and the filtrate was treated with ethereal HCl, resulting in a dense white precipitate which was collected on a filter (see Table I).

Apocodeine (2).—Codeine phosphate (10.0 g, 0.0236 mole) was rearranged as described for the morphine series. The dark reaction mixture was diluted with 300 ml of H_2O and extracted with ether. The aqueous layer was basified with concentrated NH_4OH and extracted repeatedly with ether. The combined ethereal extracts were evaporated on a steam bath, and small amounts of residual H_2O were removed by azeotroping with benzene. The solvents were completely removed under reduced pressure, the residue was taken up in ether–benzene (10:90), and this solution was chromatographed on neutral alumina. Elution with the same solvent system, with ether, and finally with ether–CH_3OH (90:10) permitted collection of fractions which formed a salt with ethereal HCl and were pooled. The HCl salt was recrystallized from C_2H_5OH–ether (charcoal) to afford 1.5 g (20%) of white crystals, mp 260–265° dec (lit.[25] mp 260–263°). *Anal.* ($C_{18}H_{20}ClNO_2$) C, H, Cl; N: calcd, 4.42; found, 3.71.

Apocodeine was freed from its HCl salt with Na_2CO_3, mp 120–123° (lit.[25] mp 122.5–124.5°).

(25) K. Folkers, *J. Amer. Chem. Soc.*, **58**, 1814 (1936).

4-[3(5)-Pyrazolyl]pyridinium Salts. A New Class of Hypoglycemic Agents

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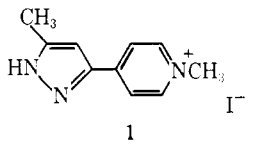
A series of 4-[3(5)-pyrazolyl]pyridinium salts has been synthesized. Many of these compounds display interesting hypoglycemic activity in alloxan-diabetic mice; a structure–activity relationship is derived.

During the course of screening of randomly selected compounds for oral hypoglycemic activity, it was discovered that 1-methyl-4-[5(3)-methyl-3(5)-pyrazolyl]pyridinium iodide (**1**) markedly lowered the blood sugar levels of fasted normal chicks. Comprehensive development of the lead was begun when it was demonstrated that this effect was just as pronounced in alloxan-diabetic mice (up to 95% reduction of blood glucose values). In this paper we delineate the structural requirements for hypoglycemic activity of the pyrazolylpyridinium salts.



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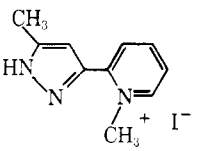

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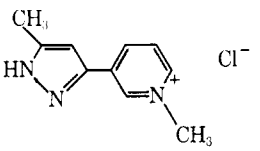

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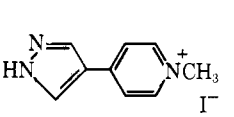
Structure–Activity Correlation.—Attention was first directed to the specificity of the location of the pyrazole–pyridinium ring attachment. Compounds **2** and **3**, the 2-pyridinium and 3-pyridinium analogs of **1**, were found to be inactive, as was **4**, in which the 4-pyrazolyl position is bonded to the 4-pyridinium position. Thus, the 4-[3(5)-pyrazolyl]pyridinium structure is required.

The presence of the pyridinium salt moiety of **1** was shown to be necessary by the absence of hypoglycemic activity in the related tertiary base **5** and piperidine salt **6**. Variations in the nature of the five-membered



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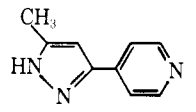

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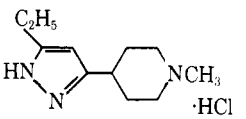


6

heterocyclic ring will be considered in subsequent papers.[2]

The effect upon activity of substituents on the 4-[3(5)-pyrazolyl]pyridinium nucleus was then explored by the synthesis and testing of an extensive series of analogs of **1** (Table I). It was found that compounds containing a hydrogen atom (**7**, **8**), alkyl group (**9**–**14**), benzyl group (**15**), or cyclopropyl ring (**16**) at the 5(3)-pyrazolyl position were active, but that the activity was destroyed by the introduction of certain electronegative substituents (**17**–**19**) or a phenyl group (**20**) at this site.

