Table II—Effect of Administration Rate on 5-Aminosalicylic Acid Biotransformation in Fasting Rats

Rat	Urinary Excretion in 48 hr: Total Recovery, % of dose		*N*-Acetyl-5-aminosalicylic Acid, % of total[a]	
	Regimen A[b]	Regimen B[c]	Regimen A[b]	Regimen B[c]
1	99.3	104	58.2	53.8
2	104	103	63.4	57.4
3	105	98.2	43.7	42.8
4	94.4	99.0	51.6	51.1
Mean	101	101	54.2	51.3
SE	2.4	1.4	4.3	3.1
Paired *t* test	N.S. ($p > 0.8$)		N.S. ($p > 0.1$)	

[a] Free and acetylated 5-aminosalicylic acid. [b] Regimen A = single 25 mg/kg ip dose. [c] Regimen B = 8.33 mg/kg ip every 20 min for three doses.

limited acetylation during their intestinal absorption in humans. Studies are currently in progress to determine whether a food-induced decrease in the gastric emptying rate can, by decreasing the rate of 5-aminosalicylic acid absorption, further increase the extent of gut wall metabolism.

These results demonstrate that orally administered 5-aminosalicylic acid is subject to both capacity-limited gut wall and systemic metabolism. A similar capacity-limited presystemic metabolic profile for 5-aminosalicylic acid may exist after oral administration of sulfasalazine to patients with ulcerative colitis and Crohn's disease. If *N*-acetyl-5-aminosalicylic acid is inactive or less active than 5-aminosalicylic acid (a possibility remaining to be explored), then the time course of local anti-inflammatory activity may be affected.

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4-Acetoxy-1,2,3,4-tetrahydro-2,2-dimethyl-6,7-methylenedioxyisoquinolinium Iodide, an Acetylcholine Analog

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Abstract □ 4-Acetoxy - 1,2,3,4 - tetrahydro - 2,2-dimethyl-6,7-methylenedioxyisoquinolinium iodide, an analog of acetylcholine, was synthesized and a pharmacological profile of its GI effects was compiled. The agent inhibited dog colonic contraction in response to pelvic nerve stimulation and to acetylcholine. In rats, the compound markedly reduced gastric acid output and the volume of gastric secretions. The lack of inhibition of chromodacryorrhea production in response to carbachol indicates a lack of anticholinergic action. The agent failed to affect the acute inflammatory response of the rat hindpaw in response to carrageenan. The precursor of the compound was ineffective in the pharmacological tests.

Keyphrases □ Acetylcholine analogs—synthesis, pharmacodynamics, structure–activity relationships □ Cholinergic agents—acetylcholine analogs, synthesis, pharmacodynamics, structure–activity relationships □ Structure–activity relationships—acetylcholine analogs

As part of a program directed toward the synthesis of novel GI agents, an acetylcholine analog was desired in which the tetraalkylammonium function of the molecule was incorporated as part of a rigid annular system. Accordingly, a route to 4-acetoxy-1,2,3,4-tetrahydro-2,2-dimethyl-6,7-methylenedioxyisoquinolinium iodide (I) was devised.

DISCUSSION

Reaction of the previously reported (1) 4-hydroxy-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (II) with methyl iodide gave the quaternary Compound III which, upon treatment with acetic anhydride, afforded the racemic acetylcholine analog I.

Compound I, 10 mg/kg iv in three dogs, caused marked, but brief (20 min), antagonism of colonic contractions in response to intermittent pelvic nerve stimulation (2). In addition, acetylcholine-induced con-

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traction of the dog colon was markedly reduced (2). In the modified Shay technique in rats (3), I (100 or 300 mg/kg po, 1 hr before stomach pylorus ligation) evoked a dose-related inhibition of gastric acid output and reduced the gastric secretion volume. The gastric acid inhibitory activity of I at 100 mg/kg po was very weak (12.5%) compared to that at the 300-mg/kg po (78.6%) dose.

When I was given orally to six rats at a dose of 300 mg/kg po and challenged 1 hr later by 0.25 mg of carbachol/kg ip (4), the signs of chromodacryorrhea (bloody tears) were not prevented, indicating that I is not an anticholinergic drug. Compound I failed to reduce the inflammatory response evoked by an injection of carrageenan into the rat hindpaw (5).

Compound III, 10 mg/kg iv, slightly inhibited dog colonic contractions in response to intermittent pelvic nerve stimulation. The contractile response of the colon to acetylcholine was reduced slightly. A dose of 300 mg/kg po in rats failed to affect the gastric secretion volume or gastric acid output in the modified Shay technique. Compound III did not inhibit the chromodacryorrhea evoked by a carbachol injection, thereby indicating no anticholinergic effect. Finally, III was totally ineffective in preventing the inflammatory response of the rat hindpaw induced by a subplantar carrageenan injection.

