dryness. The residue was dissolved in ethanol (1 ml) and hydrazine hydrate (0.16 ml) was added. After stirring for 12 hr the solvents were removed *in vacuo* and ether was added to the oily residue to produce a white, semisolid material. Tlc of this showed two widely separated, hydrazide reagent positive components, the slowest moving of which was ninhydrin positive and believed to be Pyr(3)Ala hydrazide. The components were readily resolved by elution on a column (1.4 × 25 cm) of silica gel with 15% methanol in chloroform. The amorphous derivative (145 mg, 37%), mp 96–98°, $[\alpha]^{27}D$ − 11.8° (*c* 0.75, MeOH) [lit.[17] $[\alpha]^{23}D$ −10.6° (*c* 2.42, 80% DMF)] showed one spot to hydrazide reagent and I_2 vapor: R_f^1 (silica) 0.55. *Anal.* ($C_{14}H_{17}N_5O_3$) C, H, N.

Z-Pyr(3)Ala-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH_2 (III). Benzyloxycarbonyl(pyrazolyl-3)alanine hydrazide (54 mg) was dissolved in DMF (1 ml) and cooled to −20°. Isoamyl nitrite (25 μl) and 5.9 *M* HCl in dioxane (100 μl) were then added and the mixture was stirred for 10 min followed by neutralization with triethylamine (70 μl). An ice-cold solution of the octapeptide II (80 mg) and triethylamine (12 μl) in DMF (200 μl) was added to the above mixture and stirring was continued for 30 min at −20°, 1 hr at −10°, and 24 hr at room temperature. The DMF was removed *in vacuo* whereupon tlc of the reaction mixture showed virtually complete conversion. The material was applied on a small column (1.3 × 37 cm) of CM-cellulose equilibrated with 0.002 *M* NH_4Ac buffer at pH 4.6. A pH and concentration gradient was begun immediately by introducing 0.1 *M* NH_4Ac through a 100-ml mixing flask containing starting buffer. The nonapeptide was located in fractions between 175 and 215 ml by measurement of OD at 280 nm. Lyophilization to constant weight yielded peptide III (58 mg, 57%): $[\alpha]^{28}D$ −46° (*c* 1.0, 0.1 *M* AcOH); single spot to Ehrlich reagent and I_2 vapor; R_f^1 (silica) 0.29; amino acid analysis gave Trp 0.93, NH_3 1.21, Arg 0.98, Ser 0.79, Pro 1.00, Gly 2.00, Leu 1.00, Tyr 0.90, Pyr(3)Ala 0.99.

pGlu-Pyr(3)Ala-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH_2 (IV). The benzyloxycarbonyl nonapeptide III (38 mg) was hydrogenated for 5 hr in 0.1 *M* AcOH (3 ml) over Pd black to give an almost quantitative yield of the free nonapeptide. This exhibited a single spot to Ehrlich reagent, ninhydrin, and I_2 vapor: R_f^1 (silica) 0.15; amino acid analysis gave Trp 0.99, NH_3 1.10, Arg 0.93, Ser 0.81, Pro 0.99, Gly 2.02, Leu 1.03, Tyr 0.89, Pyr(3)Ala 1.00; amino acid ratios in a leucine aminopeptidase digest are Trp 0.96, Arg not found, Gly 1.12, Pyr(3)Ala 1.01, Leu 1.05, Tyr 0.97.

The nonapeptide (28 mg) and pyroglutamic acid (8.1 mg) were dissolved in DMF (1 ml). *N*-Hydroxysuccinimide (7.2 mg) followed by DCI (14 mg) were added to the solution which was stirred (18 hr). Removal *in vacuo* of the DMF and purification of the mixture on CM-cellulose under the conditions described gave a symmetrical peak eluting between 325 and 335 ml. Tlc of an aliquot of this material (27 mg) gave a pattern of two spots of almost equal intensity and R_f when visualized with Ehrlich reagent and I_2 vapor: R_f^1 (silica) 0.14 and 0.17; amino acid analysis gave Trp 0.95, NH_3 1.13, Arg 1.01, Ser 0.81, Glu 1.50, Pro 0.97, Gly 1.98, Leu 1.03, Tyr 0.97, Pyr(3)Ala 0.99.

