Potential Antimalarial Agents. 2-{[(Dialkylamino)alkyl]amino}-3-(2-pyridyl)quinoxalines[1]

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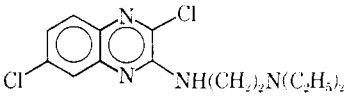
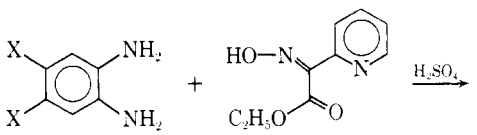
Numerous aminoquinoxaline derivatives have been synthesized and evaluated as potential antimalarial agents, but few have exhibited significant activity.[2,3] Hence, the report by Haworth and Robinson[3] that



I

2,6-dichloro-3{[2-(diethylamino)ethyl]amino}quinoxaline (I) shows greater activity than quinacrine against *Plasmodium gallinaceum* in chicks is noteworthy. Therefore, an authentic sample of I and several representative 2-{[(dialkylamino)alkyl]amino}-3-(2-pyridyl)quinoxaline derivatives (V) were prepared for evaluation against *Plasmodium berghei* in mice to further assess the potential usefulness of this class of compounds in malaria chemotherapy.



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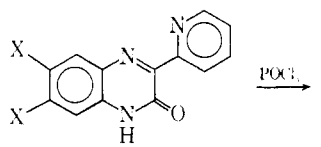

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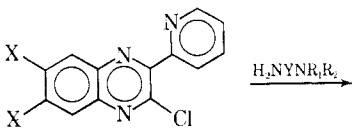
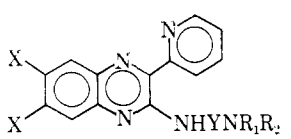


IV



V

The condensation of 2,3,6-trichloroquinoxaline with N,N-diethylethylenediamine by the method of Haworth and Robinson[3] afforded a product apparently identical with I. The melting points of the base (81–82°, lit.[3] 83–84°) and the dihydrochloride salt (256–257° dec, lit.[3] 246° dec) were close to those previously recorded, and both the base and the salt analyzed correctly (C, H, N). The nmr spectrum of the base was in accord with the structure assigned.

The 2-{[(dialkylamino)alkyl]amino}-3-(2-pyridyl)-quinoxaline derivatives (V) (Table I) were prepared by the condensation of the appropriate 2-chloro-3-(2-pyridyl)quinoxaline (IV) (Table I) with the requisite dialkylaminoalkylamine at 5° in an ether–benzene mixture. The chloroquinoxalines (IV) were obtained by allowing a substituted *o*-phenylenediamine to react with ethyl 2-pyridylglyoxylate oxime (II) in dilute sulfuric acid according to Pfeiffer and Case,[4] followed by chlorination of the resulting 3-(2-pyridyl)-2-quinoxalinols with phosphorus oxychloride. The condensation of 4-chloro-*o*-phenylenediamine with II might be expected to give a mixture of 6- and 7-chloro-3-(2-pyridyl)-2-quinoxalinol, which could ultimately lead to a mixture of isomers in the final products V. Nevertheless, the purified amines **3–7** were homogeneous by thin layer chromatography, although small amounts of a second component were detected in the crude products. The orientation of the chlorine atom in **3–7** has not been established.

2,6-Dichloro-3-{[2-(diethylamino)ethyl]amino}quinoxaline (I) and the 2-{[(dialkylamino)alkyl]amino}-3-(2-pyridyl)quinoxalines (V) (**3–7, 9, 10, 13,** and **14,** Table I) were administered subcutaneously in a single dose to mice infected with *P. berghei*.[5,6] None of the compounds, including I, caused a significant prolongation of the mean survival time of mice even at the highest dose level employed, namely 640 mg/kg. Studies are planned to confirm the reported activity of I against *P. gallinaceum* in chicks, and a satisfactory explanation is being sought for the apparent discrepancy between earlier reports[3] and results of the current investigation utilizing *P. berghei*. It should be noted that a similar discrepancy was observed among the 5-phenyl-2,4-pentadienamides.[7]

Representative compounds were also tested against other parasites *in vitro* and in mice including *Trichomonas vaginalis*, *Syphacia obvelata*, *Nematospiroides dubius*, *Hymenolepis nana*, and *Schistosoma mansoni*, and against the bacteria *Staphylococcus aureus* (UC-76), *Pseudomonas aeruginosa* (No 28), *Mycobacterium tuberculosis* ($H_{37}Rv$), *Escherichia coli* (Vogel), *Proteus mirabilis* (MGH-1), *Salmonella typhimurium* (V-31), and *Shigella sonnei* (C-10) *in vitro*. Among them, **5** suppressed *T. vaginalis in vitro* at a concentration of 25 μg/ml and completely inhibited the growth of *M. tuberculosis* ($H_{37}Rv$) at 10 μg/ml.

