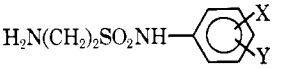
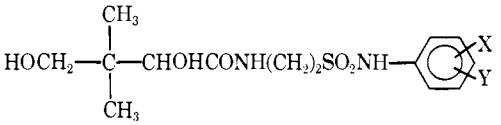
TABLE II
2-AMINOETHANESULFONANILIDES (V)



No.	X, Y	Mp, °C	Yield purified, %	Purifn solvent	Formula	Analyses[19]
Vb	4-Cl	160–162[a]	66	...	$C_8H_{11}ClN_2O_2S$	*b*
Vc	3,4-Cl_2	157–159	64	...	$C_8H_{10}Cl_2N_2O_2S$	*b*
Vd	3-CF_3	154–156	3	EtOAc	$C_9H_{11}F_3N_2O_2S$	C, H, N
Ve	4-CF_3	163–167	76	...	$C_9H_{11}F_3N_2O_2S$	C, H, N
Vf	3,5-$(CF_3)_2$	262–263 dec	44	*i*-PrOH	$C_{10}H_{10}F_6N_2O_2S \cdot HCl$	C, H, N, Cl
Vg	4-SCH_3	162–165	75	H_2O	$C_9H_{14}N_2O_2S_2$	*b*
Vh	4-$OCH_2C_6H_5$	211–214	94	H_2O	$C_{15}H_{18}N_2O_3S \cdot HCl$[c]	C, H, N

[a] Lit.[6] mp 160.5–161.5°. [b] These intermediates were not analyzed. They were homogeneous by tlc and were used directly in the next step. [c] Free base, mp 178–181°.

TABLE III
D-(+)-2,4-DIHYDROXY-3,3-DIMETHYL-N-[2-(PHENYLSULFAMOYL)ETHYL]BUTYRAMIDES (VI)



No.	X, Y	Mp, °C	Yield purified, %	Purifn solvent	$[\alpha]^{25}D$,[a] deg	Formula[c]
VIb	4-Cl	103–104[b]	59	C_6H_6	+40	$C_{14}H_{21}ClN_2O_5S$
VIc	3,4-Cl_2	141–143	66	$CHCl_3$	+38	$C_{14}H_{20}Cl_2N_2O_5S$
VIe	4-CF_3	144–146	45	H_2O	+36	$C_{15}H_{21}F_3N_2O_5S$
VIg	4-SCH_3	112–114	67	$ClCH_2CH_2Cl$	+40	$C_{15}H_{24}N_2O_5S_2$
VIh	4-$OCH_2C_6H_5$	142–144	28	$ClCH_2CH_2Cl$	+33	$C_{21}H_{28}N_2O_6S$

[a] *c* 1, 95% EtOH. [b] Lit.[6] mp 101–103° from C_6H_6. [c] All compounds were analyzed for C, H, N.

Escherichia coli (Vogel), *Streptococcus pyogenes* (C203), *Proteus mirabilis* (MGH-1), *Salmonella typhimurium* (V-31), and *Shigella sonnei* (C-10). Among them, VIh suppressed *T. vaginalis in vitro* at a concentration of 25 μg/ml and completely inhibited the growth of *S. pyogenes* (C203) at 1.25 μg/ml.

Experimental Section[18,19]

1,3-Dioxo-2-isoindolineethanesulfonic acid monopotassium salt (II) was prepared by the method of Miller and Roblin[6,11] in 83% yield.

1,3-Dioxo-2-isoindolineethanesulfonyl chloride (III) was obtained from II by the method of Miller and Roblin[6,11] in 80% yield, mp 158–162°.

1,3-Dioxo-2-isoindolineethanesulfonanilides (IV, Table I).—To a stirred solution of 0.1 mole of the substituted aniline in 75 ml of pyridine, cooled with an ice bath, was added slowly 30.1 g (0.11 mole) of 1,3-dioxo-2-isoindolineethanesulfonyl chloride (III). After the reaction mixture was stirred for 1 hr with cooling, the ice bath was removed and stirring was continued for 1.25 hr. The reaction mixture was poured into 500 ml of H_2O with vigorous stirring, and the crude product was isolated by filtration. Recrystallization from glacial or dilute AcOH gave the product.

2-Aminoethanesulfonanilides (V, Table II).—A mixture of 0.02 mole of the appropriate 1,3-dioxo-2-isoindolineethanesulfonanilide, 1.2 g (0.02 mole) of 85% hydrazine hydrate, and 100 ml of EtOH was heated under reflux for 3 hr. The reaction solution was homogeneous when refluxing began, but after 15 min a precipitate appeared. The mixture was concentrated to dryness and the residue was suspended in 200 ml of H_2O and made acidic to congo red with 4 *N* HCl. This slurry was heated on a steam bath for 10 min, cooled in an ice bath, and filtered. The filtrate was neutralized with concentrated NH_4OH to give the product. The compounds were recrystallized from the indicated solvents when necessary.