The mixture (26 mg) was then dissolved in DMF (0.5 ml) and 0.5 ml of methanol saturated with ammonia was added. After stirring for 5 hr, volatile components were removed *in vacuo* and and the products remaining were chromatographed on CM-cellulose. Lyophilization of fractions containing peptide to constant weight yielded [Pyr(3)Ala^2]-LH-RH (IV) (21 mg): $[\alpha]^{27}D$ −59° (*c* 0.81, 0.1 *M* AcOH); single spot to Ehrlich reagent and I_2 vapor; R_f^1 (silica) 0.16; R_f^1 (cellulose) 0.66; R_f^2 (silica) 0.55; R_f^3 (silica) 0.79; amino acid analysis gave Trp 1.00, NH_3 1.20, Arg 0.98, Ser 0.81, Glu 0.98, Pro 1.01, Gly 2.00, Leu 1.03, Tyr 0.92, Pyr(3)Ala 1.02.

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Potential Antileprotic Agents. 1. Inhibition of a Model Mycobacterial System by Diaryl Sulfones

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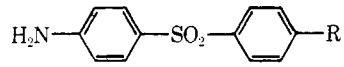
The development of a new antileprotic agent poses particular problems in view of the fact that the etiologic agent of human leprosy, *Mycobacterium leprae*, cannot be cultured in bacteriologic media. However, a correlation has been observed between minimum inhibitory concentrations (MIC) for *Mycobacterium* species 607, determined *in vitro*, and dietary MIC's for *M. leprae* growing in the mouse footpad.[1,2] Clinical therapeutic practice in the treatment of leprosy is largely dependent on the use of 4,4′-diaminodiphenyl sulfone (DDS)[3] or hydrolyzable derivatives.[4] In an effort to establish the structure–activity requirements of diaryl sulfones relative to our mycobacterial model system we have prepared a series of DDS analogs and evaluated them as growth inhibitors of *M.* sp. 607.

From the data presented in Table I it can be seen that DDS is superior to the other analogs. This result was not unexpected in view of the findings of previous investigators primarily obtained with tuberculin assay media.[5] The activity of the *N*-formyl and *N*-acetyl derivatives of DDS is probably attributable to hydrolysis back to DDS. However, the action of the 4-amino-4′-hydroxy analog is quite interesting. It is possibly caused by similarity of steric and electronic parameters when compared with DDS and would be reflected in active site binding or transport properties. The decrease of activity in the methyl ether suggests a steric interference with binding or blockage of active transport, since electronic properties would approximate the hydroxy compound. Tests conducted against *M. leprae* in the mouse footpad assay‡ show the hydroxy

† This note is dedicated to Alfred Burger in recognition of his many significant contributions to medicinal chemistry.

‡ Dr. L. Levy, U. S. Public Health Service Hospital, San Francisco, private communication.

