Prepared in a similar manner from the corresponding pyrazolylpyridine and alkyl halide, either without solvent in a bomb or under reflux in a suitable alcoholic solvent, were **1–4**, **7–18**, **20–38**. Properties are included in Table I.

4-[5(3)-Ethyl-3(5)-pyrazolyl]-1-methylpiperidine Hydrochloride (6).—A 2.0-g sample of 1-methyl-4-[5(3)-ethyl-3(5)-pyrazolyl]pyridinium chloride was hydrogenated at 2.1 kg/cm² at room temperature in 20 ml of AcOH with 0.5 g of PtO_2. After 3 hr the catalyst was removed, and the solvent was distilled on a steam bath under reduced pressure. Trituration of the oily residue with MeCN left 2.0 g of colorless solid, mp 144–155°. Recrystallization (MeCN) gave colorless prisms, mp 153–154°. *Anal.* ($C_{11}H_{20}ClN_3$) C, H, N; Cl: calcd, 14.6; found, 15.1.

1-Methyl-4-[5(3)-carboxy-3(5)-pyrazolyl]pyridinium Hydroxide Inner Salt (19).—A solution of 2.67 g (0.01 mole) of 1-methyl-4-[5(3)-ethoxycarbonyl-3(5)-pyrazolyl]pyridinium chloride, 25 ml of H_2O, and 20 ml of 1 *N* NaOH was boiled on a hot plate until 15 ml of solution remained. The solution was neutralized with dilute HCl, and the solid which separated was collected. Recrystallization ($EtOH-H_2O$) provided 1.2 g of very hygroscopic colorless needles. Properties of **19** are included in Table I.

Acknowledgment.—We thank Mr. T. L. Fields, who synthesized compounds **1**, **2**, **5**, **49**, **50**, and **51**, for permission to describe his results.

Isoxazolylpyridinium Salts. A New Class of Hypoglycemic Agents

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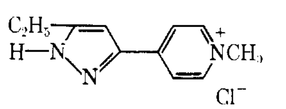
A series of 4-isoxazolylpyridinium salts has been synthesized. These compounds display interesting hypoglycemic activity in mice.

4-[3(5)-Pyrazolyl]pyridinium salts (**1**, for instance) have recently been found to display interesting hypoglycemic activity in normal chicks and alloxan-diabetic mice.[1] As part of the comprehensive development of this lead, we have investigated the replacement of the pyrazole ring with other five-membered heterocycles. In this paper we describe the synthesis of some novel 4-(isoxazolyl)pyridinium salts.



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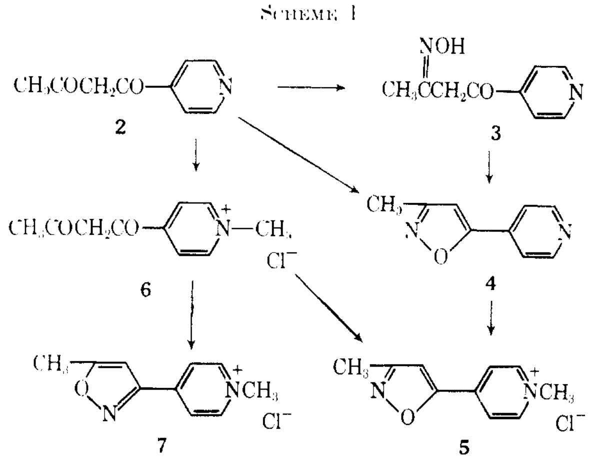
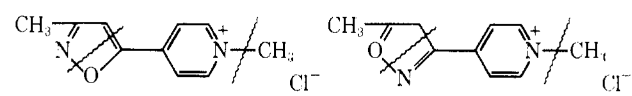
Reaction of 1-(4-pyridyl)-1,3-butanedione (**2**) with hydroxylamine hydrochloride at room temperature provided the monoxime **3**, which was readily converted to the isoxazolylpyridine **4** by heating with dilute base (Scheme I). Compound **4**, which was also prepared directly from **2** without isolation of **3**, was quaternized to 1-methyl-4-(3-methyl-5-isoxazolyl)pyridinium chloride (**5**) with methyl chloride. Alternatively, the dione **2** was first heated with methyl chloride to give the salt **6**, which, when treated with hydroxylamine hydrochloride, gave a separable mixture of **5** and **7**.

