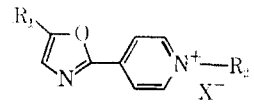
TABLE I

4-(2-OXAZOLYL)PYRIDINIUM SALTS



Compd	R_1	R_2	X	Mp, °C dec	Recrystn solvent	Formula	Analyses	% decrease in blood glucose[a] 1.5 mmol/kg	3.0 mmol/kg	Control
6	H	CH_3	Cl	244	*i*-PrOH	$C_9H_9ClN_2O \cdot H_2O$	C, H, Cl, N	55 ± 9	65 ± 13	24 ± 6
7	H	C_2H_5	Br	202–203	CH_3CN–Et_2O	$C_{10}H_{11}BrN_2O$	C, H, Br, N	54 ± 14	61 ± 7	9 ± 6
8	H	▷—CH_2	Br	213–215	CH_3CN–Et_2O	$C_{12}H_{13}BrN_2O$	C, H, Br, N	49 ± 11	72 ± 8	−11 ± 7
9	H	CH_2=$CHCH_2$	Cl	202–204	EtOH–Et_2O	$C_{11}H_{11}ClN_2O \cdot H_2O$	C, H, Cl, N	35 ± 6	47 ± 5	4 ± 2
10	H	C_6H_5CH=$CHCH_2$	Cl	126–128	CH_3CN	$C_{17}H_{15}ClN_2O \cdot H_2O$	H, Cl, N; C[b]	58 ± 13	90 ± 2	15 ± 7
11	CH_3	CH_3	I	213–214	EtOH	$C_{10}H_{11}IN_2O \cdot 0.5H_2O$	C, H, I, N	49 ± 7	83 ± 4	15 ± 7
12	See text			234–235	EtOH–Et_2O	$C_{10}H_{11}IN_2O$	C, H, I, N	21 ± 4	47 ± 7	−11 ± 7

[a] Values are means ± standard errors of four to six mice. Maximal reductions in blood glucose 3 or 5 hr after oral dosing are expressed as per cent decrease from predose levels. An increase in blood glucose is indicated by a negative sign (−). Average predose blood glucose concentration was 128 ± 3 mg/100 ml for 30 control mice. [b] C: calcd, 64.5; found, 64.0.

of pyridine quaternization[1,2] and demonstrate that alkylation has occurred on the pyridine rather than the oxazole nitrogen.

Hypoglycemic Activity.[9]—Saline solutions of compounds were administered by gavage to male CF-1 mice (Carworth Farms, 25–30 g) at doses of 1.5 and 3.0 mmol/kg; controls received an equal volume of vehicle. Blood samples (0.05 ml) obtained from retrobulbar plexuses 3 and 5 hr after dosing were assayed[3] for glucose using the method of Hoffman[10] as adapted for the Technicon AutoAnalyzer. Blood glucose was decreased 21–90% following the administration of oxazolylpyridinium salts (Table I). Further studies are in progress to compare the potency, toxicity, and mode of action of these agents with those of other hypoglycemic drugs.

Experimental Section[11]

Isonicotinamidoacetone (4).—To a cold solution of freshly prepared isonicotinoyl chloride[12] [from 20 g (0.16 mol) of isonicotinic acid] in 150 ml of dry pyridine was added, in portions, 17.6 g (0.16 mol) of aminoacetone hydrochloride[13] at such a rate that the temperature never rose above 10°. The mixture was allowed to come slowly to room temperature, stirred for 1 hr, poured into 1.5 l. of ice, and extracted with $CHCl_3$. The $CHCl_3$ solution was dried ($MgSO_4$), decolorized (Darco), and concentrated under reduced pressure to a brown solid. Recrystallization (EtOH) gave 6.5 g (23%) of tan crystals, mp 142–144°. Three recrystallizations (EtOH–pentane) gave pale yellow crystals, mp 143–144°. *Anal.* ($C_9H_{10}N_2O_2$) C, H, N.

4-(5-Methyl-2-oxazolyl)pyridine (2).—To a solution of 3.6 g (0.02 mol) of **4** in 54 ml of Ac_2O was added 4.4 ml of 85% H_3PO_4. The solution was heated under reflux for 3 hr, then cooled, and excess solvent was decanted. The tarry residue was treated with excess 1 *N* NaOH, which caused precipitation of an off-white solid. Three recrystallizations (H_2O) gave 1.3 g (40%) of colorless crystals, mp 99–100°, uv 289 mμ (ε 15,600). The analytical sample was obtained by sublimation at 60° (0.1 mm). *Anal.* ($C_9H_8N_2O$) C, H, N.