Table I. Growth Inhibition of *Mycobacterium* sp. 607 by DDS Analogs



R	MIC, nmol/ml: DDS sensitive	DDS resistant
4-NH_2	8.1	3225
4-H[a]	1288	>2576
4-OH[b]	12	2008
4-OCH_3[c]	95	>1800
4-F	319	
4-Cl[d]	120	>400
4-Br[d]	256	>500
4-NO_2[e]	432	>600
4-NHOH[f]	34.4	>1200
4-NHCHO[g]	18.1	3000
4-$NHCOCH_3$[h]	13.8	>300
4-$NHCH_3$[h]	37.3	
4-NHC_2H_5	54.4	
4-NHC_3H_7	34.4	>1200
4-NHC_4H_9	110	>650
4-NHC_5H_{11}	377	>500
4-NHC_6H_{13}	>360	>400
4-$NH(CH_2)_2OH$[i]	13.7	2500
4-$NH(CH_2)_3OH$[j]	19.6	>2400
4-$NHCH_2COOH$[i]	261.4	>2200
4-$NHCH_2COOCH_3$[k]	32.8	>800
4-NEt_2	>164	
4-$N(C_5H_{11})_2$	>257	
3-NH_2[l]	24.2	1300
2-NH_2[m]	44.2	
3,3'-Diaminodiphenyl sulfone[l]	806	
4,4'-Dihydroxydiphenyl sulfone	400	

[a]E. Knusli, *Gazz. Chim. Ital.*, **79**, 621 (1949). [b]G. W. Raiziss, L. W. Clemence, M. Severac, and J. C. Moetsch, *J. Amer. Chem. Soc.*, **61**, 2763 (1939). [c]H. Burton and E. Hoggarth, *J. Chem. Soc.*, 468 (1945). [d]K. Ganapathi and A. Venkataraman, *Proc. Indian Acad. Sci., Sect. A*, **21**, 34 (1945). [e]H. Szmant and G. Suld, *J. Amer. Chem. Soc.*, **78**, 3400 (1956). [f]E. L. Jackson, *ibid.*, **68**, 1438 (1946). [g]Reference 4. [h]H. Heymann and C. Heidelberger, *ibid.*, **67**, 1986 (1945). [i]E. L. Jackson, *ibid.*, **70**, 680 (1948). [j]E. L. Jackson, *J. Org. Chem.*, **16**, 1899 (1951). [k]Ester obtained from collection of E. L. Jackson, unpublished results. [l]B. R. Baker, A. F. Kadish, and M. Querry, *J. Org. Chem.*, **15**, 400 (1950). [m]R. O. Roblin, J. H. Williams, and G. W. Anderson, *J. Amer. Chem. Soc.*, **63**, 1930 (1941).

compound to be slightly less effective than DDS while the methoxy derivative was inactive. Of equal interest is the marked loss of activity against *M.* sp. 607 when one amino group of DDS is replaced by hydrogen. This would appear to be due to a severe decrease in active site binding, since nearly all other substituents at the 4' position show better growth inhibition.

The inhibitory activity of the 4'-monoalkylamino analogs seems to be affected by steric and distribution factors. Substitution of the nitrogen caused a substantial decrease compared with DDS, while increasing chain length caused a progressive decrease in activity. The 4'-propylamino analog was an exception (possibly due to experimental variation) to this trend, however. The 4'-hydroxyethyl- and 4'-hydroxypropylamino compounds were quite active which tends to contradict the steric considerations noted above. The 4'-carbomethoxymethylamino analog was also moderately active, but the carboxylic acid was quite inactive, probably because of inability of the carboxylate ion to penetrate the mycobacterial cell wall. Two dialkylamino analogs, the 4'-diethylamino and diamylamino compounds, were inactive as inhibitors. The 3'-amino and 2'-amino compounds were about one-third and one-fourth as active as DDS, while 3,3'-diaminodiphenyl sulfone and 4,4'-dihydroxydiphenyl sulfone were inactive. None of the compounds tested showed useful activity against the DDS-resistant strain.