Inhibition of acetylcholine-induced contraction of the dog colon by I and lack of inhibition of carbachol-induced chromodacryorrhea following I indicate a nonspecific antagonism of smooth muscle activity by I. Therefore, the action of I could be attributed to smooth muscle depression or relaxation which would inhibit any smooth muscle stimulant (*i.e.*, acetylcholine and histamine) or excitation of intrinsic cholinergic nerves. The chromodacryorrhea response to carbachol is a specific cholinergic response and can be blocked only by specific anticholinergic drugs such as atropine (4) and not by nonspecific smooth muscle relaxants.

The pharmacological profile of I and III suggests that the former possesses greater GI inhibitory activity than the latter. Such a difference in activity may be attributed to the acetyl substitution on the isoquinolinium structure. The acetyl moiety converts a relatively inactive choline into the powerful agent acetylcholine, a quaternary ammonium compound. The carbonyl atom of the acetate portion of I may possibly increase the drug–receptor affinity and cause a greater pharmacological antagonism in comparison to that of III.

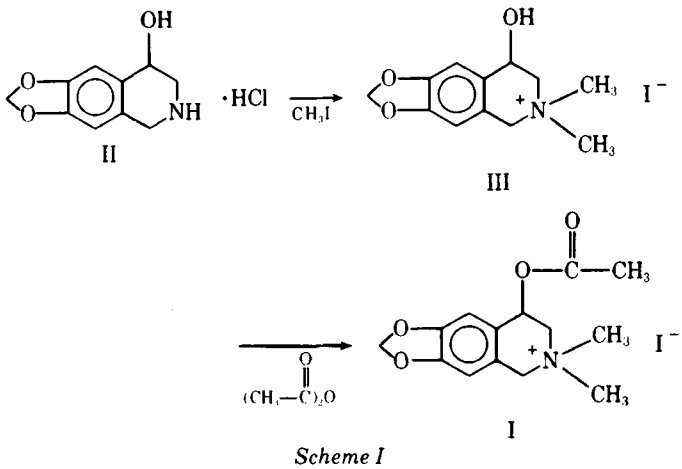
EXPERIMENTAL

Melting points were determined on a melting-point apparatus[1] and are uncorrected. IR spectra[2] were determined as mineral oil mulls. NMR spectra[3] were compared with tetramethylsilane as an internal standard.

1,2,3,4-Tetrahydro-4-hydroxy-2,2-dimethyl-6,7-methylenedioxyisoquinolinium Iodide (III)—A mixture of 84 g (0.37 mole) of 4-hydroxy-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (II) (1), 102 g (0.74 mole) of potassium carbonate, 78.8 g (0.56 mole) of methyl iodide, and 1000 ml of methanol was refluxed for 27 hr (Scheme I). The slurry was filtered while hot. The filtrate was refrigerated overnight and filtered. A light-tan solid was washed with methanol and ether and dried to give 55 g (43%) of the desired product, mp 223–226°.

An analytical sample, mp 224–226°, was obtained by recrystallization from methanol; IR: 3.03 (O–H), 9.40, and 9.70 (C–OH) μm; NMR (dimethyl sulfoxide-d_6): δ 3.25 [s, 6, $(CH_3)_2N^+$], 3.63–3.85 (m, 2, 3-CH_2), 4.56 (s, 2, 1-CH_2), 4.75–5.03 (m, 1, 4-CH), 6.05, 6.13 (d, J = 5 Hz, 1, exchangeable in D_2O, O–H), 6.08 (s, 2, –O–CH_2–O–), 6.80, and 7.08 (2 s, 2, aromatic C–H).

Anal.—Calc. for $C_{12}H_{16}INO_3$: C, 41.28; H, 4.62; I, 36.35; N, 4.01. Found: C, 41.33; H, 4.68; I, 36.10; N, 3.92.



Scheme I

4-Acetoxy-1,2,3,4-tetrahydro-2,2-dimethyl-6,7-methylenedioxyisoquinolinium Iodide (I)—A 26-g (0.075 mole) portion of III was added to 200 ml of acetic anhydride, and the reaction mixture was refluxed for 1.7 hr, cooled to room temperature, and filtered. The off-white solid was washed with 400 ml of ether and air dried, mp 249–250° dec. The yield was 28 g (97%).

An analytical sample, mp 246–248° dec., was obtained by recrystallization from 95% ethanol; IR: 5.70 (CO, ester) and 8.01 (C–O–C ester) μm; NMR (dimethyl sulfoxide-d_6): δ 2.11 (s, 3, CH_3–C=O), 3.20, 3.33 [2 s, 6, $(CH_3)_2N^+$], 4.00, 4.06 (d, J = 4 Hz, 2, 3-CH_2), 4.63 (s, 2, 1-CH_2), 5.91–6.16 (m, 1, 4-CH), 6.10 (s, 2, –O–CH_2–O–), 6.70, and 6.86 (2 s, 2, aromatic C–H).

Anal.—Calc. for $C_{14}H_{18}INO_4$: C, 42.98; H, 4.64; I, 32.44; N, 3.58. Found: C, 43.14; H, 4.54; I, 32.60; N, 3.51.

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[1] Mel-Temp.
[2] Model 137B, Perkin-Elmer.
[3] Model A-60A, Varian.