β-(2-Fluoro-3-pyridyl)-DL-alanine (Table VII, 16–18).—The cyanoacetate intermediate, **6**, was added to a warm slurry of 15% $Ba(OH)_2$ in H_2O, and the reaction mixt was heated at 70° with stirring for 3 days. Periodically, during the course of the reaction, aliquots were removed from the reaction mixture and the uv spectra determined to insure that hydrolysis of the F substituent was not occurring. At the completion of the reaction, insolubles were removed by filtration and chunks of Dry Ice were added to the filtrate until the pH had fallen to approximately 7. After removing the pptd $BaCO_3$, the pH was carefully lowered in the cold to pH 4.5 by addn of 10% H_2SO_4. The $BaSO_4$ was filtered off and the filtrate was concd to dryness *in vacuo* keeping the amino acid soln at 35° or less. The product was dissolved in a minimal amt of H_2O and Me_2CO added to near the cloud point. After standing in the refrigerator for several hours, the amino acid crystallized (Table VII).

Quaternary Furyl-, Thienyl-, and Pyrrolylpyridinium Salts. Oral Hypoglycemic Agents

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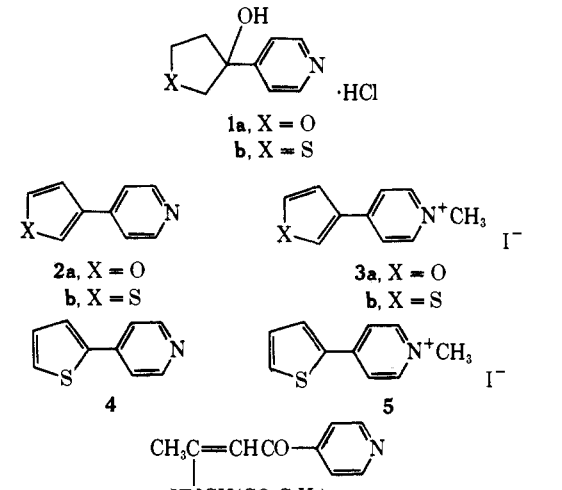
1-Methyl-4-(3-furyl)pyridinium iodide, 1-methyl-4-[2(and 3)-thienyl]pyridinium iodide, and 1-methyl-4-(5-methyl-3-pyrrolyl)pyridinium iodide have been synthesized as representatives of these classes of quaternary pyridinium salts. Blood glucose concentration of normal mice was decreased following oral administration of these compounds.

An extensive series of quaternary 4-azolylpyridinium salts including pyrazolyl,[1] isoxazolyl,[2–5] 1,2,4-oxadiazolyl,[6] thiazolyl,[7] and oxazolyl[8] derivatives has been found to display hypoglycemic activity in laboratory animals. In marked contrast, the quaternary 1,2,4-triazolyl-, 1,3,4-thiadiazolyl-, imidazolyl-, and tetrazolylpyridinium salts were ineffective in lowering blood sugar levels, and a 1,3,4-oxadiazolylpyridinium salt induced a slight non-dose-related hypoglycemia.[9] To further delineate the structural requirements for hypoglycemic activity following oral administration of quaternary pyridinium salts, we have synthesized representative furyl, thienyl, and pyrrolyl analogs and measured their effects on the blood glucose concentration of mice.

For the synthesis of 1-methyl-4-(3-furyl)pyridinium iodide (**3a**), the general method of Wynberg, *et al.*,[10] for the preparation of arylthiophenes was employed. Addition of 4-pyridyllithium[11] to tetrahydrofuran-3-one yielded the carbinol **1a**, which was dehydrated–dehydrogenated to 4-(3-furyl)pyridine (**2a**). Quaternization of **2a** gave the desired salt **3a**.



Reaction of the known 4-(3-thienyl)pyridine (**2b**)[12] and 4-(2-thienyl)pyridine (**4**)[12,13] with MeI gave the representative quaternary thienylpyridinium salts **3b** and **5**, respectively.

The pyrrolylpyridinium analog **8** was synthesized by a general method of Umio, *et al.*,[14] for the preparation of

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arylpyrroles. Condensation of diethyl aminomalonate with 4-acetoacetylpyridine gave **6**, which was cyclized to **7a** with polyphosphoric acid. Saponification to **7b** followed by thermal decarboxylation gave the pyrrolylpyridine **7c**, which was quaternized to 1-methyl-4-(5-methyl-3-pyrrolyl)pyridinium iodide (**8**).