SCHEME I



Examination of the nmr spectra of the isomeric isoxazolylpyridinium salts **5** and **7** offered a first insight into the structural assignments. The nmr spectrum of **5** displayed singlets at τ 7.55 and 2.68 (isoxazolyl CH_3 and H, respectively), while the corresponding signals for **7** were a doublet at τ 7.38 and a quartet at 3.07. If a significant degree of bond localization in the isoxazole ring is assumed, one would expect to observe allylic coupling between the 4-H and 5-CH_3 in the nmr spectrum of **7**, while the 4-H and 3-CH_3 should appear as singlets in the spectrum of **5**. Confirmation of structures **5** and **7** was obtained in the mass spectral fragmentation patterns which showed peaks at *m/e* 106 (**5a**) and 104 (**7a**), respectively. Finally, unequivocal



106 **5a** 104 **7a**

proof of structure **5** was provided by single-crystal X-ray analysis of the corresponding bromide salt **8**. In practice, differentiation between the isomer classes can most readily be made by ultraviolet spectroscopy; **5** exhibits a maximum at 293 mμ, **7** at 255 mμ.

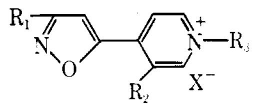
When it was observed that **5** displayed interesting hypoglycemic activity in normal and alloxan-diabetic mice,[2] the preparation of a series of analogs was undertaken. The choice of substituents considered was influenced by the structure–activity correlation already developed for the pyrazolylpyridinium salts.[1] Reaction of the appropriate dicarbonyl compound with hydroxylamine gave, in some cases, the isoxazolylpyridine **9** or **10**, in others the oxime **12** or **13**; the latter were then cyclodehydrated to the isoxazolylpyridines **11**

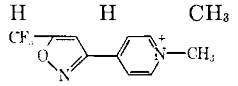
(1) V. J. Bauer, H. P. Dalalian, W. J. Fanshawe, S. R. Safir, E. C. Tocus, and C. R. Boshart, *J. Med. Chem.*, **11**, 981 (1968).

(2) S. J. Riggi, D. A. Blickens, and C. R. Boshart, *Diabetes*, in press.

TABLE I

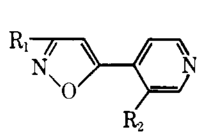
4-(ISOXAZOLYL)PYRIDINIUM SALTS



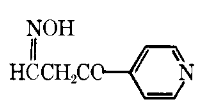
Compd	R_1	R_2	R_3	X	Mp, °C dec	Recrystn solvent	Formula	Analyses	Hypoglycemic activity in mice[a]
5	CH_3	H	CH_3	Cl	250	*i*-PrOH	$C_{10}H_{11}ClN_2O$	C, H, Cl, N	2
7		See structure **7**		Cl	221–222	CH_3CN	$C_{10}H_{11}ClN_2O$	C, H, Cl; N[b]	2
8	CH_3	H	CH_3	Br	261–263	EtOH	$C_{10}H_{11}BrN_2O$	C, H, Br, N	
15	CH_3	H	C_2H_5	I	193–194	*i*-PrOH	$C_{11}H_{13}IN_2O$	C, H, I, N	1
16	CH_3	H	*n*-C_3H_7	Br	181–183	CH_3CN	$C_{12}H_{15}BrN_2O$	C, H, Br, N	1
17	CH_3	H	▷—CH_2	Br	165–166	CH_3CN	$C_{13}H_{15}BrN_2O$	C, H, Br, N	1
18	CH_3	H	$CH_3OCH_2CH_2$	Cl	73–74	*i*-PrOH	$C_{12}H_{15}ClN_2O_2 \cdot H_2O$	C, H, Cl, N	1
19	CH_3	H	$CH_2{=}CHCH_2$	Cl	86	CH_3CN–Et_2O	$C_{12}H_{13}ClN_2O \cdot H_2O$	H, Cl; C,[c] N[d]	1
20	CH_3	H	$C_6H_5CH{=}CHCH_2$	Cl	189–191	CH_3CN	$C_{18}H_{17}ClN_2O$	C, Cl, N; H[e]	0
21	C_2H_5	H	CH_3	Cl	205–206	CH_3CN	$C_{11}H_{13}ClN_2O \cdot 0.25H_2O$	C, H, Cl, N	2
22	C_2H_5	H	C_2H_5	I	154	*i*-PrOH	$C_{12}H_{15}IN_2O$	C, H, I, N	1
23	CH_3	CH_3	CH_3	Cl	246–247	CH_3CN	$C_{11}H_{13}ClN_2O$	C, H, Cl, N	2
24	H	H	CH_3	I	212–213	MeOH	$C_9H_9IN_2O$	C, H, I, N	1
25	H	H	CH_3	Cl	182–183	CH_3CN	$C_9H_9ClN_2O$	C, Cl, N; H[f]	1
26				Cl	230	*i*-PrOH	$C_{10}H_8ClF_3N_2O$	C, H, Cl, F, N	1