Table II. Drug Cross Resistance to DDS Resistance in *Mycobacterium* sp. 607

Drug	*Mycobacterium* sp. 607, MIC, nmol/ml: Sensitive	Resistant	Δ
DDS	8.1	3225	400
Sulfalene	3.6	12143	3373
Sulfadimethoxine	6.5	5850	900
Sulformethoxine	6.9	8280	1200
Sulfamethoxypyridazine	7.1	10650	1500
Trimethoprim	34	172	5
Pyrimethamine	101	403	4
Aminopterin	742	1483	2
Rifampicin	2.2	2.2	0

It was assumed that DDS acts by inhibition of folate biosynthesis *via* interference with incorporation of *p*-aminobenzoic acid into dihydrofolate (de novo pathway) such as the sulfonamides do in other bacterial systems.[6] In Table II data are presented showing similarity of cross resistance patterns for sulfones and sulfonamides in *M.* sp. 607. Since completion of our work McCullough and Maren[7] have obtained direct proof for the proposed mechanism of action in *Escherichia coli.* Our inability to experimentally obtain a suitably active cell-free extract of *M.* sp. 607 would not allow us to verify the above mechanism, nor to evaluate the sulfones in a medium free from transport parameters.

It was of greater interest to us to develop a dihydrofolic reductase inhibitor for use with DDS in the hope of obtaining a synergistic action[8] against mycobacteria and such efforts will be reported in subsequent papers.

Most of the sulfones were prepared by previously reported procedures. However, the C_4–C_6 monoalkylamino and the two dialkylamino compounds were synthesized by methods designed to prevent or minimize contamination by DDS (Scheme I). Acylation of 4-amino-4'-nitrodiphenyl sulfone with an appropriate acid chloride followed by hydrogenation of the nitro group and $LiAlH_4$ reduction of the amido moiety afforded the monoalkyl DDS compounds. Reduction of 4-acetamido-4'-nitrodiphenyl sulfone with B_2H_6 gave 4-ethylamino-4'-nitrodiphenyl sulfone, which was again acetylated and reduced with B_2H_6 to yield 4-diethylamino-4'-nitrodiphenyl sulfone. Catalytic reduction (Rh/C) was then used to reduce the nitro group to afford 4-amino-4'-diethylaminodiphenyl sulfone. The diamyl analog was similarly prepared, but formation of the *N*-amyl-*N*-valeryl intermediate required the use of NaH to promote acylation of 4-amylamino-4'-nitrodiphenyl sulfone by valeryl chloride.

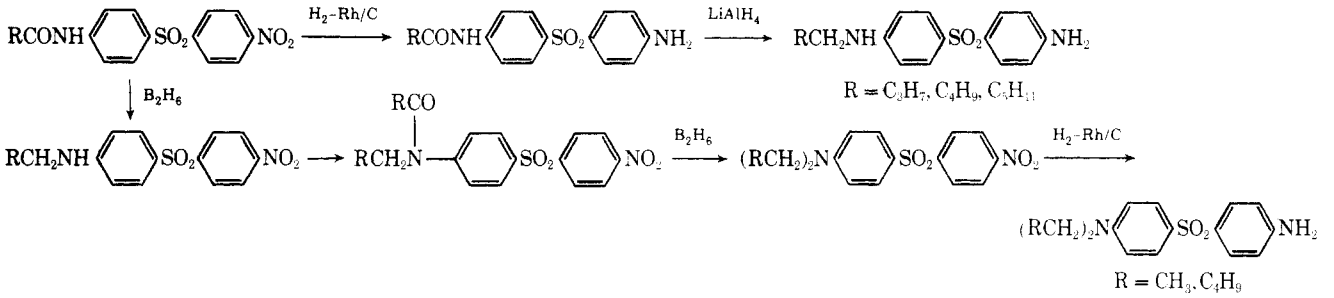
Experimental Section[§]

4-Fluoro-4'-nitrodiphenyl Sulfide. A mixture of 1.0 g (7.8 mmol) of 4-fluorobenzenethiol, 1.58 g (7.8 mmol) of 4-nitrobromobenzene, 1.08 g (7.8 mmol) of K_2CO_3, and 100 ml of 95% EtOH was stirred at reflux for 20 hr and evaporated to dryness *in vacuo.* The residue was stirred with H_2O, filtered, and dried: yield 1.95 g (100%). Recrystallization from cyclohexane gave mp 97–99.5°. *Anal.* ($C_{12}H_8FNO_2S$).