Hypoglycemic Activity.[15]—Saline solutions of compounds were administered by gavage to male CF-1-S mice (Carworth Farms, 25–30 g) at doses of 0.1–1.0 mmole/kg; controls received an equal volume of vehicle. Blood samples (0.05 ml) obtained from retrobulbar plexuses 0, 3, and 5 hr after dosing were assayed for blood glucose using the method of Hoffman[16] as adapted for the Technicon AutoAnalyzer. Blood glucose concentration was markedly decreased after administration of **3a**, **3b**, **5**, and **8** (Table I). Mortality observed within 24 hr after dosing may have been a consequence of the low blood glucose concentrations of 19–33 mg % determined after drug treatment.

TABLE I

HYPOGLYCEMIC EFFECT OF FURYL-, THIENYL-, AND PYRROLYLPYRIDINIUM SALTS

Iodide salts	Dose, mmole/kg	% decrease in blood glucose[a] 3 hours after dosing	5	24 hr, dead/treated
1-Methyl-4-(3-furyl)pyridinium (**3a**)	0.5	39 ± 13	19 ± 17	0/6
	1.0	85 ± 2	all dead	6/6
1-Methyl-4-(3-thienyl)pyridinium (**3b**)	0.5	76 ± 12	48 ± 10	1/6
1-Methyl-4-(2-thienyl)pyridinium (**5**)	0.5	76 ± 2	73 ± 2	4/6
1-Methyl-4-(5-methyl-3-pyrrolyl)pyridinium (**8**)	0.1	28 ± 9	60 ± 6	0/6
	0.2	80 ± 4	81 ± 4	5/6

[a] Values are means ± standard errors of 5–6 mice at 3 hr, and 3–6 mice at 5 hr after oral dosing, depending upon survivors. Data are expressed as per cent decrease in blood glucose concns from predose levels. Average predose blood glucose concn of 24 control mice was 136 ± 3 mg/100 ml. Changes in blood glucose of control animals ranged between a 13% increase to a 17% decrease throughout the experiment.

Experimental Section[17]

Tetrahydro-3-(4-pyridyl)-3-furanol·HCl (1a).—A soln of 16 g (0.095 mole) of 4-bromopyridine (freshly liberated from the HCl salt and assayed with $HgCl_2$)[11] in 300 ml of Et_2O was added dropwise during 1 hr with stirring under N_2 to a cold (−50 to −30°) soln of 42 ml (0.066 mole) of 1.6 *M* *n*-BuLi in hexane and 200 ml of Et_2O. The mixt was stirred for 0.5 hr. A soln of 5.4 g (0.063 mole) of tetrahydrofuran-3-one in 50 ml of Et_2O was added during 5 min. The mixt was stirred at −30° for 4 hr and then allowed to come to room temperature overnight. It was cooled, 125 ml of 3 *N* HCl was added slowly, the layers were separated, the aq soln was made alk with NH_4OH, and the basic soln was extd with $CHCl_3$. The $CHCl_3$ soln was dried ($MgSO_4$) and concd to a liquid, which was evaporatively distd at 135° (12 mm). The distillate was dissolved in ethanolic HCl, and addition of Et_2O gave 2.4 g (19%) of off-white solid, mp 160–165°. Recrystn (EtOH–Et_2O) gave colorless crystals, mp 167–168°. *Anal.* ($C_9H_{12}ClNO_2$) C, H, Cl, N.

4-(3-Furyl)pyridine (2a).—A mixture of 2.4 g (0.012 mole) of **1a**, 0.5 g of S, and 0.5 g of $KHSO_4$ was fused at 225° for 1 hr, cooled, diluted with H_2O, made alk with 1 *N* NaOH, and extd with $CHCl_3$. The $CHCl_3$ soln was dried ($MgSO_4$) and concd to a yellow solid. Chromatography on silica gel ($CHCl_3$ eluent) gave 0.25 g (14%) of an unstable, tacky, colorless solid, which was used in the next reaction without further purification.

