dride to give bis[*p*-(3-sydnonyl)phenyl] sulfone (Ib) in 95% conversion. The bissydnone was characterized by elemental analysis, by its acid hydrolysis to the dihydrazine IIf, and by its reaction with benzylamine resulting in 70% conversion to bis{*p*-[N-(N'-benzylcarbamyl)methyl-N-nitrosoamino]phenyl} sulfone (IIe).

On refluxing with concentrated HCl followed by basification Ib gave bis(*p*-hydrazinophenyl) sulfone (IIf) in 65% conversion, identical with an authentic sample prepared by the method of Heymann and Heidelberger.[2]

The products were tested on mice infected with *Plasmodium berghei*[3] and were rated as curative if at least one of the test animals treated with the product survived 60 days after treatment. The dinitrile IIb was curative at 160, 320, and 640 mg/kg without any toxic effects. The dicarboxylic acid IIc, the diamide IIe, as well as the disydnone Ib did not have any effect. The bisnitrosated dicarboxylic acid IId and the dihydrazine IIf were not tested.

Experimental Section

Bis{*p*-[N-(cyanomethyl)amino]phenyl} Sulfone (IIb).—To a stirred mixture of 49.6 g of bis(*p*-aminophenyl) sulfone (IIa), 36 g of paraformaldehyde, and 1400 ml of glacial AcOH was added 78 g of KCN. An exothermic reaction took place and the temperature rose to 50°. The mixture was heated for 4 hr at 50–76°; 39 g of KCN was added, heated for additional 3 hr at the same temperature, and allowed to stand overnight. To the greenish solution was added 900 ml of ice water and the resulting greenish precipitate was filtered off. The filtrate was mixed with 2 kg of crushed ice and the resulting granular solid was collected and washed with ice water until the washings were neutral. The solid was dried *in vacuo* at 110° for 5 hr to furnish 63.2 g (98%) of crude product, mp 185–189°. A small portion was recrystallized from EtOH–petroleum ether (bp 30–60°) to raise the melting point to 191–195°. *Anal.* ($C_{16}H_{14}N_4O_2S$) C, N; H: calcd, 4.30; found, 4.88.

Bis{*p*-[N-(carboxymethyl)amino]phenyl} Sulfone (IIc).—A mixture of 16.3 g of IIb and 200 ml of 10% aqueous KOH was refluxed with stirring for 18 hr. NH_3 was liberated smoothly and a solution was obtained. It was concentrated to *ca.* 100 ml by distillation. The residue was filtered to remove a small amount of solid, and the filtrate was poured into 900 ml of H_2O, acidified with concentrated HCl, and chilled in ice. The resulting solid was recrystallized from EtOH to give 12.8 g (78%) of crude product, mp 190–195° dec. An additional recrystallization from H_2O narrowed the melting point range to 192–195° dec. On introducing the melting point capillaries at 150–160° instantaneous decomposition was noted. *Anal.* ($C_{16}H_{16}N_2O_6S \cdot H_2O$) H, N, H_2O; C: calcd, 50.26; found, 50.83.

Bis[*p*-(3-sydnonyl)phenyl] Sulfone (Ib).—To a stirred solution of 3.7 g of IIc in 20 ml of concentrated HCl, 100 ml of AcOH, and 75 ml of H_2O at 10° was added a solution of 1.8 g $NaNO_2$ in 5 ml of H_2O. Within a few minutes a solid precipitated out. The mixture was stirred for 1.5 hr and diluted with 350 ml of ice water. The solid was collected, dried, and recrystallized from Me_2CO–petroleum ether (bp 30–60°) to give 3 g of crude IId.

A stirred mixture of 2.2 g of IId, 200 ml of ether, and 4 ml of trifluoroacetic anhydride was refluxed for 2.5 hr. The solid was collected, washed with Et_2O, and recrystallized from DMF (Darco)–Et_2O–petroleum ether (bp 30–60°) to give 1.9 g (96% based on nitroso compound) of product, mp 246–248°. *Anal.* ($C_{16}H_{10}N_4O_6S$) C, H, N.

Bis{*p*-[N-(N-benzylcarbamoyl)methyl-N-nitrosoamino]-phenyl} Sulfone (IIe).—A mixture of 3.9 g of Ib and 15 ml of benzylamine was heated to 120–125° during 30 min and was maintained at this temperature for additional 3.5 hr. To the mixture cooled to room temperature was added 25 ml of EtOH; the solid was collected, washed with EtOH (three 20-ml portions) and Et_2O (two 25-ml portions), and dried to give 4.3 g (72%) of solid, mp 214–215°. It was recrystallized from DMF–EtOH: mp 215–216°. *Anal.* ($C_{30}H_{28}N_6O_6S$): C, N; H: calcd, 4.67; found, 5.40.

