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

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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-carbobenzyloxy-4-piperidone (3) with diethyl phosphonoacetate gave ethyl
1-carbobenzyloxy-4-n-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)

The present paper is concerned with the synthesis and activity of compound
1a, in which the choline and acetoxo 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-carbobenzyloxy-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 so-
dium cyanoborohydride and formaldehyde to provide 12 in good yield. The stereo-
chemistry 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. The treatment of 12 with methyl
iodide gave the desired compound 1a.

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.15

Inhibition (%) 13 14 15

Concentration log (g/ml)
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, 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-Carboxbenzoxyst-4-piperidine (3) — 4-Piperidine hydrochloride (27.5 g) was added to stirred 10% NaOH (208 ml) with ice-cooling. Stirring was continued, and carboxbenzoxyl chloride (22 g) in toluene (75 ml) was added dropwise. After being stirred for 2 h, the mixture was extracted with CHCl₃ and the organic layer was washed (H₂O) and dried (MgSO₄). The solvent was evaporated off, and the residue was distilled, bp₄ 170°C, mp 37—38°C (29.2 g, 96.2%).
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<th>6</th>
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(DMSO₆-d₆)
Ethyl 1-Carbobenzoxy-4-α-piperidine-4-acetate (5)—A solution of diethyl phosphonoacetate (4) (23.1 g) in abs. Et₂O (50 ml) was added under stirring to a suspension of NaH (2.3 g) in abs. Et₂O (17 ml) under an N₂ atmosphere. When the evolution of H₂ subsided, 3 (20 g) in a mixture of abs. Et₂O (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% NaHCO₃, and sat. NaCl, successively), and dried (Na₂SO₄), 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 N₂ 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-epoxy-piperidine-4-acetate (7)—m-Chloroperbenzoic acid of 85% purity (9.3 g) was added to a solution of 6 (11.2 g) in CHCl₃ (370 ml), and the whole was left to stand overnight. Excess acid was then decomposed by addition of 10% Na₂SO₄ and the mixture was extracted with 10% K₂CO₃. The CHCl₃ layer was washed (H₂O) and dried (MgSO₄), 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-dihydroxy-piperidine-4-acetic Acid Lactone (8)—A mixture of 7 (11.5 g), Me₂CO (150 ml), and 2 × H₂SO₄ (13 ml) was heated at 105°C for 6 h, neutralized with K₂CO₃, and diluted with Et₂O (25 ml). The organic layer was dried over MgSO₄ and concentrated to leave an oil (9.7 g, 93%). A part of the oil was purified by PTLC.

1-Carbobenzoxy-4,4′-piperidine-4,3-acetolactone (9)—Fresh distilled SOCl₂ (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 CHCl₃ (25 ml) and the solution was washed (10% HCl then H₂O), dried (MgSO₄), and concentrated to leave an oil, which was distilled (bp₉₅ 154—156°C, mp 94°C) and purified from MeOH, mp 95°C (352 mg, 73%).

cis-1-Carbobenzoxy-piperidine-4,3-acetolactone (10)—Compound 9 (1.5 g) was hydrogenated with PtO₂ (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 NaBH₄CN (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 H₂O (5 ml). The solution was extracted with CHCl₃ and the organic layer was dried (Na₂SO₄), and distilled to give an oil, bp₁₅ 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 NaBH₄CN 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 Me₂CO (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