4-(2-Methyl-5-oxazolyl)pyridine (3).—To a suspension of 1.8 g (0.01 mol) of 4-acetylaminoacetylpyridine (**5**)[7] in 27 ml of Ac_2O was added 2.2 ml of 85% H_3PO_4. The mixture was heated under reflux for 1 hr and cooled. The supernatant liquid was decanted, excess 1 *N* NaOH was added to the tarry residue, and the oily mixture was extracted with $CHCl_3$. The $CHCl_3$ solution was dried ($MgSO_4$) and concentrated under reduced pressure to an off-white solid. Sublimation at 90° (12 mm) gave 0.95 g (59%) of colorless needles, mp 79–81°, uv 310 mμ (ε 20,820). *Anal.* ($C_9H_8N_2O$) C, H, N.

1-Methyl-4-(2-oxazolyl)pyridinium Chloride (6).—A mixture of 2.1 g (0.014 mol) of 4-(2-oxazolyl)pyridine (**1**)[6] and 5 ml of MeCl was heated at 100° for 4 hr in a glass-lined steel bomb. The excess MeCl was allowed to evaporate and the solid residue was recrystallized (*i*-PrOH) to give 0.3 g (20%) of off-white crystals, mp 244° dec, uv 312 mμ (ε 16,900). *Anal.* ($C_9H_9ClN_2O \cdot H_2O$) C, H, Cl, N.

4-(Oxazolyl)pyridinium salts (7–12) were prepared by reaction of **1**, **2**, and **3** with an alkyl halide either in a bomb at 100–120° for 4–18 hr without solvent (as for **6**, above) or in EtOH under reflux. Properties are listed in Table I.

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

(10) W. S. Hoffman, *J. Biol. Chem.*, **120**, 51 (1937).

(11) 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 determined by Mr. W. Fulmor and staff in MeOH with a Cary 11 spectrophotometer.

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Hypoglycemic Quaternary Azolylpyridinium Salts. Inactive Analogs

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A number of quaternary azolylpyridinium salts, including members of the pyrazolyl-,[1] isoxazolyl-,[2] 1,2,4-oxadiazolyl-,[3] oxazolyl-,[4] and thiazolylpyridinium[5] salt families, have been found to display interesting hypoglycemic activity in laboratory animals, and 1-methyl-4-(3-methyl-5-isoxazolyl)pyridinium chloride (**1**) has been chosen[6,7] for study as a potential antidiabetic drug. Other classes of azolylpyridinium salts have been examined and found to lack hypoglycemic activity in mice. In this report, we describe the syntheses and properties of these compounds.

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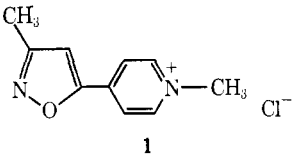

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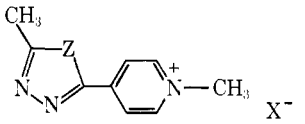
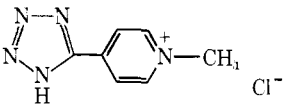
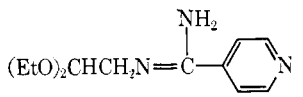


2a, Z = NH; X = Cl
b, Z = O; X = I
c, Z = S; X = I

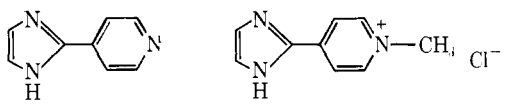


3

Reaction of 4-(5-methyl-1,2,4-triazol-3-yl)pyridine,[8] 4-(5-methyl-1,3,4-oxadiazol-2-yl)pyridine,[9] 4-(5-methyl-1,3,4-thiadiazol-2-yl)pyridine,[9] and 4-(5-tetrazolyl)pyridine[10] with MeCl or MeI provided the desired quaternary salts **2a–c**, **3**. For the synthesis of an imidazolyl analog, 4-cyanopyridine was converted by the method of Schaefer and Peters[11] to methyl isonicotinimidate, which was allowed to react with aminoacetaldehyde diethyl acetal to yield the amidino acetal **4**. Acidic cyclization of **4** gave the imidazolylpyridine **5**, which was quaternized to the desired salt **6**.



4



5 6

Compounds **2a–c**, **3**, and **6** (0.5–3.0 mmol/kg) were administered orally as saline solutions to male mice (Carworth Farms, 18–25 g); controls received an equal volume of vehicle. Blood glucose levels were determined[12] 3 and 5 hr after dosing by the method of Hoffman[13] as adapted for the Technicon AutoAnalyzer. Glucose concentrations were not different from controls, except for an uninteresting slight nondose related hypoglycemia following administration of **2b**.

Experimental Section[14]

1-Methyl-4-(5-methyl-1,2,4-triazol-3-yl)pyridinium Chloride (2a).—A mixture of 3.0 g (0.019 mol) of 4-(5-methyl-1,2,4-triazol-3-yl)pyridine[8] and 10 ml of MeCl was heated for 20 hr at 85° in a glass-lined steel bomb. The excess MeCl was allowed to evaporate, and the residual solid was recrystallized (EtOH) to provide 1.2 g (30%) of colorless crystals, mp 290–291° dec. Three recrystallizations gave colorless needles, mp 281–284° dec, uv 283 mμ (ε 13,400). *Anal.* ($C_9H_{11}ClN_4 \cdot 0.25H_2O$) C, H, Cl; N: calcd: 26.1; found, 26.7.

