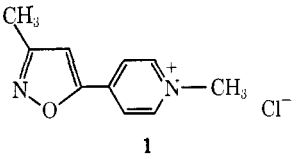

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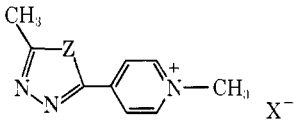
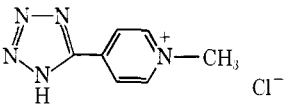
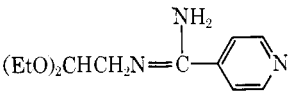


2a, Z = NH; X = Cl
b, Z = O; X = I
c, Z = S; X = I



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**.



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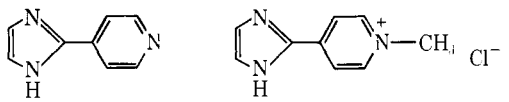

5 6

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.

(8) Y. Postovskii and N. N. Vereshchagina, *J. Gen. Chem. USSR*, **29**, 2105 (1959).

(9) F. H. McMillan, F. Leonard, R. I. Meltzer, and J. A. King, *J. Am. Pharm. Assoc.*, **42**, 457 (1953).

(10) D. D. Libman and R. Slack, *J. Chem. Soc.*, 2253 (1956).

(11) F. C. Schaefer and G. A. Peters, *J. Org. Chem.*, **26**, 412 (1961).

(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]

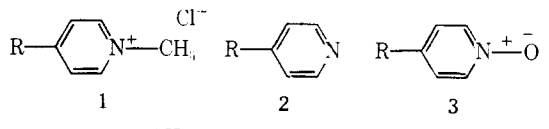
(1) V. J. Bauer, H. P. Dalalian, W. J. Fanshawe, S. R. Safir, E. C. Tocus, and C. R. Boshart, *J. Med. Chem.*, **11**, 981 (1968).

(2) V. J. Bauer, W. J. Fanshawe, H. P. Dalalian, and S. R. Safir, *ibid.*, **11**, 984 (1968); D. A. Blickens and S. J. Riggi, *Toxicol. Appl. Pharmacol.*, **14**, 393 (1969).

(3) G. E. Wiegand, V. J. Bauer, S. R. Safir, D. A. Blickens, and S. J. Riggi, *J. Med. Chem.*, **12**, 891 (1969).

oxazolyl- (**1d**),[4] and 1,2,4-oxadiazolylpyridinium (**1e**)[5] compounds have been found to display hypoglycemic activity in laboratory animals. In each case, the azolylpyridine base precursor (**2**) of the quaternary salt was found to be devoid of this activity. It was therefore concluded that a positive charge on the pyridine nitrogen is one of the structural requirements for activity in this series.

The possibility that the corresponding 4-azolylpyridine 1-oxides, in which at least a partial positive charge must reside upon the pyridyl nitrogen, might also exhibit hypoglycemic activity was investigated. The 4-azolylpyridines **2** were converted to the desired N-oxides **3** with peracetic acid under conventional conditions.[6] The structures of the products, inferred from elemental compositions, were confirmed by ir spectroscopy. Reaction of the N-oxide **3a** with methyl *p*-



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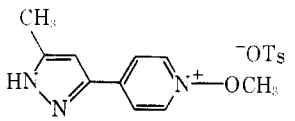

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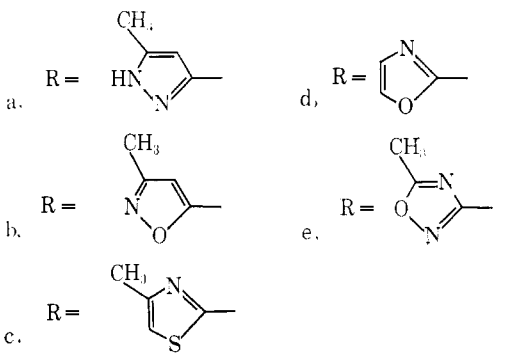

toluenesulfonate gave the 1-methoxypyridinium salt **4**, a compound which also satisfies the postulated electronic requirement for activity.

Compounds **3** and **4** were tested[7] for hypoglycemic activity in male mice (Carworth Farms, 18–25 g). Test compounds (0.5–3.0 mmoles/kg) were administered orally as saline solutions or carboxymethylcellulose suspensions; controls received an equal volume of vehicle. Blood glucose concentrations determined by the method of Hoffman[8] as adapted for the Technicon AutoAnalyzer were not different from controls.