The hydrogen atom at the 4-pyrazolyl or 3-pyridyl position could be replaced by a methyl group (**21**, **22**) with retention of activity.

When the N-methyl substituent of **1** was replaced with larger alkyl groups (**23**–**29**), activity was retained. Alkenyl substituents on the pyridine nitrogen gave **30**–**34** which displayed hypoglycemic activity. Compound **35**, in which the N-methyl had been replaced by cyclopropylmethyl, was active, but **36** with a phenacyl and **37**, with an ethoxycarbonylmethyl substituent, were inactive.

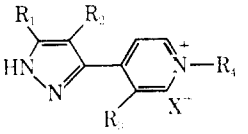
Since alkyl groups at the 5(3)- and 4-pyrazolyl positions led to active compounds, the tetrahydroindazole

(1) Author to whom inquires should be addressed.

(2) V. J. Bauer, W. J. Fanshawe, H. P. Dalalian, and S. R. Safir, *J. Med. Chem.*, **11**, 984 (1968).

TABLE I

PYRAZOLYLPYRIDINIUM SALTS



Compd	R_1	R_2	R_3	R_5	X	Mp, °C	Recrystn solvent	Formula	Analyses	Hypoglycemic effect in alloxan-ized mice[a]
1	CH_3	H	H	CH_3	I	252–253	MeOH	$C_{10}H_{12}IN_3$	C, H, I, N	2
2		See **2** in text				166–168	EtOH–EtCOMe	$C_{10}H_{12}IN_3$	C, H, I, N	0
3		See **3** in text				276–278	MeOH	$C_{10}H_{12}ClN_3$	C, H, Cl, N	0
4		See **4** in text				223–225	MeOH	$C_9H_{10}IN_3$	H, I; C, N[b]	0[c]
7	H	H	H	CH_3	I	189–190	MeOH	$C_9H_{10}IN_3$	C, H, I, N	2
8	H	H	H	CH_3	Cl	232–233	*i*-PrOH	$C_9H_{10}ClN_3 \cdot 0.25H_2O$	C, H, Cl; N[d]	2
9	CH_3	H	H	CH_3	Cl	251–252	*i*-PrOH	$C_{10}H_{12}ClN_3$	C, H, Cl, N	2
10	C_2H_5	H	H	CH_3	I	213–214	MeOH	$C_{11}H_{14}IN_3$	C, H, I, N	2
11	C_2H_5	H	H	CH_3	Cl	250–251	MeOH	$C_{11}H_{14}ClN_3$	C, H, Cl, N	2
12	*i*-C_4H_9	H	H	CH_3	I	206–207	Me_2CO	$C_{13}H_{18}IN_3$	C, H, I, N	1
13	*n*-C_6H_{13}	H	H	CH_3	I	78–79	MeOH–Me_2CO	$C_{15}H_{22}IN_3$	H, I, N; C[e]	2
14	*n*-C_6H_{13}	H	H	CH_3	Cl	191–192	MeOH–Me_2CO	$C_{15}H_{22}ClN_3$	C, H, Cl, N	
15	$C_6H_5CH_2$	H	H	CH_3	I	224	EtOH–H_2O	$C_{16}H_{16}IN_3$	C, H, I, N	1
16		H	H	CH_3	Cl	259–261	*i*-PrOH	$C_{12}H_{14}ClN_3$	C, H, Cl, N	1
17	CF_3	H	H	CH_3	Cl	254	EtOH	$C_{10}H_9ClF_3N$	C, Cl, F, N; H[f]	0
18	$COOC_2H_5$	H	H	CH_3	Cl	201–202	MeOH–Et_2O	$C_{12}H_{14}ClN_3O_2 \cdot H_2O$	H, Cl, N; C[g]	0
19	COO^-	H	H	CH_3		315	EtOH–H_2O	$C_{10}H_9N_3O_2 \cdot 0.5H_2O$	H, N; C[h]	0