1-Methyl-4-(5-methyl-1,3,4-oxadiazol-2-yl)pyridinium Iodide (2b).—A solution of 1.61 g (0.01 mol) of 4-(5-methyl-1,3,4-oxadiazol-2-yl)pyridine,[9] 1.50 g (0.011 mol) of MeI, and 10 ml of MeOH was heated under reflux for 1 hr. An orange solid, 1.60 g, mp 150–250°, separated and was collected. Three recrystallizations (MeOH–H_2O) gave 0.31 g (10%) of orange needles, mp 275–277° dec, uv 217 (ε 17,900) and 278 mμ (ε 19,200). *Anal.* ($C_9H_{10}IN_3O$) C, H, I, N.

1-Methyl-4-(5-methyl-1,3,4-thiadiazol-2-yl)pyridinium Iodide (2c).—A solution of 1.77 g (0.01 mol) of 4-(5-methyl-1,3,4-thiadiazol-2-yl)pyridine,[9] 1 ml of MeI, and 10 ml of MeOH was heated under reflux for 2 hr. Upon cooling 2.58 g (81%) of a yellow solid, mp 225–230°, separated and was collected. Two recrystallizations (MeOH) gave yellow prisms, mp 226–227° dec, uv 218 (ε 18,100) and 287 mμ (ε 16,400). *Anal.* ($C_9H_{10}IN_3S$) C, H, I, N, S.

1-Methyl-4-(5-tetrazolyl)pyridinium Chloride (3).—A mixture of 7.8 g (0.053 mol) of 4-(5-tetrazolyl)pyridine[10] and 10 ml of MeCl was heated at 130° in a glass-lined steel bomb for 18 hr. The excess MeCl was allowed to evaporate, and the colorless residue was recrystallized (MeOH–H_2O) to provide 3.2 g (31%) of colorless crystals, mp 238–239°. Four recrystallizations gave the analytical sample, mp 235° dec, uv 277 mμ (ε 13,600). *Anal.* ($C_7H_8ClN_5$) C, H, Cl, N.

N-(Formylmethyl)isonicotinamidine Diethyl Acetal (4).—A solution of 20.8 g (0.20 mol) of 4-cyanopyridine and 1.1 g (0.02 mol) of NaOMe in 200 ml of MeOH was stirred at room temperature for 20 hr. To this solution of methyl isonicotinimidate was added 52 ml (0.20 mol) of 3.8 *N* HCl in EtOH and 26.6 g (0.20 mol) of aminoacetaldehyde diethyl acetal. The solution was heated under reflux for 4 hr and was concentrated under reduced pressure. The residual oil was treated with 160 ml of 0.5 *N* NaOH, and the resultant mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was dried ($MgSO_4$) and concentrated to give a white solid. Recrystallization (EtOAc–petroleum ether (bp 30–60°)) gave 34.1 g (72%) of colorless crystals, mp 92–94°. Several recrystallizations provided the analytical sample, mp 93–94°, uv 265 mμ (ε 3900). *Anal.* ($C_{12}H_{19}N_3O_2$) C, H, N.

4-(2-Imidazolyl)pyridine (5).—To 30 ml of 12 *N* H_2SO_4 was added in portions 2.3 g (0.01 mol) of **4**. The solution was then heated for 30 min on a steam bath, cooled, and made basic by the dropwise addition of 10 *N* NaOH. The solution was extracted with $CHCl_3$. The $CHCl_3$ solution was dried ($MgSO_4$) and concentrated to a white solid. Two recrystallizations (EtOAc–petroleum ether) gave 0.5 g (35%) of colorless crystals, mp 211–212°, uv 290 mμ (ε 15,390). *Anal.* ($C_8H_7N_3$) C, H, N.

1-Methyl-4-(2-imidazolyl)pyridinium Chloride (6).—A mixture of 2.9 g (0.02 mol) of **5** and 5 ml of MeCl was heated at 120° in a glass-lined steel bomb for 18 hr. The excess MeCl was allowed to evaporate, and the solid residue was recrystallized (EtOH) three times to provide 2.5 g (64%) of pale yellow crystals, mp 277–278° dec, uv 345 mμ (ε 21,510). *Anal.* ($C_9H_{10}N_3Cl$) C, H, Cl, N.

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(12) Testing data was supplied by Drs. D. A. Blickens and S. J. Riggi of the Metabolic Chemotherapy Department of these laboratories.

(13) W. S. Hoffman, *J. Biol. Chem.*, **120**, 51 (1937).

(14) 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.

4-Azolylpyridine 1-Oxides. Analogs of the Hypoglycemic 4-Azolylpyridinium Salts

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A number of 4-azolylpyridinium salts, including the pyrazolyl- (**1a**),[1] isoxazolyl- (**1b**),[2] thiazolyl- (**1c**),[3]

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