4-Fluoro-4'-nitrodiphenyl Sulfone. To a hot (steam bath) stirred solution of 1.9 g (7.6 mmol) of 4-fluoro-4-nitrodiphenyl sulfide in HOAc (50 ml) was added dropwise 2.6 ml (23.5 mmol) of 30% H_2O_2. The solution was heated 20 min, treated with another 1.7 ml of H_2O_2, heated 30 min, and kept at room temperature for

§ Compounds followed by empirical formulas were analyzed for C, H, and N; values found were ±0.4 of theory.

Scheme I



16 hr. After removal of most of the HOAc *in vacuo*, the residue was diluted with H_2O (50 ml) and the white precipitate collected to yield 1.91 g (89%). Recrystallization from C_6H_6 gave mp 163–165°. *Anal.* ($C_{12}H_8FNO_4S$).

4-Amino-4′-fluorodiphenyl Sulfone. A mixture of the nitro fluoro sulfone (0.50 g), 25 mg of 5% Rh/C, and 20 ml of MeOH was stirred under H_2 (1 atm) for 5 hr (theoretical uptake). The catalyst was removed and the solution concentrated to 10 ml to afford white crystals (0.29 g, 64%), mp 203–208° (lit.[9] mp 200–201°).

4-Butyramido-4′-nitrodiphenyl Sulfone. To an ice-cold, stirred suspension of 4-amino-4′-nitrodiphenyl sulfone (2.20 g, 8 mmol) in 2,6-lutidine (20 ml) was slowly added 1.70 g (16 mmol) of butyryl chloride. After 10 min the mixture was heated for 15 min at 95–100° and poured into 450 ml of ice H_2O. The precipitate was collected and recrystallized from EtOH–H_2O to afford 1.92 g (35%), mp 185–189°. *Anal.* ($C_{16}H_{16}N_2O_5S$).

Similarly prepared were the *N*-valeryl [63%, mp 170–171° ($C_{17}H_{18}N_2O_5S$)] and *N*-hexanoyl compounds [51%, mp 164–168° ($C_{18}H_{20}N_2O_5S$)].

4-Amino-4′-butyramidodiphenyl Sulfone. A mixture of the nitro sulfone (1.80 g), 5% Rh/C (300 mg), and MeOH (100 ml) was stirred under H_2 (1 atm) for 4 hr (theoretical uptake). After removal of catalyst and solvent the crude product was crystallized (C_6H_6–*i*-PrOH): 0.80 g (50%); mp 185–189°. *Anal.* ($C_{16}H_{18}N_2O_3S$).

The *N*-valeryl [66%, mp 163–167° ($C_{17}H_{20}N_2O_3S$)] and *N*-hexanoyl compounds [87%, mp 158–160° ($C_{18}H_{22}N_2O_3S$)] were similarly obtained.

4-Amino-4′-butylaminodiphenyl Sulfone. A mixture of 4-amino-4′-butyramidodiphenyl sulfone (0.80 g, 2.5 mmol), $LiAlH_4$ (0.28 g, 7.5 mmol), and THF (20 ml) was stirred at reflux for 15 hr. After decomposition of excess hydride with MeOH and H_2O, the THF was evaporated and the residue extracted with Et_2O. The extract was dried ($MgSO_4$) and evaporated to dryness. The residue was crystallized (EtOH–H_2O) to yield 0.37 g (51%), mp 195–196° (lit.[10] mp 193–199°); *N*-amyl compound (50%), mp 151–153° (lit.[10] 150–151°); *N*-hexyl (50%), mp 154–156° (lit.[10] 152–153°).