20	C_6H_5	H	H	CH_3	I	211–212	EtOH	$C_{15}H_{14}IN_3$	C, H, I, N	0
21	H	CH_3	H	CH_3	I	213–214	EtOH	$C_{10}H_{12}IN_3$	C, H, I, N	1
22	CH_3	H	CH_3	CH_3	Cl	263–265	EtOH	$C_{11}H_{14}ClN_3$	C, H, Cl, N	2
23	CH_3	H	H	C_2H_5	I	175–176[i]	EtOH	$C_{11}H_{14}IN_3$	C, H, I, N	2
24	CH_3	H	H	*n*-C_3H_7	Br	247–248	MeOH	$C_{12}H_{16}BrN_3$	C, H, Br, N	2
25	CH_3	H	H	*i*-C_3H_7	Br	217–218	*i*-PrOH	$C_{12}H_{16}BrN_3$	C, H, Br, N	1
26	CH_3	H	H	*i*-C_3H_7	Cl	242–243	*i*-PrOH	$C_{12}H_{16}ClN_3$	C, H, Cl, N	1
27	CH_3	H	H	*n*-C_4H_9	Br	211–212	CH_3CN	$C_{13}H_{18}BrN_3$	C, H, Br, N	2
28	CH_3	H	H	*n*-C_4H_9	Cl	195–196	*i*-PrOH	$C_{13}H_{18}ClN_3$	C, H, Cl, N	2
29	CH_3	H	H	*i*-C_4H_9	Br	235–236	*i*-PrOH	$C_{13}H_{18}BrN_3$	C, H, Br, N	2
30	CH_3	H	H	$CH_2{=}CHCH_2$	Cl	243–244	EtOH	$C_{12}H_{14}ClN_3$	C, H, Cl, N	1
31	CH_3	H	H	$CH_2{=}C(CH_3)CH_2$	Cl	229–230	*i*-PrOH	$C_{13}H_{16}ClN_3$	C, H, Cl, N	2
32	CH_3	H	H	$(CH_3)_2C{=}CHCH_2$	Cl	194–195	*i*-PrOH–Me_2CO	$C_{14}H_{18}ClN_3$	C, H, Cl, N	2
33	CH_3	H	H	$CH_3CH{=}CHCH_2$	Cl	162–163	CH_3CN	$C_{13}H_{16}ClN_3$	H, Cl, N; C[j]	2
34	CH_3	H	H	$C_6H_5CH{=}CHCH_2$	Cl	207–208	*i*-PrOH	$C_{18}H_{18}ClN_3 \cdot 0.5H_2O$	C, H, Cl, N	2
35	CH_3	H	H		Br	220–221	*i*-PrOH	$C_{13}H_{16}BrN_3$	C, H, Br, N	2
36	CH_3	H	H	$C_6H_5COCH_2$	Br	269–270	EtOH	$C_{17}H_{16}BrN_3O$	C, H, Br, N	0
37	CH_3	H	H	$C_2H_5OOCCH_2$	Br	179–180	EtOH	$C_{13}H_{16}BrN_3O_2$	C, H, Br, N	0
38	$-(CH_2)_4-$		H	CH_3	I	245–246	MeOH	$C_{13}H_{16}IN_3$	C, H, I, N	0

[a] Reduction in blood glucose levels, calculated as a percentage change from the predose control value: 35–95% reduction = 2, 15–35% = 1, less than 15% = 0. [b] *Anal.* Calcd: C, 37.6; N, 14.6. Found: C, 38.2; N, 15.3. [c] Tested in the normal chick; in this series, an excellent correlation exists between activity in the normal chick and the alloxan-hyperglycemic mouse. [d] N: calcd, 20.9; found, 20.2. [e] C: calcd, 48.5; found, 47.9. [f] H: calcd, 3.44; found, 3.95. [g] C: calcd, 50.4; found, 50.9. [h] C: calcd, 56.6; found, 57.2. [i] Lit.[6] mp 159–163°. [j] C: calcd, 62.5; found, 62.0.

analog **38**, in which these substituents are joined to form a six-membered ring, was prepared but failed to show activity.

