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

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In order to examine the structure–activity relationship for cholinergic action, *cis*-1-methylpiperidine-4,3-acetolactone methiodide (**1a**) was designed and synthesized. The reaction of 1-carbobenzoxy-4-piperidone (**3**) with diethyl phosphonoacetate gave ethyl 1-carbobenzoxy-$\Delta^{4,a}$-piperidine-4-acetate (**5**), which was isomerized to the endo-isomer (**6**). Compound **6** was converted to an unsaturated lactone (**9**). Hydrogenation of **9** followed by methylation gave **1a**.

The compound **1a** showed no acetylcholine-like activity but did show a weak atropine-like antagonistic effect to acetylcholine.

Keywords——cholinergic agent; muscarinic activity; design and synthesis; semi-rigid skeleton; piperidinium salt; dose-response curve; structure–activity relationship

A series of acetylcholine-like compounds with rigid skeletons has been synthesized and their cholinomimetic activities were examined.[1–3]

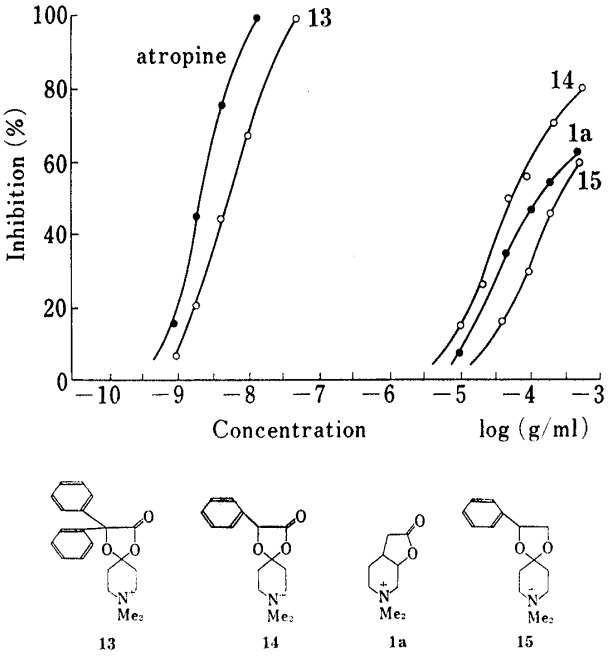
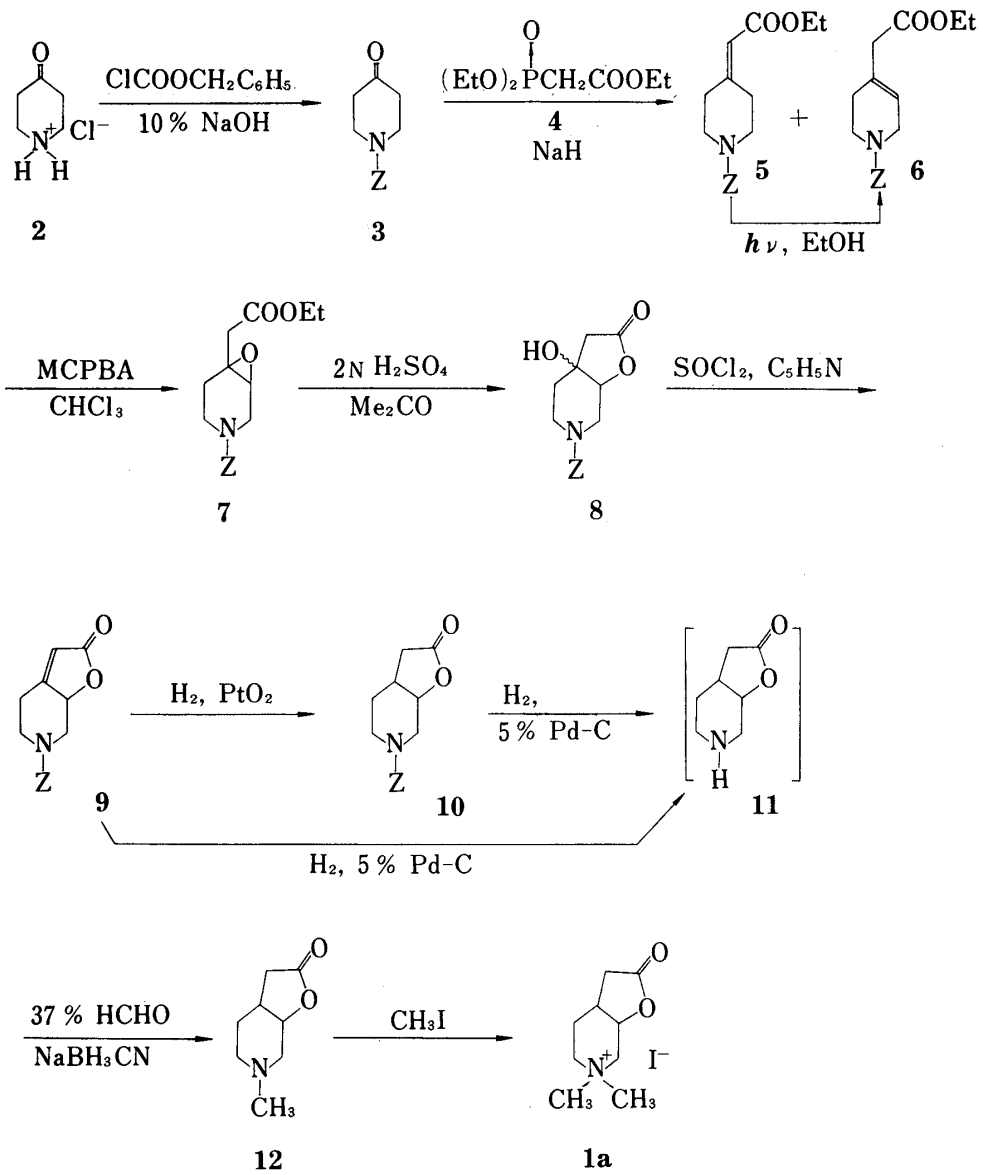


