(Na_2SO_4), and charcoaled to give 107 g of yellow oil. Distillation through a 7.5-cm Vigreux column gave 98.8 g (93%) of crude ester. A center cut served as analytical sample.

***p*-Chlorophenylglyoxylic Acid.**—A mixture of 37 ml (0.35 mole) of PhCl, 48.4 g (0.35 mole) of ethoxalyl chloride, and 200 ml of $Cl_2CHCHCl_2$ was cooled to 0°. With stirring 47 g (0.35 mole) of $AlCl_3$ was added at 0° during 30 min. The mixture was stirred 30 min more at 0° and warmed gradually over 30 min up to 45° where a brisk evolution of HCl began. Heating was interrupted until the HCl evolution stopped. The mixture was stirred on the steam bath for 3 hr, cooled, and poured onto a mixture of 200 g of ice and 200 ml of 12 *N* HCl. Steam distillation removed the solvent; the brown tar remaining was taken into Et_2O and the aqueous phase was extracted with Et_2O. The combined Et_2O extracts were washed with H_2O followed by dilute HCl, charcoaled, and dried (Na_2SO_4) to give 57 g of brown gum. The gum was taken up in hot PhH and hexane was added to the cloud point. On cooling there was obtained 21.7 g (33%) of crude tan solid, mp 89–91°, lit.[8] mp 90°.

2-Chloroethyl Pyruvate Diethyl Ketal (3).—A mixture of 15.0 g (0.1 mole) of 2-chloroethyl pyruvate, 26 ml (0.15 mole) of ethyl orthoformate, 1.5 g of *p*-toluenesulfonic acid monohydrate, and 24 ml of absolute EtOH was allowed to stand 48 hr and then refluxed 8 hr. Using a minimum amount of heat, low-boiling components were removed at the aspirator and the residue was poured into ice water containing 40 ml of 5% $NaHCO_3$. After extraction into 1,2-dichloroethane, the organic phase was washed with H_2O until the washings were neutral, dried, charcoaled, and stripped to give a residue of yellow oil. Careful removal of forerun in a 5-cm Vigreux column gave the crude product, 13.7 g (61%), bp 106–113° (6 mm). On redistillation a center cut furnished the analytical sample.

2-Chloropropyl Phenylglyoxylate (9).—To a stirred solution of 25.5 g (0.17 mole) of phenylglyoxylic acid in 100 ml of DMF was added 23.5 ml (0.17 mole) of Et_3N followed by 17.5 ml (0.17 mole) of 1-bromo-2-chloropropane. With the protection of a drying tube the mixture was stirred on the steam bath 5 hr and cooled. The precipitate was filtered and washed with 25 ml of hexane. The DMF solution was poured into ice water, the oil was taken into $CHCl_3$, and the aqueous phase was extracted with $CHCl_3$. The hexane extract was concentrated and taken into $CHCl_3$. The combined $CHCl_3$ extracts were washed with 2% $NaHCO_3$ and H_2O, dried (Na_2SO_4), charcoaled, and concentrated to an oil which was fractionated in a 7.5-cm Vigreux column to yield 12.1 g (31%). A center cut served as analytical sample.

2-Chloroethyl *m*-Nitrophenylglyoxylate (15).—*m*-Nitrobenzaldehyde was converted into the cyanohydrin using the procedure of Buck.[9] Without characterization the cyanohydrin was hydrolyzed by heating in concentrated HCl on the steam bath 18 hr to give *m*-nitromandelic acid,[10] mp 114–116°, in 20% yield. This acid was esterified with 2-chloroethanol in 88% yield to give 2-chloroethyl *m*-nitromandelate (**26**), mp 86–87°. *Anal.* ($C_{10}H_{10}ClNO_5$) C, H, Cl. N-Bromosuccinimide (4.25 g, 0.0238 mole) was stirred in 100 ml of refluxing CCl_4. To this was added a solution of 6.2 g (0.0238 mole) of 2-chloroethyl *m*-nitromandelate in 75 ml of CCl_4. After 12 hr of heating under reflux the mixture was cooled and the solid was filtered off and discarded. A drop of allyl alcohol was added to decolorize. The solution was dried ($NaSO_4$) and charcoaled. After the solvent was removed by careful distillation on the steam bath the oily residue distilled to give 83% yield of **15**, bp 162–164° (0.02 mm).

Acknowledgment.—The authors are indebted for spectroscopic data to Dr. R. Kullnig and staff and for elementary analytical data to Mr. K. Fleischer and staff.

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Quaternary Oxazolylpyridinium Salts. Oral Hypoglycemic Agents

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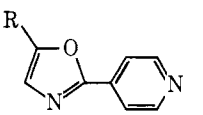
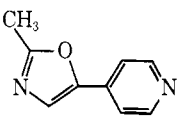
A number of quaternary azolylpyridinium salts, including members of the pyrazolyl-,[1] isoxazolyl-,[2–4] and 1,2,4-oxadiazolylpyridinium[5] salt families, have been found to display hypoglycemic activity in laboratory animals. As part of a comprehensive development of this lead, we have investigated the replacement of the azolyl ring with other five-membered heterocycles. We describe herein the synthesis of some novel 4-(oxazolyl)pyridinium salts.

The 4-(oxazolyl)pyridinium salts **6–12** (Table I) were obtained by quaternization of the appropriate oxazolylpyridine bases **1**, **2**, and **3**. The base **1** was prepared as described by Dadkah and Prijns.[6] The



1, R = H
2, R = CH_3



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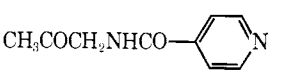

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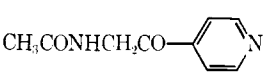

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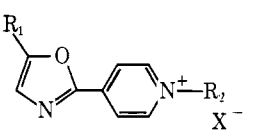
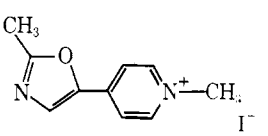


6–11



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bases **2** and **3** were obtained by dehydration of the amido ketones **4** and **5**,[7] respectively, using a procedure developed by Ott, *et al.*,[8] for the preparation of aryloxazoles. In the nmr spectrum of the base **1** the pyridyl protons appear as two doublets at δ 7.73 and 8.75. Upon quaternization to **6**, these signals shift to new values of δ 8.42 and 9.02. These changes, a downfield displacement of both doublets, as well as a smaller separation between chemical shifts, are diagnostic

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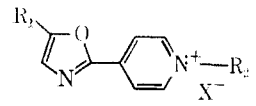
TABLE I
4-(2-OXAZOLYL)PYRIDINIUM SALTS



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.

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(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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