Bis(*p*-hydrazinophenyl) Sulfone (IIf).—A mixture of 2 g of Ib and 20 ml of concentrated HCl was stirred at room temperature for 1 hr. There was a steady evolution of CO_2. The mixture was refluxed for 30 min and was then diluted with 140 ml of ice water. The resulting clear solution was treated with Darco and filtered. The filtrate was chilled and made basic by slow addition of 20% aqueous NaOH; the solid was collected, washed well with ice water, and purified by repeating the above process of slow precipitation from acid solution; 0.95 g (66%) of the pure product, mp 189–192° dec, was obtained. It was identical with a sample of IIf prepared by the method of Heymann and Heidelberger.[2]

Acknowledgment.—This study was supported by the U. S. Army Medical and Development Command and is Contribution No. 347 to the Army Research Program on Malaria. The screening of the compounds was carried out by Dr. L. Rane of University of Miami, Florida.

(2) H. Heymann and C. Heidelberger, *J. Am. Chem. Soc.*, **67**, 1986 (1945).
(3) T. S. Osdene, P. B. Russel, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).

The Photoactivity of Quinolinemethanols

I. GORDON FELS

Division of Biochemistry, Virginia Institute for Scientific Research, Richmond, Virginia

Received January 23, 1968

The phototoxicity that is experienced experimentally and clinically with quinolinemethanols[1,2] is of immediate concern. These compounds as a class possess very potent antimalarial activity, and, in general, they are looked upon as one of the most promising sources from which new antimalarial drugs will be derived. However, their phototoxicity restricts their use, and it is to an understanding of this property that the present communication addresses itself.

A phototoxic reaction may be considered a photosensitization in which light energy is absorbed by a sensitizing molecule which produces a chemical change in some other molecule. The toxic reaction occurs because of deleterious products that result from the chemical change. Because most photosensitization reactions require oxygen, it appeared profitable to investigate the photooxidative ability of several quinolinemethanols as sensitizers toward different substrates.

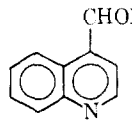
Experimental Section

The O_2 uptake was measured in a conventional Warburg apparatus at 25°. The substrates were N,N-dimethyphenylenediamine, phenylenediamine, cysteine, and tryptophan, respectively. All substrates, at concentrations of 10 mg/ml, were dissolved in ethylene glycol monomethyl ether. The uv light was obtained from two GE black light lamps, 15 W, held about 15 cm from the reaction vessels. Although it was necessary for

(1) F. Y. Wiselogle, Ed., A Survey of Antimalarial Drugs, 1941–1945, J. W. Edwards, Ann Arbor, Mich., 1946, p 348.
(2) W. E. Rothe and D. P. Jacobus, Abstracts, Division of Medicinal Chemistry, 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967, Abstract 37.

TABLE I

QUINOLINEMETHANOLS



No.	Nuclear substituents	Miscellaneous	R	Photochemical index
I	7-Cl-6-OCH_3-2-(4-$OCH_3C_6H_4$)		Diethylaminomethyl	3.62
II	7-Cl-6-OCH_3-2-(4-$OCH_3C_6H_4$)		Dihexylaminomethyl	2.81
III	6-OCH_3-2-(3,4-$Cl_2C_6H_3$)		Dioctylaminomethyl	2.72
IV	7-Cl-6-OCH_3-2-(4-$OCH_3C_6H_4$)		Dibutylaminomethyl	2.70
V	6,7-Cl_2-2-C_6H_5		2-Piperidyl	2.23
VI	6-OCH_3-2-(3,4-$Cl_2C_6H_3$)		Bis(2-ethoxyethylaminomethyl)	1.94
VII	6,8-Cl_2-2-(3-$CF_3C_6H_4$)		Dihexylaminomethyl	1.66
VIII	7-Cl-6-OCH_3-2-(4-ClC_6H_4)		Butylaminomethyl	1.61
IX	6-OCH_3-2-(3,4-$Cl_2C_6H_3$)		Diethylaminomethyl	1.43
X	6-OCH_3-2-(3,4-$Cl_2C_6H_3$)		Dibutylaminomethyl	1.40
XI	6-OCH_3-2-(3,4-$Cl_2C_6H_3$)		Dihexylaminomethyl	1.15
XII	6-Cl-2-(3,4-$Cl_2C_6H_3$)		Diethylaminomethyl	1.10
XIII	6,8-Cl_2-2-(2,6-$Cl_2C_6H_3$)		Dibutylaminomethyl	0.65
XIV	6-OCH_3		5-Vinyl-2-quinuclidyl (quinine)	0.04
XV		Chloroquin		0.44
XVI		Metoquin		0.001
XVII		8-Methoxypsoralen		0.001
XVIII		Quinoline		0.00[a]

[a] Exhibited photochemical activity after 3 hr.