Fig. 1. Dose-response Curve of inhibition of the Contraction of Guinea-pig Ileum induced by ACh

A comparison of the antagonistic effects of atropine (100 %), **1a**, and related compounds previously reported.[2b]

The present paper is concerned with the synthesis and activity of compound **1a**, in which the choline and acetoxy moieties of acetylcholine (ACh) are fused to form a piperidinium ring and a five-membered lactone, respectively. The synthetic route to **1a** is shown in Chart 1. Reaction of *N*-carbobenzoxy-4-piperidone (**3**) with diethyl phosphonoacetate (**4**) gave compound **5**, which was photo-isomerized to endo-type **6**. A convenient route to the unsaturated lactone **9** was established; epoxidation of **6** to **7** followed by hydrolysis to give the hydroxy-lactone **8**, which was converted to **9** by dehydration with pyridine–thionyl chloride. Catalytic hydrogenations of **9** selectively gave **10** or **11**. The free amine **11** was so unstable that it was directly methylated with sodium cyanoborohydride and formaldehyde to provide **12** in good yield. The stereochemistry of **12** was assumed to be *cis* on the basis of a coupling constant of 4 Hz for the C-2 and C-4 protons on the piperidine ring.[4] Treatment of **12** with methyl iodide gave the desired compound **1a**.



2 3 5 6 7 8 9 10 11 12 1a

Z=$COOCH_2C_6H_5$

Chart 1

Pharmacology and Discussion

The Magnus test of **1a** using guinea-pig ileum showed no contraction even at 10^{-3} g/ml concentration under the conditions described in the previous papers,[2,3] but **1a** had a weak antagonistic effect. Figure 1 shows the inhibition of the contraction caused by ACh based on the action of atropine as 100%. The lack of contractile response with **1a** suggests that appropriate spatial location of the *C*-methyl and trimethylammonium groups is essential for activity.

Experimental

1-Carbobenzoxy-4-piperidone (3)——4-Piperidone hydrochloride (27.5 g) was added to stirred 10% NaOH (208 ml) with ice-cooling. Stirring was continued, and carbobenzoxy chloride (22 g) in toluene (75 ml) was added dropwise. After beeing stirred for 2 h, the mixture was extracted with $CHCl_3$ and the organic layer was washed (H_2O) and dried ($MgSO_4$). The solvent was evaporated off, and the residue was distilled, bp_2 170°C, mp 37—38°C (29.2 g, 96.2%).

TABLE I. ^{1}H-NMR Spectral ($CDCl_3$) and Analytical Data

Compd.	NMR Protons attached on 2	3	4	5	6	$CO_2CH_2C_6H_5$	4-CH or -CH_2	CO_2Et	N–CH_3	Analysis (%) Found (Calcd.) C	H	N
3	3.82 (t, 6 Hz)	2.45 (t, 6 Hz)	—	2.45 (t, 6 Hz)	3.82 (t, 6 Hz)	5.20(s) 7.38(s)	—	—	—	66.94 (66.98	6.48 6.55	6.00 6.12)
5	3.60 (m)	2.30 (t, 6 Hz)	—	2.95 (t, 6 Hz)	3.60 (m)	5.15(s) 7.35(s)	5.72(s)	1.28 (t, 7 Hz) 4.16 (q, 7 Hz)	—			
7	3.0—3.9 (m)	3.0—3.9 (m)	—	1.7—2.2 (m)	3.0—3.9 (m)	5.11(s) 7.33(s)	2.55 (d, 16 Hz) 2.68 (d, 16Hz)	1.27 (t, 7 Hz) 4.16 (q, 7 Hz)	—			
8	3.7—3.9 (m)	4.28 (t, 4 Hz)	—	1.85 (t, 5 Hz)	3.3—3.6 (m)	5.11(s) 7.33(s)	2.61(s)	—	—			
9	4.4—5.1 (m)	4.4—5.1 (m)	—	2.3—3.0 (m)	2.3—3.0 (m)	5.19(s) 7.40(s)	5.89(s)	—	—	65.92 (65.90	5.53 5.56	5.13 5.22)
10	1.2—2.0 (m)	4.0—4.6 (m)	2.1—2.9 (m)	3.1—3.5 (m)	3.1—3.5 (m)	5.12(s) 7.32(s)	1.2—2.2(m)	—	—	65.44 (65.51	6.22 6.11	5.09 5.22)
12	2.4—2.8 (m)	4.53 (q, 4 Hz)	2.8—3.3 (m)	1.6—2.0 (m)	2.4—2.8 (m)	—	2.10 (d, 4 Hz)	—	2.31 (s)			
1a ($DMSO_{d-6}$)	3.4—3.9 (m)	4.6—5.1 (m)	1.6—2.3 (m)	3.4—3.9 (m)	3.4—3.9 (m)	—	1.6—2.3 (m)	—	3.10 (s) 3.18 (s)	36.38 (26.48	5.43 5.48	4.71 4.50)