Synthesis.—The pyrazolylpyridinium salts were prepared by a conventional reaction sequence (Scheme I). Thus, a pyridinecarboxylic acid ester was condensed with a ketone to provide a 1-(pyridyl)-1,3-alkyldione, or ethyl formate was allowed to react with a pyridyl alkyl ketone to provide a 1,3-dione salt. The crude dicarbonyl compound was allowed to react with hydrazine to provide a pyrazolylpyridine, which was then quaternized to the pyrazolylpyridinium salt with an alkyl halide.

Hypoglycemic Activity.—Male mice from Manor Farms weighing 18–25 g were employed. A 2% aqueous solution of alloxan monohydrate (80 mg/kg) was rapidly injected into the tail vein of unfasted animals. Five to seven days later average blood glucose concentration, determined in 0.02-ml samples of tail vein blood using the method of Hoffman[3] as adapted for the Technicon Auto-Analyzer, averaged 480 mg %, four to five times the normal fasting level. The test compounds were dissolved or suspended in 0.5% aqueous sodium carboxymethylcellulose for administration orally. The intended dose, usually 0.25–1.5 mmoles/kg, was contained in 0.2 ml/25 g of body weight. Blood glucose concentrations were determined on samples obtained 4 hr after dosing; results are included in Table I.

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

SCHEME I

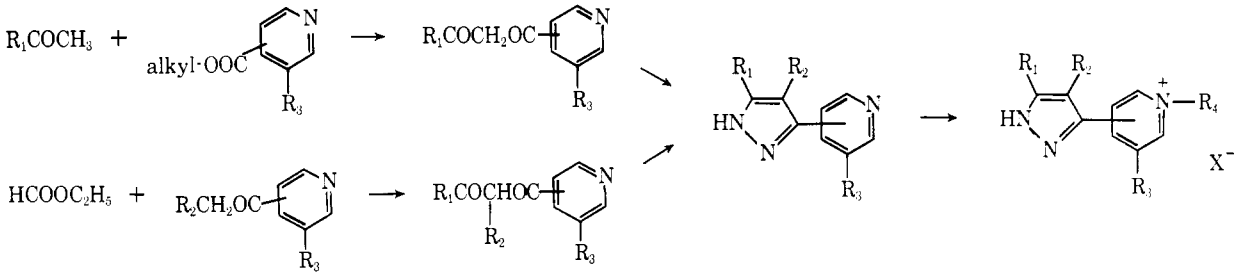
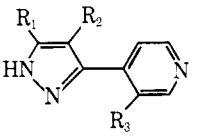