the light to penetrate several centimeters of water, the reaction could be followed readily as soon as the antimalarial was added from the side arm. A control containing solvent and substrate only was run concurrently in each experiment. When cysteine was the substrate, 5% KOH and filter paper were added to the inner well to trap any possible H_2S and CO_2 that might evolve. All antimalarials were in concentrations of 2×10^{-6} *N*. Using this experimental procedure, several quinolinemethanols in addition to other compounds were investigated.[3]

In order to establish a comparison, a photochemical index was arbitrarily established using N,N-dimethylphenylenediamine as the substrate.

$$\text{photochemical index} = (O_x - O_c)/O_c$$

where O_x = the average hourly O_2 uptake (μl) of the unknown and O_c = the average hourly O_2 uptake (μl) of the control. A 3-hr observation period was used.

Using this designation, the photochemical index of the various compounds is given in Table I. The results are offered as semiquantitative for no attempt was made to determine the quantity of light affecting each vessel. That this is a factor influencing the results is indicated by the variability of the controls, the standard deviation being $\pm 15\%$ of the mean. The significant feature of the data nevertheless is that the quinolinemethanols as a class of compounds are photodynamically active, independent of biological metabolism. Moreover, the reaction which produces brownish black oxidation products is strictly photochemical, not taking place in the dark, but proceeding slowly even with light from a tungsten lamp. Similar results were obtained with phenylenediamine as substrate.

The nonspecificity of the photochemical reaction is shown in Figure 1 where cysteine is used as a substrate. Irradiation of the control, containing the substrate and solvent, produced a small amount of gas evolution, presumably NH_3. However, in the presence of a small amount of 7-chloro-α-(dihexylaminomethyl)-6-methoxy-2-(4-methoxyphenyl)-4-quinolinemethanol (II), the cysteine is rapidly oxidized. The use of tryptophan which is restricted by poor solubility also resulted in oxidation.

This suggests that a widespread series of photooxidations is involved in the phototoxicity experienced clinically when the quinolinemethanols are used. The fact that 8-methoxypsoralen (XVII), a phototoxic agent, is not photochemically active under

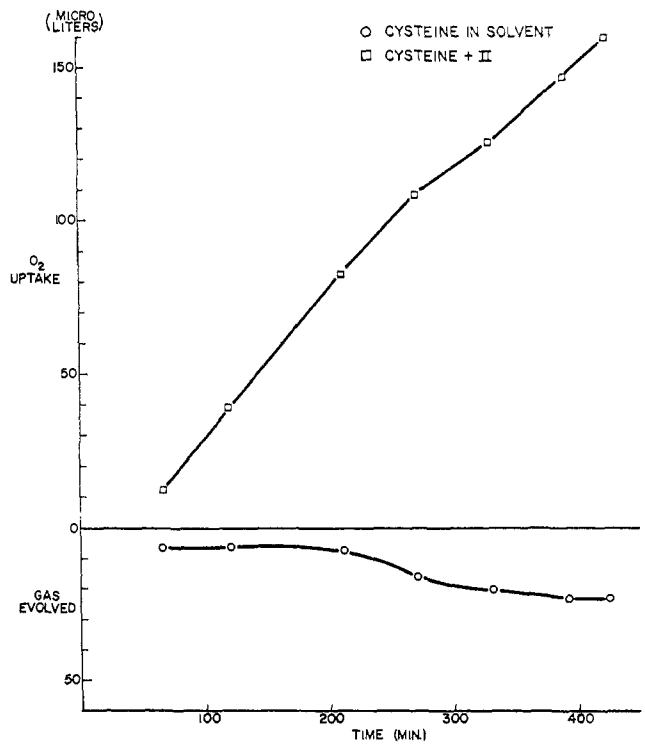


Figure 1.—Photooxidation of cysteine by II.

the present conditions suggests that the mechanism of phototoxicity is different from that of the quinolinemethanols. The absence of the O_2 requirement for methoxypsoralen photooxidations has previously been demonstrated.[4]

The observation that quinoline is photoactive, although weakly so, points to the heterocyclic nitrogen as the photochemical center of the quinolinemethanols. Whether or not the mechanism procedes through N-oxide formation remains to be determined. The photoactivity of nitroquinoline N-oxides has been demonstrated.[5]

(3) The writer is indebted to Dr. J. S. Gillespie, Jr., Virginia Institute for Scientific Research, and Dr. R. E. Strube, Division of Medicinal Chemistry, Walter Reed Army Medical Center, for a gift of the antimalarials. Dr. J. Kaiser of Paul B. Elder Company graciously provided the 8-methoxypsoralen.

(4) E. L. Oginsky, G. S. Green, S. G. Griffith, and W. L. Fowlkes, *J. Bacteriol.*, **78**, 821 (1959).

(5) C. Nagata, K. Fuzii, and S. S. Epstein, *Nature*, **215**, 972 (1967).