Experimental Section[9]

4-Azolylpyridine 1-Oxides (3).—To a stirred solution of 0.1 mole of 4-azolylpyridine (**2**)[1–5] in 160 ml of AcOH was added 16 ml of 30% H_2O_2. The solution was heated on a steam bath for 3 hr, diluted with 160 ml of H_2O, and concentrated under reduced pressure to a yellow solid. Recrystallization provided pure compounds; details are included in Table I.

TABLE I
4-AZOLYLPYRIDINE 1-OXIDES

3	Mp, °C	Recryst solvent	Yield, %	Formula[a]	ir (KBr), μ (N→O)[b]
a	259–261	*i*-PrOH	24	$C_9H_9N_3O$	8.12
b	153–154	*i*-PrOH	40	$C_9H_8N_2O_2$	7.92
c	125–127	*i*-PrOH	34	$C_9H_8N_2OS$	8.05
d	185–187[c]	MeCN	42	$C_8H_6N_2O_2$	7.90
e	158–160	EtOH	46	$C_8H_7N_3O_2$	7.98

[a] N-Oxide absorption has been observed in the region 7.67–8.33 μ (L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1958, p 308). [b] Mp 186° was reported by M. Brufani, G. Giacomello, and M. L. Stein, *Gazz. Chim. Ital.*, **91**, 767 (1961). [c] All compounds were analyzed for C, H, N.

1-Methoxy-4-[5(3)-methyl-3(5)-pyrazolyl]pyridinium *p*-Toluenesulfonate (4).—A solution of 1.0 g (6.0 mmoles) of **3a**, 1.1 g (6.0 mmoles) of MeOTs, and 30 ml of EtOH was heated under reflux for 2 hr. Hexane was added to the solution, and 1.1 g of a solid separated and was collected. Three recrystallizations (CH_3CN) gave 0.4 g (19%) of colorless needles, mp 174–175°. *Anal.* ($C_{17}H_{19}N_3O_4S$) C, H, S; N: calcd, 11.63; found, 12.36.

5,5-Diarylpenta-2,4-dienoic Acid Amides as Potential Antimalarial Agents. II[1]

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A number of aryl unsaturated acid amides have been prepared for antimalarial testing[2–4] based on the reported activity of N-isopropyl-5-(*p*-chlorophenyl)-2,4-pentadienamide against *Plasmodium gallinaceum* in the chick,[5] and other criteria.[2]

Testing results have now been obtained on a number of the compounds presented in Table I. These data appear to confirm the conclusion of Werbel that the reported *P. gallinaceum* activity may be spurious, and at least cannot be extrapolated to the *Plasmodium berghei* case.[4]

The present series of compounds expands the list of bis(*p*-chlorophenyl)pentadienoic acid amides as well as introducing several new structural types. None of the compounds tested for antimalarial activity[6] (**1–5**, **7**, **9**, **16**, **19**, **20**, **25**), including the α-methyl derivative **7** of

(1) This work was supported by the U. S. Army Medical Research and Development Command under Contract No. DA-49-193-MD-2750. This is Contribution No. 578 from the Army Research Program on Malaria.

(2) W. T. Colwell, J. H. Lange, and D. W. Henry, *J. Med. Chem.*, **11**, 749 (1968).

(3) L. M. Werbel, N. Headen, and E. F. Elslager, *ibid.*, **10**, 306 (1967).

(4) L. M. Werbel, N. Headen, and E. F. Elslager, *ibid.*, **11**, 1073 (1968). These authors question the *P. gallinaceum* assay results.

(5) G. R. Coatney, W. C. Cooper, N. B. Eddy, and J. Greenberg, "Survey of Antimalarial Agents," Public Health Service Publication No. 193, U. S. Government Printing Office, Washington, D. C., 1953, p 139.

(6) All *P. berghei* bioassays reported herein were performed by Dr. Leo Rane of the University of Miami by a published procedure (C. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967)). Testing results were supplied through the courtesy of Dr. David F. Jacobus of the Walter Reed Army Institute of Research.

(4) G. E. Wiegand, V. J. Bauer, S. R. Safir, D. A. Blickens, and S. J. Riggi, *J. Med. Chem.*, **12**, 943 (1969).

(5) W. J. Fanshawe, V. J. Bauer, S. R. Safir, D. A. Blickens, and S. J. Riggi, *ibid.*, **12**, 381 (1969).

(6) E. Ochiai, *J. Org. Chem.*, **18**, 534 (1953).

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

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

(9) 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. Spectral data were supplied by Mr. W. Fulmor and staff.