TABLE II

PYRAZOLYLPYRIDINES



Compd	R_1	R_2	R_3	Mp, °C	Recrystn solvent	Formula	Analyses
5	CH_3	H	H	180–183[a]	EtOH–H_2O	C_9H_9N	
39	C_2H_5	H	H	116–117	Me_2CO	$C_{10}H_{11}N_3$	C, H, N
40	i-C_4H_9	H	H	156–157	Me_2CO	$C_{12}H_{15}N_3$	C, H, N
41	n-C_6H_{13}	H	H	111–112	Me_2CO	$C_{14}H_{19}N_3$	C, H, N
42	▷—	H	H	126–127	CH_3CN	$C_{11}H_{11}N_3$	C, H, N
43	CF_3	H	H	184–185[b]	i-PrOH–H_2O	$C_9H_6F_3N_3$	
44	H	H	H	157–158	Me_2CO	$C_8H_7N_3$	C, H, N
45	H	CH_3	H	Oil[c]		$C_9H_9N_3$	
46	$COOC_2H_5$	H	H	209–210	EtOH	$C_{11}H_{11}N_3O_2$	C, H, N
47	CH_3	H	CH_3	136–138	CH_3CN	$C_{10}H_{11}N_3$	C, H, N
48	$-(CH_2)_4-$		H	198–199	Me_2CO	$C_{12}H_{15}N_3$	C, H, N
49	C_6H_5	H	H	207–208	ErOH	$C_{14}H_{11}N_3$	C, H, N
50	$C_6H_5CH_2$	H	H	136–137	C_6H_6	$C_{15}H_{13}N_3$	H, N; C[f]
51	2-[5(3)-Methyl-3(5)-pyrazolyl]pyridine			115–116	CCl_4	$C_9H_9N_3$	C, H, N
52	3-[5(3)-Methyl-3(5)-pyrazolyl]pyridine			137[d]		$C_9H_9N_3$	
53	4-(4-Pyrazolyl)pyridine			198–200[e]		$C_8H_7N_3$	

[a] Lit.[6] mp 177–178°. [b] Lit.[7] mp 190°. [c] Characterized as the methiodide, **21**, Table I. [d] Lit.[8] mp 137–138°. [e] Lit.[9] mp 198–199°. [f] C: calcd, 76.6; found, 75.9.

Experimental Section[4]

4-[5(3)-Ethyl-3(5)-pyrazolyl]pyridine (39).—A mixture of 137 g (1 mole) of methyl isonicotinate, 200 ml of EtCOMe, 1 l. of Et_2O, and 59 g (1.1 moles) of NaOMe was heated under reflux with stirring on a steam bath for 3 hr. The mixture was cooled, acidified with 100 ml of AcOH, and diluted with 500 ml of H_2O. The Et_2O layer was separated, and the H_2O phase was extracted with Et_2O. The Et_2O solution was dried ($MgSO_4$) and concentrated under reduced pressure to provide 137 g of a red liquid.

This liquid was added during 15 min with stirring to 300 ml of 100% hydrazine hydrate; the temperature of the solution rose to 85°. The mixture was stirred at room temperature for 1 hr, diluted with 450 ml of H_2O, and cooled overnight at 5°. The solid which separated was collected and dried. Two recrystallizations (Me_2CO) provided colorless crystals. The properties of **39** are listed in Table II; nmr ($CDCl_3$), τ 8.75 (t, J = 7 cps, 3, CH_2CH_3), 7.32 (q, J = 7 cps, 2, CH_2CH_3), 3.55 (s, 1, 4-pyrazolyl), 2.33 and 1.41 (d, J = 7 cps, 2 each, pyridyl), and −2.99 (broad, 1, NH).

Prepared in a similar manner from the requisite ketone and pyridinecarboxylate[5] were **40–42** and **47–50**; properties are also summarized in Table II. Prepared by literature methods were **5**,[6] **43**,[7] **52**,[8] and **53**.[9]

4-[3(5)-Pyrazolyl]pyridine (44).—A mixture of 74 g (1 mole) of ethyl formate, 61 g (0.5 mole) of 4-acetylpyridine, 54 g (1 mole) of NaOMe, and 900 ml of C_6H_6 was heated under reflux with stirring for 18 hr. The mixture was cooled, and 65 g of a light brown solid was collected by filtration. The solid was added to a stirred solution of 97 g (0.9 mole) of hydrazine dihydrochloride in 650 ml of H_2O. After 2 hr the solution was neutralized with NaOH, and the solid which separated was collected and recrystallized (Me_2CO) to provide colorless crystals. The properties of **44** are included in Table II.

Prepared in a similar manner from 4-propionylpyridine was **45**. Compound **46** was prepared from ethyl sodium isonicotinoylpyruvate[10] by reaction with hydrazine dihydrochloride as described above.