1-Methyl-4-(3-furyl)pyridinium Iodide (3a).—A solution of 0.25 g (1.7 mmoles) of **2a**, 3 ml of MeI, and 20 ml of MeCN was heated under reflux for 2 hr and concd to dryness. The residue was recrystd (EtOH–Et_2O) to provide 0.28 g (58%) of yellow crystals: mp 215–217°, uv 312 mμ (ε 11,770). *Anal.* ($C_{10}H_{10}INO$) C, H, N; I: calcd, 44.2; found, 43.7.

1-Methyl-4-(3-thienyl)pyridinium iodide (3b) was prepd in a like manner from **2b**:[12] yellow crystals (MeCN–Et_2O); mp 176–177° dec; uv 312 mμ (ε 15,760). *Anal.* ($C_{10}H_{10}INS$) C, H, N, S; I: calcd, 41.9; found, 41.3.

1-Methyl-4-(2-thienyl)pyridinium iodide (5) was prepd in a like manner from **4**:[12,13] yellow needles (*i*-PrOH); mp 181° dec; uv 338 (ε 48,200). *Anal.* ($C_{10}H_{10}INS$) C, H, I, N, S.

Diethyl (2-Isonicotinoyl-1-methylvinyl)aminomalonate (6).—A mixt of 7.7 g (0.047 mole) of 4-acetoacetylpyridine, 10.6 g (0.05 mole) of diethyl aminomalonate·HCl; 125 ml of C_6H_6, and 5 ml of NEt_3 was heated under reflux with stirring for 3.5 hr and was filtered. The filtrate was concd to an oily solid, which was triturated with Et_2O to provide 9.0 g (60%) of crystals, mp 88–94°. Recrystn (*i*-PrOH) gave colorless plates, mp 90–91°. *Anal.* ($C_{16}H_{20}N_2O_5$) C, H, N.

4-(2-Ethoxycarbonyl-5-methyl-3-pyrrolyl)pyridine (7a).—A mixt of 8.0 g (0.025 mole) of **6** and 30 g of polyphosphoric acid was heated on a steam bath for 30 min, quenched with H_2O, neutralized with Na_2CO_3, and filtered to provide 5.1 g (89%) of off-white crystals, mp 152–154°. Recrystn (EtOH) gave pale yellow crystals, mp 165–166°. *Anal.* ($C_{13}H_{14}N_2O_2$) C, H, N.

4-(2-Carboxy-5-methyl-3-pyrrolyl)pyridine (7b).—A soln of 4.5 g (0.019 mole) of **7a**, 4.5 g of NaOH, 40 ml of EtOH, and 40 ml of H_2O was heated under reflux for 4 hr, concd to 60 ml, and acidified with HOAc. The colorless solid, 2.1 g (54%), mp 227–229°, which sepd was collected and recrystd (EtOH–H_2O) to provide off-white crystals, mp 214° dec. *Anal.* ($C_{11}H_{10}N_2O_2$) C, H, N.

4-(5-Methyl-3-pyrrolyl)pyridine (7c).—A 1.5-g (7.5 mmoles) sample of **7b** was heated at 180° (15 mm) in a sublimation apparatus for 3 hr. The sublimate, 1.0 g of pale yellow solid, was recrystd (CH_3CN) to give 0.91 g (77%) of colorless crystals: mp 228–229° dec; uv 303 mμ (ε 10,700). *Anal.* ($C_{10}H_{10}N_2$) C, H, N.

1-Methyl-4-(5-methyl-3-pyrrolyl)pyridinium Iodide (8).—A soln of 0.91 g (5.7 mmoles) of **7c**, 0.7 ml of MeI, and 10 ml of CH_3CN was heated under reflux for 4 hr, cooled, and filtered to provide 1.5 g (88%) of yellow crystals, mp 218° dec. Recrystn (*i*-PrOH) gave yellow needles: mp 210–211° dec, uv 306 (ε 24,300), 361 mμ (ε 32,800). *Anal.* ($C_{11}H_{13}IN_2$) C, H, I, N.

(15) Technical assistance of Mr. E. Locke, Mr. H. Siegriest, and Miss L. Will is greatly appreciated.

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(17) Melting points were determined in a Hershberg apparatus and are uncorrected. Microanalyses were performed by Mr. L. M. Brancone and staff; where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within 0.4% of the theoretical values. Uv spectra were recorded in MeOH solution with a Cary 11 spectrophotometer by Mr. W. Fulmor and staff.