Ethyl 1-Carbobenzoxy-$\Delta^{4,\alpha}$-piperidine-4-acetate (5)——A solution of diethyl phosphonoacetate (**4**) (23.1 g) in abs. Et_2O (50 ml) was added under stirring to a suspension of NaH (2.3 g) in abs. Et_2O (17 ml) under an N_2 atmosphere. When the evolution of H_2 subsided, **3** (20 g) in a mixture of abs. Et_2O (73 ml) and abs. benzene (30 ml) was added dropwise and the mixture was allowed to stand overnight. The supernatant was decanted from the precipitate, washed (10% HCl, 5% $NaHCO_3$, and sat. NaCl, successively), and dried (Na_2SO_4), and the solvent was evaporated off (25.7 g, 99%). The crude product was used directly for the next step.

Ethyl 1-Carbobenzoxy-1,2,5,6-tetrahydropyridine-4-acetate (6)——Compound **5** (3.3 g) in EtOH (330 ml) was irradiated with a high-pressure mercury lamp (450 watt) at 22°C for 5.5 h under an N_2 stream. Removal of the solvent by evaporation left the crude product as an oil (84%). This was used directly in the next step.

Ethyl 1-Carbobenzoxy-3,4-epoxypiperidine-4-acetate (7)——*m*-Chloroperbenzoic acid of 85% purity (9.3 g) was added to a solution of **6** (11.2 g) in $CHCl_3$ (370 ml), and the whole was left to stand overnight. Excess acid was then decomposed by addition of 10% Na_2SO_3 and the mixture was extracted with 10% K_2CO_3. The $CHCl_3$ layer was washed (H_2O) and dried ($MgSO_4$), and the solvent was evaporated off to leave an oil (11.5 g, 97%). A part of the crude product was purified by preparative thin-layer chromatography (PTLC).

1-Carbobenzoxy-3,4-dihydroxypiperidine-4-acetic Acid Lactone (8)——A mixture of **7** (11.5 g), Me_2CO (130 ml), and 2 N H_2SO_4 (13 ml) was refluxed for 6 h, neutralized with K_2CO_3, and diluted with Et_2O (25 ml). The organic layer was dried over $MgSO_4$ and concentrated to leave an oil (9.7 g, 93%). A part of the oil was purified by PTLC.

1-Carbobenzoxy-$\Delta^{4,\alpha}$-piperidine-4,3-acetolactone (9)——Fresh distilled $SOCl_2$ (0.16 ml) was added to an ice-cooled solution of **8** (512 mg) in pyridine (1.2 ml). After being stirred overnight, the mixture was diluted with $CHCl_3$ (25 ml) and the solution was washed (10% HCl then H_2O), dried ($MgSO_4$), and concentrated to leave an oil, which was distilled ($bp_{0.35}$ 154—156°C, mp 94°C) and purified from MeOH, mp 95°C (352 mg, 73%).

***cis*-1-Carbobenzoxypiperidine-4,3-acetolactone (10)**——Compound **9** (1.5 g) was hydrogenated with PtO_2 (70.4 mg) in MeOH to give crystals (MeOH), mp 68°C (1.44 g, 95.4%).

***cis*-1-Methylpiperidine-4,3-acetolactone (12)**——(i) From **10**: Compound **10** (185 mg) was hydrogenated with 5% Pd-C in MeOH (5 ml). The catalyst was filtered off and 37% HCHO (51 mg) and $NaBH_3CN$ (42.7 mg) were added to the filtrate. After being stirred for 2 h, the mixture was evaporated to dryness *in vacuo* and the residue was dissolved in H_2O (5 ml). The solution was extracted with $CHCl_3$ and the organic layer was dried (Na_2SO_4), and distilled to give an oil, bp_{16} 135°C (70 mg, 66.9%).

(ii) From **9**: Compound **9** (806 mg) was reduced with Pd-C (400 mg) in MeOH. The catalyst was removed and the filtrate was treated with HCHO and $NaBH_3CN$ as described in procedure (i), giving **12** (254 mg, 56%).

***cis*-1-Methylpiperidine-4,3-acetolactone Methiodide (1a)**——MeI (0.5 ml) was added to **12** (254 mg) in Me_2CO (2 ml). After 24 h, the crystals were filtered and purified from EtOH, mp 196°C (423 mg, 86.9%).

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References and Notes

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