[a] Maximum reduction in blood glucose levels in the dosage range 125–500 mg/kg calculated as a percentage change from the predose control value: 50–80% reduction = 2, 15–50% reduction = 1, less than 15% reduction = 0. [b] N: calcd, 13.3; found, 12.8. [c] C: calcd, 56.6; found, 57.2. [d] N: calcd, 11.0; found, 10.5. [e] H: calcd, 5.44; found, 6.09. [f] H: calcd, 4.61; found, 5.13.

and 14. Reaction of the tertiary bases **4**, **9–11**, and **14** with a variety of halides gave the isoxazolylpyridinium salts **8** and **15–26** (Table I). The decision as to which isomeric isoxazole class was formed in each reaction was based upon spectral (uv and, when applicable, nmr) data.



9, $R_1 = C_2H_5$; $R_2 = H$
10, $R_1 = R_2 = CH_3$
11, $R_1 = R_2 = H$



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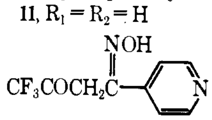

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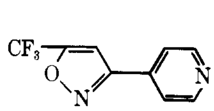

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Hypoglycemic Activity.—Male mice from Manor Farms weighing 18–25 g were employed. Test compounds (125, 250, or 500 mg/kg) were dissolved in 0.9% saline and administered by gavage in a volume of 0.2 ml/25 g of mouse; controls received an equal volume of vehicle. Blood samples (0.02–0.03 ml) obtained from tail veins 4 hr after dosing were assayed for blood glucose (estimated as reducing sugar content) using the method of Hoffman[3] as adapted for the Technicon autoanalyzer. Results are included in Table I. Detailed studies of the pharmacology and metabolic effects of the isoxazolylpyridinium salts will be published elsewhere.[4]

(3) W. S. Hoffman, *J. Biol. Chem.*, **120**, 51 (1937).
(4) D. A. Blickens and S. J. Riggi, to be published.

Experimental Section[5]

1-(4-Pyridyl)-1,3-butanedione 3-Oxime (3).—To a solution of 24 g (0.15 mole) of 1-(4-pyridyl)-1,3-butanedione,[6] 20 g (0.29 mole) of $HONH_3^+Cl^-$, 100 ml of H_2O, and 50 ml of EtOH was added during 0.5 hr with stirring 20 g of Na_2CO_3. After 0.5 hr, a colorless precipitate, 28 g, mp 155–160°, was collected. Three recrystallizations (EtOH) provided colorless crystals: mp 169–170° (lit.[7] mp 164–165°); nmr ($CDCl_3$), τ 8.02 (s, 3, CH_3), 6.58 (s, 2, CH_2), 2.50 and 1.33 (d, J = 6 cps, 2 each, pyridyl); uv, 258 mμ (ϵ 5000). *Anal.* ($C_9H_{10}N_2O_2$) C, H, N.

4-(3-Methyl-5-isoxazolyl)pyridine (4). A.—To a stirred solution of 21.7 g (0.13 mole) of 1-(4-pyridyl)-1,3-butanedione,[6] 14 g (0.2 mole) of $HONH_3^+Cl^-$, 150 ml of H_2O, and 100 ml of EtOH was added at room temperature during 0.5 hr 14 g of Na_2CO_3. The solution was heated under reflux for 12 hr, and 100 ml of solvent was allowed to distil. The mixture was extracted with C_6H_6, and the C_6H_6 solution was concentrated under reduced pressure to 17.5 g of a colorless solid, mp 50–55°. Recrystallization (C_6H_6–hexane) gave colorless needles: mp 67–68°; nmr ($CDCl_3$), τ 7.63 (s, 3, CH_3), 3.43 (s, 1, 4-isoxazolyl), 2.40 and 1.27 (d, J = 6 cps, 2 each, pyridyl); uv, 263 mμ (ϵ 22,900). *Anal.* ($C_9H_8N_2O$) C, H, N.

