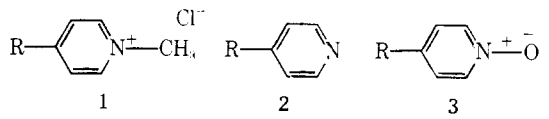
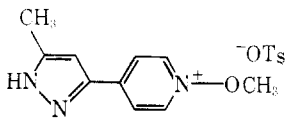
oxazolyl- (**1d**),[4] and 1,2,4-oxadiazolylpyridinium (**1e**)[5] compounds have been found to display hypoglycemic activity in laboratory animals. In each case, the azolypyridine base precursor (**2**) of the quaternary salt was found to be devoid of this activity. It was therefore concluded that a 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*-



1 2 3



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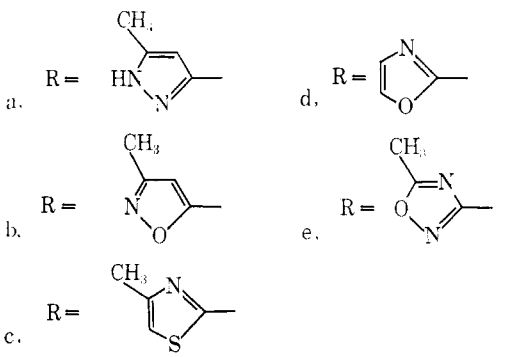

toluenesulfonate gave the 1-methoxypyridinium salt **4**, a compound which also satisfies the postulated electronic requirement for activity.

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**, 366 (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.

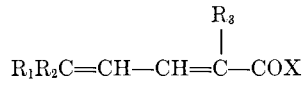
(6) All *P. berghei* bioassays reported herein were performed by Dr. Leo Rane of the University of Miami by a published procedure (C. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967)). Testing results were supplied through the courtesy of Dr. David P. Jacobus of the Walter Reed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

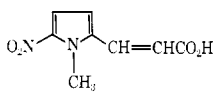
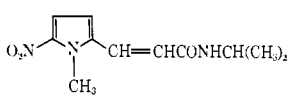
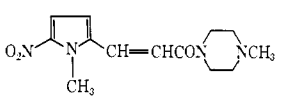
(7) Testing data were supplied by Drs. D. A. Blickens and S. J. Riggi of the Metabolic Chemotherapy Department of these laboratories.

(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.

TABLE I: PENDADIENOIC AND -DIYNOIC ACIDS AND AMIDES AND RELATED COMPOUNDS



No.	R_1	R_2	R_3	X	Yield, %	Mp, °C	Analyses[c]
1	*p*-ClC_6H_4	*p*-ClC_6H_4	H	$N(n\text{-}Pr)_2$	52	Oil	C, H_1 N
2				NHC_6H_5	36	190–195	C, H_1 N
3					43	145–150	C, H, N
4				$N(n\text{-}C_6H_{13})_2$	34	65–68	C, H, N
5					37	164–170	C, H, N
6			CH_3	OH	32	183–191	C, H
7			CH_3	NEt_2	13	Oil	C_1 H, N
8	2-Naphthyl	H	H	OH	14	165–195	C, H
9				NEt_2	38	112–128	C, H, N
10	2-Furyl	H	H	OH	9	160–172	*a*
11				OCH_3	21	Oil	C, H[a]
12				NEt_2	41	Oil	C, H, N
13				NH_2	25	174–180	C, H, N
14	5-Nitro-2-furyl	H	H	OH	14		*b*
15				NH_2	10	205–208	C, H, N
16				NEt_2	40	175–179	C_1 H, N
17	5-Nitro-2-thienyl	H	H	OH	91	260 dec	
18				OCH_3	61	172–174	C, H, N
19				NEt_2	56	152.5–155	C_1 H, N
20				$NH(i\text{-}Pr)$	66	185–189	C, H, N
21	1-Methyl-5-nitropyrrol-2	H	H	OCH_3	40 (5)	186–190	C, H, N
22					51	223–224	C, H, N
23					72	159–163	C, H, N
24					38	117–127	C, H, N
25	$C_6H_5C{\equiv}CC{\equiv}CCONEt_2$				28	Oil	C, H
26	*p*-$FC_6H_4C{\equiv}CC{\equiv}CCO_2H$				19	157 dec	C, H
27	*p*-$FC_6H_4C{\equiv}CC{\equiv}CCONEt_2$				18	Oil	C, H, N

[a] R. J. Rallings and J. C. Smith, *J. Chem. Soc.*, 618 (1953). These authors report mp 22–23° for **11**. [b] Kyorin Pharmaceutical Co., Ltd., British Patent 982,730 (1965); *Chem. Abstr.*, **62,** P14633*a* (1965). [c] Values within ±0.4% of theoretical were obtained for all analyses indicated.

the most active member of the previous series, extended the survival time of *P. berghei* infected mice in the assay beyond 0.5 day at the 640-mg/kg level. No toxicity was observed at the 640-mg/kg level.

The preparation of the bis(*p*-chlorophenyl) series (**1**–**5**) has been given previously.[2] The α-methyl compound **6** was prepared *via* the addition of carbethoxyethylidenetriphenylphosphorane to 3,3-bis(*p*-chlorophenyl)acrolein followed by hydrolysis. The acrolein was derived from lithium acetylide addition to the benzophenone followed by acid-catalyzed rearrangement of the resulting carbinol.[2]

Compound **8** was prepared as a mixture of geometrical isomers from the Reformatsky reaction of β-naphthaldehyde with γ-bromocrotonate according to the general procedure of Miller and Nord.[7]

The nitrothiophene ester **18** was prepared by treatment of 3-(5-nitro-2-thienyl)acrolein[8] with carbomethoxymethylenetriphenylphosphorane. Acid **17** was obtained from ester **18** by ester interchange in H_2SO_4–HOAc solution. The corresponding N-methylpyrrole ester **21**, prepared both by addition of the ylide derived from methyl γ-bromocrotonate to 1-methyl-5-nitropyrrole-2-aldehyde[9] (5% yield), and by treatment of 1-methyl-5-nitropyrrole-2-acrolein[9] with carbomethoxymethylenetriphenylphosphorane (40% yield), could not be hydrolyzed.

The N-methylnitropyrrole acrylic acid **22** was formed by a Doebner reaction on 1-methyl-5-nitropyrrole-2-aldehyde.

The diacetylenic acids were prepared by the Cu(I)-catalyzed coupling of 3-bromopropiolic acid with phenylacetylene and *p*-fluorophenylacetylene.[7,10]

All of the dienoic acid amides were obtained by the mixed anhydride method, and the diynoic acid amides by *in situ* diethylamine treatment of the acid chlorides which had been generated by the sodium salt–oxalyl chloride method.

(7) R. E. Miller and F. F. Nord, *J. Org. Chem.*, **16**, 1720 (1951).
(8) G. Carrara, R. Ettore, F. Fava, G. Rolland, E. Testa, and A. Vecchi, *J. Am. Chem. Soc.*, **76**, 4391 (1954).
(9) P. Fournari, *Bull. Soc. Chim. France*, 488 (1963).
(10) W. Chodkiewicz, *Ann. Chim.* (Paris), **2**, 819 (1957).