1-Methyl-4-[5(3)-ethyl-3(5)-pyrazolyl]pyridinium Chloride (11).—A mixture of 44 g (0.25 mole) of 4-[5(3)-ethyl-3(5)-pyrazolyl]pyridine and 250 ml of MeCl was heated at 90° in a bomb for 18 hr. The excess MeCl was allowed to evaporate, and the solid residue was recrystallized (MeOH) to provide colorless crystals. The analytical data for **11** are listed in Table I; uv (MeOH), 302 mμ (ε 19,100); nmr (D_2O), τ 8.60 (t, J = 7 cps, 3, CH_2CH_3), 7.18 (q, J = 7 cps, 2, CH_2CH_3), 5.43 (s, 3, NCH_3), 3.20 (s, 1, 4-pyrazolyl), 1.86 and 1.13 (d, J = 7 cps, 2 each, pyridyl).

(4) 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. Nmr spectra were determined on a Varian A-60 spectrometer with TMS or 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt as an internal standard, and uv spectra were recorded with a Cary 11 spectrophotometer by Mr. W. Fulmor and staff.

(5) O. Isler, H. Gutmann, O. Straub, B. Fust, E. Böhni, and A. Studer, *Helv. Chim. Acta*, **38**, 1033 (1955).

(6) L. Fabbrini, *Farmaco, Ed. Sci.*, **9**, 603 (1954).

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

(8) G. A. C. Gough and H. King, *J. Chem. Soc.*, 350 (1933).

(9) Z. Arnold, *Collect. Czech. Chem. Commun.*, **28**, 863 (1963).

(10) S. Fatutta and A. Stener, *Gazz. Chim. Ital.*, **88**, 89 (1958).

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.* ($C_{11}H_{19}ClN_2$) 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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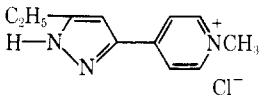
A series of 4-isoxazolylpyridinium salts has been synthesized. These compounds display interesting hypoglycemic activity in mice.

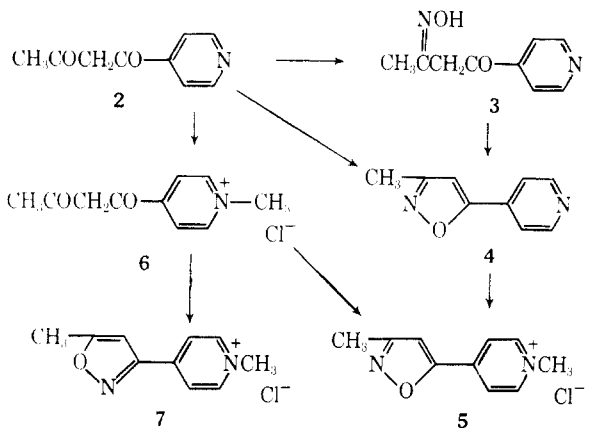
4-[3(5)-Pyrazolyl]pyridinium salts (**1**, for instance) have recently been found to display interesting hypoglycemic activity in normal chicks and alloxan-diabetic mice.[1] As part of the comprehensive development of this lead, we have investigated the replacement of the pyrazole ring with other five-membered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



1

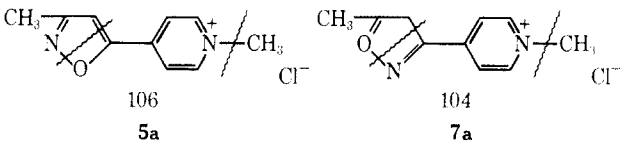
Reaction of 1-(4-pyridyl)-1,3-butanedione (**2**) with hydroxylamine hydrochloride at room temperature provided the monoxime **3**, which was readily converted to the isoxazolylpyridine **4** by heating with dilute base (Scheme I). Compound **4**, which was also

SCHEME I



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**.

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. Bhekens, and C. R. Boshart, *Diabetes*, in press.