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Antimalarial Agents. 7. Compounds Related to 4,4′-Bis(aminophenyl) Sulfone[1]

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4,4′-Bis(acetamidophenyl) sulfone (I) and its lower homolog (II) are highly active[2] against *Plasmodium berghei* in mice. Since they are less toxic[2] than 4,4′-bis(aminophenyl) sulfone [4,4′-diamino(diphenyl sulfone), DDS, III], it was of interest to investigate the antimalarial activity of some other DDS-related compounds in which one or both NH_2 groups of III were replaced by NSO, NHOH, $NHNH_2$, NO_2, etc. Our study also included structures containing the moieties S, SO, SO_2CH_2, and SO_2S instead of the SO_2 bridge, as well as a pyridine analog of DDS.

The *N*-sulfinylamines XII [mp 149–152°, from PhH, 62% yield, *Anal.* ($C_{12}H_8N_2O_3S_2$): C, H, N] and XXIII [mp 126–128° from 1:1 petr ether–PhMe, 86% yield, *Anal.* ($C_{12}H_9NS_2O_3$): N] were synthesized from the corresponding amines by the method for 4,4′-bis(sulfinylaminophenyl) sulfone (IV) described in the Experimental Section, which includes the preparation of the remaining new compounds.

The testing[1c] was carried out by a method described previously[3] and the detailed data are listed in Tables I–IV.

None of the compounds reported here was more active than I in the mice test. Replacement of one of the NH_2 groups of DDS (III) with H or Cl resulted in total loss of antiplasmodial activity (XXII–XXVII) but not of toxicity (XXII). The oxidation of one NH_2 to NO_2, however, did not render the resulting structures completely inactive provided that the second NH_2 of III was not disubstituted as in the inactive VII, XIV, XVII, and XX. The activity of the sydnones XVIII and XIX, and of the *N*-sulfinyl structure XII, in which the second NH_2 is disubstituted, can be explained by the relative ease of hydrolysis of the sydnonyl and *N*-sulfinyl moieties to $NHNH_2$ (XIII) and NH_2 (XI), respectively. The relative activity of the pairs I–VIII, I–IX, V–XI, and VIII–IX leads to the speculation that a possible metabolism of the NO_2 group to NH_2, rather than the reverse, could be part of the mode of action of

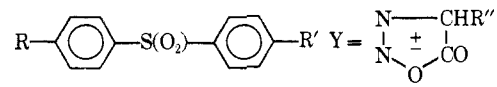
(1) (a) Part 6, *J. Med. Chem.*, **13**, 1002 (1970); (b) this study was supported by U. S. Army Medical Research and Development Command. This is Contribution No. 889 from the Army Research Program on Malaria; (c) the compounds were tested by Dr. L. Rane of the University of Miami, Florida; (d) analyses are indicated by symbols of the elements, since analytical results obtained for these elements were within ±0.4% of the theoretical values.

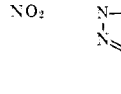
(2) Test data supplied by Dr. Bing Poon of Walter Reed Army Institute for Research.

(3) T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).

TABLE I

ACTIVITY OF

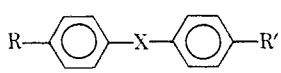


No.	Structure R	Structure R′	% cures or (CIST[h]) at mg/kg 40	160	640
1[a]	R′	NHAc	20	100	100
II[a]	R′	NHCOH	20	100	60[m]
III[a]	R′	NH_2	(8.0)	40	20[m]
IV	R′	NSO	(11.8)	20	*m*
V[b]	NH_2	NHOH	20	100	*m*
VI[c]	NH_2	$NHNH_2$	(10.4)	20	40[m]
VII[c]	NH_2	$N(NO)CH_2COX$[n]	(0.2)	(0.2)	(0.6)
VIII[d]	NO_2	NHAc	(8.3)	60	80
IX[b]	NHOH	NHAc	60[i]	60	100
X[e]	NH_2	NHAc	40	60[k]	40[m]
XI[f]	NO_2	NH_2	(8.2)	40	100
XII	NO_2	NSO	(6.6)	40	60[m]
XIII[c]	NO_2	$NHNH_2$	(13.9)	100[l]	*m*
XIV[c]	NO_2	$NAcCH_2CO_2Et$	(0.2)	(0.2)	(0.2)
XV[c]	NO_2	$NHCH_2CO_2Et$	(3.1)	(7.7)	80
XVI[c]	NO_2	$NHCH_2CO_2H$	(2.0)	(7.3)	40
XVII[c]	NO_2	$N(NO)CH_2CO_2H$	(0.2)	(0.2)	*m*
XVIII[c]	NO_2	Y (R″ = H)	(3.5)	20	60
XIX[c]	NO_2	Y(R″ = Br)	(5.3)	40	80
XX	NO_2	$N(Ac)CH(Me)CO_2Et$	(0.5)	(0.7)	(1.9)
XXI	NO_2	$NHCH(Me)CO_2Et$	(4.7)	(9.7)	80
XXII[g]	H	NH_2	(1.3)[j]	(4.1)	(4.4)[m]
XXIII	H	NSO	(0.8)	(1.2)	(1.8)
XXIV	H	$NHCH_2CO_2Et$	(0.9)	(0.9)	(1.1)
XXV	H	Y(R″ = H)	(0.5)	(0.7)	(1.9)
XXVI	Cl	$N(NO)CH_2CO_2H$	(1.5)	(0.7)	*m*
XXVII	Cl	Y(R″ = H)	(0.7)	(1.5)	(3.7)
XXVIII[c]	NO_2		(0.7)	(0.7)	(0.9)