B.—A solution of 0.2 g of **3**, 2 ml of H_2O, 1 ml of EtOH, and 0.1 g of Na_2CO_3 was heated under reflux for 5 hr, diluted with H_2O, and extracted with Et_2O. The Et_2O layer was dried ($MgSO_4$) and concentrated under reduced pressure to a colorless solid. Recrystallization (hexane–Me_2CO) gave 0.15 g of colorless needles, mp 64°; ir identical with that of authentic **4**, above.

1-Methyl-4-(3-methyl-5-isoxazolyl)pyridinium Chloride (5).—A mixture of 4.0 g (0.025 mole) of **4** and 10 ml of MeCl was heated for 15 hr at 75° in a glass-lined steel bomb. The excess MeCl

(5) 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 in MeOH solution with a Cary 11 spectrophotometer and nmr spectra were determined with a Varian A-60 spectrometer with TMS or 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt as an internal standard by Mr. W. Fulmor and staff. Partition chromatography was carried out by Mr. C. Pidacks and staff.
(6) L. Fabbrini, *Farmaco, Ed. Sci.*, **9**, 603 (1954).
(7) R. Tscherne, *Monatsh. Chem.*, **22**, 615 (1901).

was allowed to evaporate, and the residual solid was recrystallized (*i*-PrOH) to provide 4.0 g (76%) of crystals, mp 248–249° dec. Two recrystallizations gave colorless prisms: mp 250° dec; nmr (D_2O), τ 7.53 (s, 3, CCH_3), 5.41 (s, 3, NCH_3), 2.63 (s, 1, 4-isoxazolyl), 1.52 and 0.92 (d, J = 7 cps, 2 each, pyridinium); all uv, 293 mμ (ϵ 19,725).

4-Acetoacetyl-1-methylpyridinium Chloride (6).—A mixture of 5.0 g (0.03 mole) of 1-(4-pyridyl)-1,3-butanedione[6] and 20 ml of MeCl was heated at 95° for 15 hr in a glass-lined steel bomb. The excess MeCl was allowed to evaporate, and the residual solid was washed with Et_2O to provide 4.9 g (77%) of tan crystals mp 192–196° dec. Five recrystallizations (*i*-PrOH) gave pale yellow prisms: mp 197–198° dec; nmr (D_2O), τ 7.59 (s, 3, CCH_3), 5.46 (s, 3, NCH_3), 1.50 and 1.00 (d, J = 7 cps, 2 each, pyridinium); uv, 229 mμ (ϵ 19,700). *Anal.* ($C_{10}H_{12}ClNO_2$) C, H, Cl, N.

1-Methyl-4-(5-methyl-3-isoxazolyl)pyridinium Chloride (7).—A mixture of 10 g (0.047 mole) of **6**, 3.5 g (0.05 mole) of $HONH_3^+Cl^-$, and 125 ml of EtOH was heated under reflux with stirring for 3 hr, cooled, and diluted with 200 ml of Et_2O. The solid which separated was recrystallized (*i*-PrOH) to provide 5.2 g of crystals, mp 100–120° dec, which was shown by nmr to be a 1:1 mixture of **5** and **7**. The mixture was subjected to partition chromatography on Celite 560 (Johns-Manville) using a heptane–*n*-BuOH–0.01 *N* HCl (3:20:10) system. From a 2.0-g sample was eluted at 4.5 hold-back volumes 0.7 g of a solid, mp 219–220°. Recrystallization (CH_3CN) gave pure **7**: mp 221–222°; nmr (D_2O), τ 7.38 (d, J = 0.5 cps, 3, CCH_3), 5.55 (s, 3, NCH_3), 3.07 (q, J = 0.5 cps, 1, 4-isoxazolyl), 1.56 and 0.98 (d, J = 7 cps, 2 each, pyridinium); uv, 255 mμ (ϵ 15,000).

4-(3-Ethyl-5-isoxazolyl)pyridine (9) was prepared from crude 1-(4-pyridyl)-1,3-pentanedione[1] and hydroxylamine hydrochloride by the method described above for the synthesis of **4**. The crude product was crystallized (hexane) to provide colorless crystals, mp 48–49°. *Anal.* ($C_{10}H_{10}N_2O$) C, H, N.