(18) Melting points (corrected) were taken in open capillary tubes in a Thomas–Hoover capillary melting point apparatus.

(19) Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values.

D-(+)-2,4-Dihydroxy-3,3-dimethyl-N-[2-(phenylsulfamoyl)-ethyl]butyramides (VI, Table III).—A mixture of 0.015 mole of the requisite 2-aminoethanesulfonanilide (V) and 3.9 g (0.03 mole) of D-(−)-pantolactone was heated in a melt at 100–115° for 2 hr. The melt was cooled and crystallized from the solvents indicated.

Acknowledgments.—The authors are indebted to Dr. Leo Rane of the University of Miami and to Dr. Paul E. Thompson and Dr. M. W. Fisher of Parke, Davis and Company for the biological testing. We also wish to thank Mr. C. E. Childs and associates for the microanalyses, and Dr. J. M. Vandenbelt and coworkers for determination of the spectral data reported herein.

Derivatives of 5-Phenyl-2,4-pentadienoic Acid as Potential Antimalarial Agents[1]

LESLIE M. WERBEL, NANCY HEADEN, AND EDWARD F. ELSLAGER

Research Laboratories, Parke, Davis and Company, Ann Arbor, Michigan 48106

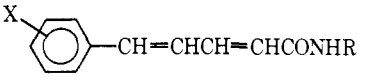
Received May 3, 1968

The reported effectiveness of 5-(*p*-chlorophenyl)-*N*-isopropyl-2,4-pentadienamide (Ia) against *Plasmodium gallinaceum* in the chick[2] prompted the synthesis of

(1) This investigation was supported by the U. S. Army Medical Research and Development Command under Contract DA-49-193-MD-2754. This is Communication No. 382 to the Army Research Program on Malaria.

(2) G. R. Coatney, W. C. Cooper, N. B. Eddy, and J. Greenberg, "Survey of Antimalarial Agents," Public Health Service Publication No. 193, Washington, D. C., 1953, pp 98, 139, 262, 276.

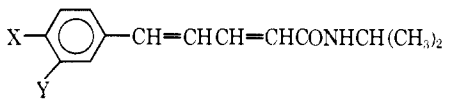
TABLE I
5-PHENYL-2,4-PENTADIENAMIDES



No.	X	R	Mp, °C[a]	Yield (purified), %	Reaction cond[a]	Purifien solvent	Formula	Analyses[b]
1	H	$NHCSNH_2$	220–221	h	A	EtOH–H_2O	$C_{12}H_{12}N_2OS$	C, H, N
2	H	$N(CH_3)OCH_3$	68–69	25	A	EtOH–H_2O	$C_{13}H_{15}NO_2$	C, H, N
3	H	$CH_2CH_2N(C_2H_5)_2$	164–165	87	B	*i*-PrOH	$C_{17}H_{24}N_2O \cdot C_7H_6O_3$[k]	C, H, N
4	H	$N(CH_2CO_2C_2H_5)COCH{=}CHCH{=}CHC_6H_5$	198–199	8[d]	A	EtOH–H_2O	$C_{25}H_{26}N_2O_5$	H, N; C[e]
5	H	$N[CH_2CH_2N(C_2H_5)_2]COCH{=}CHCH{=}CHC_6H_5$	190–192	6[d]	A	MeCN	$C_{28}H_{33}N_3O_2$	C, H, N
6	3,4-Cl_2	$NHCOCH_3$	260–262	26	C	DMF–H_2O	$C_{20}H_{22}Cl_2N_2O_2$	C, H, N
7	3,4-Cl_2	$NHCO_2C_2H_5$	190–192	16	D	EtOH–H_2O	$C_{24}H_{14}Cl_2N_2O_3 \cdot 0.5H_2O$	C, H, N; Cl[f]
8	3,4-Cl_2	$NHSO_2C_6H_4$-*p*-CH_3	209–210	16	E	EtOH	$C_{26}H_{16}Cl_2N_2O_2S$	C, H, N
9	3,4-Cl_2	$N(CH_2CH_2OH)COCH{=}CHCH{=}CHC_6H_3$-3,4-$Cl_2$	196–198	21[d]	B	...	$C_{21}H_{20}Cl_4N_2O_3$	H, N; C[e]
10	3,4-Cl_2	$(CH_3)_2NHCOCH{=}CHCH{=}CHC_6H_3$-3,4-$Cl_2$	211–213	15	C	EtOH–H_2O	$C_{20}H_{20}Cl_4N_2O_2$	C, H, N

