of *p*-aminobenzoic acid for the synthesis of dihydropteroate. Dihydrofolate and folinic acid reverse the inhibition caused by **3a** but not by sulfanilamide, indicating that sulfanilamide or its metabolites exert additional inhibition at a metabolic point beyond the reduction of dihydrofolate to tetrahydrofolate. This does not appear to be the case with **3a**. Whether **3a** is actually coupled with the pteridine in a manner similar to the sulfonamides is under investigation.

The biological activity of the adamantyl derivative of *p*-aminobenzamide as compared to the inactivity of the cyclohexyl and phenyl derivatives raises the question whether the latter residues prevent the binding of *p*-aminobenzamide moiety to the active site of dihydropteroate synthetase, whereas the adamantyl group enhances it. Alternatively, differences in uptake of the compounds into the cell might account for the difference in their activity. The observation that joining of the adamantyl group to the active sulfanilamide produces an inactive compound does not aid in making a choice between these alternatives. Studies with isolated enzymes designated to pinpoint accurately the mode of action of **3a** in comparison with sulfanamides are now being conducted in our laboratory.

Experimental Section[10]

N¹-Adamantyl-*p*-aminobenzamide (3a).—Adamantylamine hydrochloride (5 g) was dissolved in 55 ml of H_2O. A solution of 1.1 g of NaOH in 55 ml of H_2O was added. The precipitated free base of adamantylamine was extracted with 125 ml of Et_2O. Et_2O was dried for at least 1 hr over KOH and then 4.95 g of *p*-nitrobenzoyl chloride (1) was added. The precipitate was filtered off and kept on the filter until all Et_2O was removed. This product was stirred for 15 min with H_2O, filtered, washed with H_2O, and dried at room temperature under vacuum (**2a**); yield 6 g (79%), mp 172–175°. N¹-Adamantyl-*p*-nitrobenzamide (**2a**) (6 g) was dissolved in a mixture of 196 ml of EtOH and 92 ml of 2 *N* HCl. This solution was stirred for 30 min with 6.5 g of Zn dust. The Zn was filtered off and the solution was poured into 1300 ml of H_2O which was then adjusted to pH 4. After standing overnight at 5°, the white crystals were collected by filtration, washed with H_2O, and dried at room temperature under vacuum; yield 3.6 g. The crude material was dissolved in 590 ml of 1 *N* HCl, the solution was clarified with Darco G60 and the pH was adjusted to 10; yield 2.8 g (52%), mp 169–171°. *Anal.* ($C_{17}H_{22}N_2O$) C, H, N.

N¹-Cyclohexyl-*p*-aminobenzamide (3b).—A mixture of *p*-nitrobenzoyl chloride (1) (1.8 g) and cyclohexylamine (1.7 g) was dissolved in 20 ml of absolute Et_2O. The precipitate was handled in exactly the same way as described for corresponding adamantylamine derivative; yield 1.84 g (76%), mp 200–203°. A sample of **2b** (1.8 g) was stirred with 60 ml of EtOH, 28 ml of 2 *N* HCl, and 2 g of Zn dust for 2 hr. After filtering, the solution was poured into 400 ml of H_2O and the pH of this mixture was adjusted to 4.0. The precipitate was then handled as described for **3a**; yield 550 mg (35%), mp 176–178°. *Anal.* ($C_{13}H_{18}N_2O$) C, H, N.

N¹-Adamantylsulfanilamide (6).—Trifluoroacetylsulfanilyl chloride (**4**) was prepared by a modification of the procedure by Schroeter.[11] The modification involved the use of trifluoroacetic anhydride (in place of Ac_2O) which was added in small portions (15 ml followed by two times 10 ml) to 10.65 g of solid sodium sulfanilate, yield 10.3 g, mp 144–149°. N-Trifluoroacetylsulfanily chloride (**4**) (5 g) and adamantylamine (from 5 g of adamantylamine hydrochloride) were refluxed for 60 min in 200 ml of EtOH. This solution was added to 2.5 l. of 1.0 *N* HCl. The precipitate (**5**) was filtered, washed with H_2O, and dried under vacuum at 60°; yield 3.7 g (47%), mp 220–225°. A sample of N¹-adamantyltrifluoroacetylsulfanilamide (**5**) (3.5 g) was refluxed for 2 hr with 350 ml of EtOH and 87.5 ml of 5 *N* HCl. The solution was evaporated to dryness under reduced pressure at 30° over KOH to trap HCl. The residue was taken up in 20 ml of H_2O, filtered, washed with H_2O, and dried under vacuum at room temperature over KOH, yield of the crude product was 2.31 g, mp 167–172°. For purification the material was dissolved in 40 ml of EtOH, the solution was clarified with Darco G60, and filtered. The filtrate was added to 400 ml of 0.05 *M* HCl. The initially formed fine precipitate was filtered off and discarded. After standing overnight in the refrigerator, the product crystallized. It was dried at 50° under vacuum; yield 0.4 g (15%), mp 179–180°.

Anal. ($C_{16}H_{22}N_2O_3S$) C, H, N, S.

(10) Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. The melting points reported are uncorrected. The melting points of *p*-aminobenzoic acid derivatives were taken in a Thiele tube; those of sulfanilic acid derivatives in Fisher-Johns melting point apparatus.

(11) G. Schroeter, *Chem. Ber.*, **39**, 1559 (1906).

Antimalarial Agents. III. Bis[*p*-(3-sydnonyl)phenyl] Sulfone

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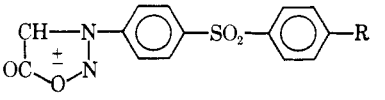
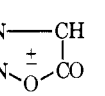
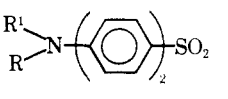
3-[*p*-(4-Aminophenylsulfonyl)phenyl]sydnone (Ia)[1] was found to be curative at the rate of 80 mg/kg of mouse infected with *Plasmodium berghei* and was devoid of any toxic effects at 640 mg/kg. Since Ia is the monosydnone derived from the antimalarial agent bis(*p*-aminophenyl) sulfone (DDS, IIa), it was of considerable importance to test the bissydnone of DDS. The synthesis and properties of this bissydnone, *i.e.*, bis[*p*-(3-sydnonyl)phenyl] sulfone (Ib), are reported here. Bis(*p*-aminophenyl) sulfone (IIa) was cyanomethylated on both nitrogens with paraformaldehyde and KCN in AcOH to give an excellent yield of bis{*p*-[*N*-(cyanomethyl)amino]phenyl} sulfone (IIb).



I

Ia, R = NH_2

b, R = 



II

IIa, R = R¹ = H

b, R = H; R¹ = CH_2CN

c, R = H; R¹ = CH_2COOH

d, R = NO; R¹ = CH_2COOH

e, R = NO; R¹ = $CH_2C(O)NHCH_2Ph$

f, R = H; R¹ = NH_2

The latter was hydrolyzed to bis{*p*-[*N*-(carboxymethyl)amino]phenyl} sulfone (IIc) by heating with aqueous KOH. It was nitrosated and the crude nitroso compound IId was treated with trifluoroacetic anhy-

(1) I. C. Popoff and G. H. Singhal, *J. Med. Chem.*, **11**, 631 (1968).

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]

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(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

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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.