3-Methyl-4-(3-methyl-5-isoxazolyl)pyridine (10) was prepared from crude 1-(3-methyl-4-pyridyl)-1,3-butanedione[1] and $HONH_3^+Cl^-$ by the method described above for the synthesis of **4**. The crude product was crystallized (Et_2O) to provide colorless crystals, mp 87–88°. *Anal.* ($C_{10}H_{10}N_2O$) C, H, N.

1-(4-Pyridyl)-1,3-propanedione 3-Oxime (12).—A solution of 8.6 g (0.05 mole) of crude 1-(4-pyridyl)-1,3-propanedione sodium salt,[1] 3.6 g (0.05 mole) of $HONH_3^+Cl^-$, and 75 ml of H_2O was adjusted to pH 8 with $NaHCO_3$. After 1 hr a tan solid, 5.4 g (73%), mp 147–148° dec, separated. Three recrystallizations (EtOH) gave colorless crystals, mp 153–154° dec. *Anal.* ($C_8H_8N_2O_2$) C, H, N.

4-(5-Isoxazolyl)pyridine (11).—A mixture of 38 g (0.22 mole) of **12** and 150 ml of AcCl was heated under reflux for 2 hr. The excess AcCl was distilled under reduced pressure, and the residue was dissolved in H_2O. The solution was neutralized with 5 *N* NaOH, and the mixture was extracted with Et_2O. The Et_2O solution was dried ($MgSO_4$) and concentrated to 18 g of a yellow solid. Recrystallization (Et_2O) gave 8.7 g (30%) of tan crystals, mp 100–102°. Three recrystallizations gave colorless crystals, mp 100–102°. *Anal.* ($C_8H_6N_2O$) C, H, N.

1-(4-Pyridyl)-4,4,4-trifluoro-1,3-butanedione 1-Oxime (13). A solution of 2.2 g (0.01 mole) of 1-(4-pyridyl)-4,4,4-trifluoro-1,3-butanedione,[8] 0.7 g (0.01 mole) of $HONH_3^+Cl^-$, 0.7 g of Na_2CO_3, 20 ml of EtOH, and 5 ml of H_2O was heated under reflux for 12 hr. The solution was concentrated to a volume of 5 ml and diluted with 50 ml of H_2O: colorless crystals, 2.0 g (90%), mp 185°, separated. Two recrystallizations (*i*-PrOH–H_2O) provided colorless crystals, mp 187°. *Anal.* ($C_9H_7F_3N_2O_2$) C, F, N; H: calcd, 3.04; found, 3.70.

4-(5-Trifluoromethyl-3-isoxazolyl)pyridine (14).—To 25 ml of concentrated H_2SO_4 was added during 15 min with stirring 10.0 g (0.04 mole) of **13**. After 20 min, the solution was poured onto ice, diluted with 500 ml of H_2O, and made basic with 100 ml of 10 *N* NaOH; a solid, 7.5 g, mp 75–81°, separated. Recrystallization (EtOH–H_2O) gave 6.5 g (79%) of colorless prisms, mp 81–83°. Three recrystallizations followed by sublimation at 50° (0.05 mm) gave the analytical sample, mp 82–83°. *Anal.* ($C_9H_5F_3N_2O$) C, H, N; F: calcd, 26.6; found, 26.1.

Isoxazolylpyridinium salts 8 and 15–26 were prepared by reaction of the isoxazolylpyridines **4** and **9–12** with an alkyl halide either in a bomb without solvent (as for **5**, above) or in an alcoholic solvent under reflux. Properties are listed in Table I; uv spectra for **21**, 292 mμ (ϵ 20,200); for **23**, 292 mμ (ϵ 19,200); for **25**, 289 mμ (ϵ 19,000); and for **26**, 247 mμ (ϵ 14,250); nmr (D_2O) for **26**, τ 5.43 (s, 3, NCH_3), 2.08 (q, J = 1 cps, 1, 4-isoxazolyl), 1.52 and 0.89 (d, J = 7 cps, 2 each, pyridinium).

Acknowledgments.—The synthesis of **4** was developed by Mr. T. L. Fields. Mass spectral studies were performed by Dr. J. Karliner, and X-ray structure analysis by Dr. J. H. van den Hende. Interpretation of nmr spectra was provided by Mr. G. Morton. Hypoglycemic testing was carried out by Drs. D. A. Blickens and S. J. Riggi of the Department of Metabolic Chemotherapy. We thank our colleagues for permission to report their results.

(8) H. A. Wagner, U. S. Patent 3,200,128 (Aug 10, 1965).