[a] A, pyridine at room temperature for 1–3 days; B, $CHCl_3$ at room temperature for 1–2 days; C, C_6H_6 at room temperature for 1–3 days; D, C_6H_6 under reflux for 3 hr; E, THF under reflux for 16 hr. [b] $C_7H_6O_4$ = 2,4-dihydroxybenzoic acid. [c] C: calcd, 71.75; found, 72.16. [d] Absence of an exchangeable proton determined *via* infrared spectra in $CHCl_3$–D_2O allows assignment as the N,N′ rather than the N,N derivative. [e] C: calcd, 54.77; found, 54.30. [f] Absence of carbonyl absorption above 1660 cm^{-1} and the presence of only one labile proton (D_2 exchange) allow assignment of the N,N′ structure. [g] Melting points (corrected) were taken in open capillary tubes in a Thomas–Hoover capillary melting point apparatus. [h] Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. [i] Cl: calcd, 20.97; found, 21.08.

various 5-phenyl-2,4-pentadienamides for antimalarial evaluation.[3] Surprisingly, none of them, including Ia, was active against normal strains of *Plasmodium berghei* in mice.[3] Subsequently, the pentadienamides Ia–e have been evaluated against *P. gallinaceum* in the chick.[4] Using 9–12-day-old chicks and a standard



Ia, X = Cl; Y = H
b, X = Cl; Y = Cl
c, X = CH_3; Y = H
d, X = Br; Y = H
e, X = C_6H_5; Y = H

inoculum of *P. gallinaceum*, a consistently uniform disease, fatal to 100% of the untreated control birds within 72–96 hr, was produced. In this test, as in the mouse test,[5,6] the antimalarial activity of candidate substances was assessed by comparing the maximum survival times of treated and untreated animals. None of the pentadienamides (Ia–e) exhibited activity against *P. gallinaceum* when administered in a single subcutaneous dose of 240 mg/kg. The apparent discrepancy between earlier reports[3] and results of the current investigations remains unexplained.

Before it was confirmed that these materials lacked appreciable effects against *P. berghei* and *P. gallinaceum*, it was deemed of interest to vary the nitrogen functionality in this system. The derivatives described in Table I were prepared by condensation of a 5-phenyl-2,4-pentadienoic acid chloride with the desired amine or hydrazine derivative under known conditions. None was active against normal strains of *P. berghei* when administered to mice in a single subcutaneous dose of 640 mg/kg.[5,6]

(3) L. M. Werbel, N. Headen, and E. F. Elslager, *J. Med. Chem.*, **10**, 366 (1967).

(4) Antimalarial studies utilizing *P. gallinaceum* in chicks were carried out under the auspices of the Walter Reed Army Institute of Research, and test results were supplied through the courtesy of Dr. David P. Jacobus.

(5) Antimalarial screening against *P. berghei* was carried out by Dr. Leo Rane of the University of Miami, and test results were supplied through the courtesy of Dr. David P. Jacobus of the Walter Reed Army Institute of Research.

(6) For a description of the test method see T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).

Carcinogenic Activity of Analogs of *p*-Dimethylaminoazobenzene. VI. Activity of the Benzimidazole and Benzthiazole Analogs[1]

ELLIS V. BROWN AND C. J. SANCHORAWALA

Department of Chemistry, University of Kentucky, Lexington, Kentucky 40506

Received March 11, 1968

In previous reports[2,3] we have shown that the unsubstituted ring of *p*-dimethylaminoazobenzene (DAB) can be replaced by pyridine and pyridine N-oxide and thus we have obtained a number of compounds with varying degrees of carcinogenic activity. The interesting results observed in the pyridine series led us to investigate the isomeric *p*-dimethylaminophenylazoquinolines and their corresponding N-oxides.[4] In this new series, we have the possibility of attaching the azo linkage to either the pyridine or benzene rings of the quinoline nucleus and thereby preparing compounds which can be considered pyrido analogs of DAB or benzo analogs of the previously prepared pyridine azo compounds. As might have been anticipated from the results obtained in the pyridine series, the 4-substituted isomer was the most active of the compounds substituted on the pyridine side of the quinoline nucleus. However, the high activity of the 5- and 6-substituted compounds was quite surprising and in contrast to the lack of activity in the 7- and 8-substituted compounds.

In this paper we wish to report the preparation and testing for carcinogenic activity of a number of *p*-dimethylaminophenylazobenzimidazoles and -benzthiazoles. N,N-Dimethyl-*p*-(4-benzimidazolylazo)aniline and N,N-dimethyl-*p*-(5-benzimidazolylazo)aniline have been prepared by Montanari.[5] So far we have been

(1) Presented at the 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1968.

(2) E. V. Brown, *et al.*, *Cancer Res.*, **14**, 22 (1954).

(3) E. V. Brown, *et al.*, *ibid.*, **14**, 715 (1954).

(4) E. V. Brown, R. M. Novack, and A. A. Hamdan, *J. Natl. Cancer Inst.*, **26**, 1461 (1961).

(5) F. Montanari, *Boll. Sci. Fac. Chim. Ind. Bologna*, **11**, 4066 (1953).