding a small amount of ice, then extracted with ether. The organic layer was dried (K_2CO_3), and the solvent removed to leave an oil (1 g, 61.7%). The product was converted to the methiodide (**27**).

1-Methylpiperidine-3-spiro-2′-(4′-methyl-5′-oxodioxolane) Methiodide (**27**)——A solution of the dioxolane (**26**) (1 g) in acetone (2 ml) and MeI (1 ml) was allowed to stand overnight in a refrigerator. The resulting crystals of crude methiodide were collected by filtration and recrystallized from MeOH–EtOH (1.2 g, 68.6 %), mp 219—220°. *Anal.* Calcd. for $C_{10}H_{18}INO_3$: C, 36.71; H, 5.55; N, 4.28. Found: C, 36.65; H, 5.36; N, 4.51. IR ν_{max}^{KCl} cm^{-1}: 1815 (COO).

Hydrogenation of 13 to 19a with Rhodium on Alumina——A solution of the keto-ester **13** (1 g) in AcOH (20 ml) was shaken with 5% Rh–Al_2O_3 (200 mg) at 50—60° under H_2 (70 atom) for 9 hr. After cooling to room temperature, the catalyst was removed by filtration and the filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in H_2O (10 ml), made alkaline with K_2CO_3 and extracted with $CHCl_3$ (15 ml×3). The extract was dried (K_2CO_3) and the solvent removed by distillation to leave an oily residue which was distilled, $bp_{0.7}$ 110—130° (bath temp.) (588 mg, 70%). The product was identical with **19a** (TLC and NMR spectra).

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