4-Ethylamino-4′-nitrodiphenyl Sulfone. To an ice-cold stirred solution of 1 *M* borane (6.5 ml, 6.5 mmol) in THF was slowly added 1.00 g (3.1 mmol) of 4-acetamido-4′-nitrodiphenyl sulfone in 50 ml of THF. The solution was refluxed for 8 hr, cooled to 0–5°, treated with 2 *N* HCl (3 ml), and warmed for 15 min. The THF was removed *in vacuo* and the residue treated with 20% NaOH. The orange solid was collected, washed with H_2O, and dried: yield 0.90 g (94%). Recrystallization (95% EtOH) gave mp 215–227° (lit.[10] mp 223°). *Anal.* ($C_{14}H_{14}N_2O_4S$).

Similar reduction of 4-valeramido-4′-nitrodiphenyl sulfone afforded the 4-amylamino-4′-nitrodiphenyl sulfone (70%): mp 136–140° (lit.[10] 142–143°).

4-*N*-Acetyl-*N*-ethylamino-4′-nitrodiphenyl Sulfone. A mixture of 4-ethylamino-4′-nitrodiphenyl sulfone (0.80 g), HOAc (3 ml), and Ac_2O (0.36 ml) was refluxed for 2 hr, cooled, and poured over ice. The precipitate was collected, washed with H_2O, and dried (0.80 g, 88%). Recrystallization (*i*-PrOH) gave mp 136–140°. *Anal.* ($C_{16}H_{16}N_2O_5S$).

4-*N*-Valeryl-*N*-amylamino-4′-nitrodiphenyl Sulfone. A mixture of 4-amylamino-4′-nitrodiphenyl sulfone (4.36 g, 12.5 mmol), NaH (55% in oil, 0.82 g, 18.8 mmol), DMF (5.8 ml), and C_6H_6 (150 ml) was stirred at reflux under N_2 for 2 hr, cooled, and treated with valeryl chloride (2.96 ml, 25 mmol), Reflux was continued for 15 hr. After washing with H_2O, the organic phase was dried ($MgSO_4$) and evaporated *in vacuo*, and the residue was crystallized from cyclohexane: yield 4.79 g (91%). Recrystallization (95% EtOH) gave mp 85–87.5°. *Anal.* ($C_{22}H_{28}N_2O_5S$).

4-Diethylamino-4′-nitrodiphenyl Sulfone. Reduction of the *N*-ethyl-*N*-acetyl nitro sulfone with BH_3 in a manner similar to that described above for 4-acetamido-4′-nitrodiphenyl sulfone afforded the *N,N*-diethyl nitro sulfone (74%); recrystallization (*i*-PrOH) gave mp 139–142°. Chromatography on silica gel (elution with Et_2O–C_6H_6, 3:7) followed by recrystallization (EtOH) gave the analytical sample, mp 148–155°. *Anal.* ($C_{16}H_{18}N_2O_4S$).

4-Diamylamino-4′-nitrodiphenyl Sulfone. Analogous reduction of the *N*-amyl-*N*-valeryl nitro sulfone gave the *N,N*-diamyl nitro sulfone (90%); recrystallization (95% EtOH) gave mp 126–129°. *Anal.* ($C_{22}H_{30}N_2O_4S$).

4-Amino-4′-diethylaminodiphenyl Sulfone. Hydrogenation of the diethylamino nitro sulfone over 5% Rh/C in MeOH afforded the amino sulfone: yield (48%); mp 192–222° after recrystallization from EtOH. *Anal.* ($C_{16}H_{20}N_2O_2S$).

4-Amino-4′-diamylaminodiphenyl Sulfone. Similar hydrogenation of the diamylamino nitro sulfone yielded the amino diamylamino sulfone (50%), mp 136–140° (95% EtOH). *Anal.* ($C_{22}H_{32}N_2O_2S$).

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Potential Antileprotic Agents. 2. Inhibition of Mycobacterial Dihydrofolic Reductase

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As part of a program for developing new antileprotic agents we have focused attention upon disruption of folate

†This note is dedicated to Alfred Burger in recognition of his many significant contributions to medicinal chemistry.