Experimental Section[8,9]

6,7-Substituted 3-(2-Pyridyl)-2-quinoxalinols (II) (Table I). A solution of 0.1 mole of ethyl 2-pyridylglyoxylate oxime[10] and

(1) This investigation was supported by U. S. Army Medical Research and Development Command Contract DA-49-193-MD-2734. This is Contribution No. 323 to the Army Research Program on Malaria.

(2) F. Y. Wiselogle, "A Survey of Antimalarial Drugs, 1941–1945," Vol. II, J. W. Edwards, Ann Arbor, Mich., 1946, pp 1463–1470.

(3) R. D. Haworth and S. Robinson, *J. Chem. Soc.*, 777 (1948).

(4) F. R. Pfeiffer and F. H. Case, *J. Org. Chem.*, **31**, 3384 (1966).

(5) The antimalarial screening 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).

(7) L. M. Werbel, N. Headen, and E. F. Elslager, *ibid.*, **10**, 366 (1967).

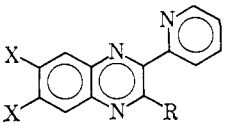
(8) Melting points (corrected) were taken in open capillary tubes in a Thomas-Hoover capillary melting point apparatus.

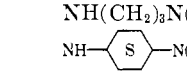
(9) Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values.

(10) Purchased from the Aldrich Chemical Co., Milwaukee, Wis.

TABLE I

2,6,7-SUBSTITUTED 3-(2-PYRIDYL)QUINOXALINES



No.	X, X	R	Mp, °C	Yield purified, %	Purifcn solvent	Formula	Analyses[a]
1	H, Cl	OH	121–124	70	EtOH–H_2O	$C_{13}H_8ClN_3O$	H, N; C[a]
2	H, Cl	Cl	106–109	65	EtOH–H_2O	$C_{13}H_7Cl_2N_3$	C, H, N
3	H, Cl	$NH(CH_2)_3N(CH_3)_2$	222–225 dec	48	*i*-PrOH	$C_{18}H_{20}ClN_5\cdot 2HCl$	C, H, N
4	H, Cl	$NH(CH_2)_2N(CH_2)_4$	244–246	53	MeOH	$C_{19}H_{20}ClN_5\cdot 2HCl$	C, H, N
5	H, Cl	$NH(CH_2)_2N(C_2H_5)_2$	208–210	88	MeOH–Et_2O	$C_{19}H_{22}ClN_5\cdot 2HCl$	C, H, N
6	H, Cl	$NH(CH_2)_3N(CH_2)_4$	110–112 dec	19	*i*-PrOH–Et_2O	$C_{20}H_{22}ClN_5\cdot 2HCl$	C, H, N
7	H, Cl		151–153	27	*i*-PrOH–Et_2O	$C_{21}H_{24}ClN_5\cdot 2HCl\cdot 0.9H_2O$	C, H, N, Cl, H_2O
8	Cl, Cl	OH	217–219	50	MeOH	$C_{13}H_7Cl_2N_3O$[b]	C, H, N
9	Cl, Cl	$NH(CH_2)_2N(C_2H_5)_2$	258–259 dec	84	MeOH	$C_{19}H_{21}Cl_2N_5\cdot HCl$	C, H, N
10	Cl, Cl	$NH(CH_2)_3N(CH_2)_4$	233–235 dec	91	MeOH–Et_2O	$C_{20}H_{21}Cl_2N_5\cdot 2HCl$	C, H, N
11	CH_3, CH_3	OH	219–222	35	MeOH	$C_{15}H_{13}N_3O$	H, N; C[c]
12	CH_3, CH_3	Cl	135–137	55	EtOH–H_2O	$C_{15}H_{12}ClN_3$	C, H, N
13	CH_3, CH_3	$NH(CH_2)_3N(CH_3)_2$	248–250	64	EtOH	$C_{20}H_{25}N_5\cdot 2HCl\cdot 1.67H_2O$	C, H, N, H_2O
14	CH_3, CH_3	$NH(CH_2)_2N(C_2H_5)_2$	236–238	63	*i*-PrOH	$C_{21}H_{27}N_5\cdot 2HCl\cdot 0.33H_2O$	C, H, N, H_2O

[a] C: calcd, 60.57; found, 59.72. [b] The chloro compound from **8** was not obtained analytically pure. The crude material, mp 126–130°, was used directly for the next step. [c] C: calcd, 71.69; found, 71.19.

0.1 mole of a substituted *o*-phenylenediamine in 350 ml of 35% H_2SO_4 was stirred at 75° for 18 hr. The solid which formed on heating was removed by filtration and dissolved in H_2O. The solution was adjusted to pH 8 with NH_4OH and the solid which formed was removed by filtration, washed thoroughly with H_2O, and recrystallized to yield the product.

6,7-Substituted 2-Chloro-3-(2-pyridyl)quinoxalines (IV) (Table I).—A slurry of 0.4 mole of a 6,7-substituted 3-(2-pyridyl)-2-quinoxalinol in 200 ml of $POCl_3$ was heated under reflux for 7 hr. The resulting solution was cooled, poured slowly into 4 l. of iced H_2O, and made basic with NH_4OH. The product was removed by filtration and recrystallized.

2-{[(Dialkylamino)alkyl]amino}-3-(2-pyridyl)quinoxalines (V) (Table I).—A solution of 0.01 mole of a 6,7-substituted 2-chloro-3-(2-pyridyl)quinoxaline and 0.02 mole of diamine in 50 ml of Et_2O and 15 ml of C_6H_6 was held at 5° for 24–48 hr. The solid amine hydrochloride which formed was removed by filtration. The ether solution was washed successively with H_2O, dilute NaOH, and H_2O, and then dried over Na_2SO_4. To this solution was added *i*-PrOH saturated with gaseous HCl to give the hydrochloride salt of the product which was removed by filtration and recrystallized.

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.

Antimalarial Agents. I. Reduction of Sydnone Derivatives

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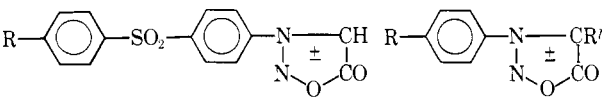
3-{*p*-[(4-Aminophenyl)sulfonyl]phenyl}sydnone (Ia) and other amino-substituted sydnones related to the antimalarial drug bis(*p*-aminophenyl) sulfone (DDS) are of interest to us in our program on antimalarial agents because of their structural relationship to DDS and 3-piperonylsydnone. The latter compound was active against *Plasmodium berghei* in the mouse.[1] The logical way to prepare Ia seemed to be the reduction of 3-{*p*-[(4-nitrophenyl)sulfonyl]phenyl}sydnone (Ib),



Ia, R = NH_2
b, R = NO_2
c, R = AcNH
d, R = Cl

IIa, R = NO_2; R^1 = H
b, R = NH_2; R^1 = H
c, R = NO_2; R^1 = Me
d, R = NH_2; R^1 = Me
e, R = R^1 = H
f, R = HONH; R^1 = H
g, R = AcON(Ac); R^1 = H
h, R = AcNH; R′ = H

which we had synthesized in an eight-step reaction sequence. Another approach would be the hydrolysis of 3-{*p*-[(4-acetamidophenyl)sulfonyl]phenyl}sydnone (Ic) or the replacement of Cl with NH_2 in 3-{*p*-[(4-chlorophenyl)sulfonyl]phenyl}sydnone (Id). However the sydnone ring of Ic and Id should be opened under the hydrolytic conditions or the amination reaction conditions. Thus the reduction of the nitrosydnone Ib was chosen for the preparation of the aminosydnone Ia. The more readily available 3-(*p*-nitrophenyl)sydnone (IIa) appeared to be a good model for this reduction study before we initiated any work with the nitro compound Ib.

A search of the literature revealed that although 3-(*p*-nitrophenyl)sydnone (IIa) is known, 3-(*p*-aminophenyl)sydnone (IIb) has not been described. Similarly, 3-(*p*-nitrophenyl)-4-methylsydnone (IIc) is known, but 3-(*p*-aminophenyl)-4-methylsydnone (IId) is unknown.

(1) W. H. Hyberg and C. C. Cheng, *J. Med. Chem.*, **8**, 531 (1965).