[a] Test data supplied by Dr. Bing Poon of Walter Reed Army Institute for Research. [b] S. Owari, *Yakugaku Zasshi*, **71**, 246 (1951). [c] G. H. Singhal and I. C. Popoff, *J. Heterocycl. Chem.*, **5**, 217 (1968). [d] C. W. Ferry, J. S. Buck, and R. Baltzly, "Organic Syntheses," Collected Vol. 3, Wiley, New York, N. Y., 1955, p 239. [e] G. W. Raizis, L. W. Clemence, M. Severac, and J. C. Moetsch, *J. Amer. Chem. Soc.*, **61**, 2763 (1939). [f] Yo. O. Gabel and F. L. Grinberg, *Zh. Prikl Khim. (Leningrad)*, **12**, 1481 (1939); *Chem. Abstr.*, **34**, 6244[4] (1940). [g] W. R. Waldron and E. E. Reid, *J. Amer. Chem. Soc.*, **45**, 2406 (1923). [h] Change in survival time, *i.e.*, mean survival time of treated mice minus the mean survival time of the control. [i] CIST of 10.3 at 20 mg/kg. [j] CIST of 1.9 and 1.7 at 80 and 20 mg per kg, respectively. [k] 80% cures at 320 mg/kg. [l] 20% cures at 320 mg/kg. [m] See Table IV for toxicity data. [n] X = $NHCH_2Ph$.

TABLE II

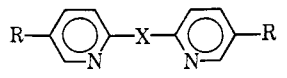
ACTIVITY OF



No.	Structure R	Structure R′	X	CIST[h] or (% cures) at mg/kg 40	160	640
XXIX[a]	NO_2	$NHCH_2CO_2Et$	S	5.7	7.7	14.1
XXX[a]	NO_2	$N(Ac)CH_2CO_2Et$	S	0.2	0.4	0.8
XXXI[b]	R′	NH_2	SO	4.1	8.7	*i*
XXXII[c]	R′	NHAc	SO	3.8	6.8	(40)[j]
XXXIII[d]	R′	NO_2	SO	3.3	8.5	(60)
XXXIV[e]	R′	NH_2	SO_2S	0.5	0.7	2.3
XXXV[f]	R′	NHAc	SO_2S	0.1	0.1	0.3
XXXVI[g]	R′	NH_2	SO_2CH_2	0.1	0.1	0.3
XXXVII	R′	NHAc	SO_2CH_2	0.1	0.1	0.3
XXXVIII	NO_2	NH_2	SO_2CH_2	1.4	1.4	1.8
XXXIX[g]	NO_2	NHAc	SO_2CH_2	1.0	1.2	1.2

[a] See footnote *c* of Table I. [b] M. Gazdar and S. Smiles, *J. Chem. Soc.*, 1833 (1908). [c] W. Braun, German Patent 964,593 (1957); *Chem. Abstr.*, **53**, P12240*h* (1959). [d] H. H. Szmant and J. J. McIntoch, *J. Amer. Chem. Soc.*, **73**, 4356 (1951). [e] B. J. Boldyrev and L. M. Khovalko, *Zh. Obsch. Khim.*, **31**, 3483 (1961); *Chem. Abstr.*, **57**, 9719*e* (1962). [f] C. Bere and S. Smiles, *J. Chem. Soc.*, 2359 (1924). [g] B. R. Baker and M. V. Querry, *J. Org. Chem.*, **15**, 413 (1950); [h] See footnote *h* of Table I. [i] See Table IV for toxicity data. [j] 20% cures at 320 mg/kg.

TABLE III
ACTIVITY OF



No.	Structure R	Structure X	CIST[d] at mg/kg 40	160	640
XL[a]	NO_2	S	0.1	0.3	0.7
XLI[b]	NO_2	SO_2	0.1	0.3	0.5
XLII[c]	NH_2	SO_2	0.6	0.6	1.0

[a] A. R. Surrey and H. J. Lindwall, *J. Amer. Chem. Soc.*, **62**, 1697 (1940). [b] A. Tchitchibabin and M. Bertougee, French Patent 866,482 (1941); *Chem. Abstr.*, **43**, P5050c (1949). [c] L. L. Bambas, *J. Amer. Chem. Soc.*, **67**, 668 (1945). [d] See footnote *h* of Table I.

TABLE IV
TOXICITY DATA

No.	% toxic deaths at mg/kg 160	320	640
II	0	0	40
III	0	40	80
IV	60	*a*	100
V	0	*a*	100
VI	0	20	60
X	20	20	60
XII	0	40	40
XIII	0	80	100
XVII	0	*a*	100
XXII	0	100	100
XXVI	0	*a*	100
XXXI	0	*a*	100

[a] Not tested.

these structures. It should be noted that monoacetylated DDS (X) was only slightly less toxic than DDS. A partial oxidation of NH_2 of X to NHOH of IX removed completely the toxic side effect without activity reduction. Similarly, the conversion of $NHNH_2$ (XIII) and NH_2 (XXII) into a sydnone ring (XVIII or XIX and XXV, respectively) resulted in total loss of toxicity. Reduction of the SO_2 bridge to SO or S, its replacement by the asymmetrical moieties, SO_2CH_2 or SO_2S, or substitution of α-pyridyl for Ph of III resulted in considerable (XXXII, XXXIII), or, in most cases, in total, loss of activity against *P. berghei*.

Experimental Section

4,4′-Bis(*N*-sulfinylaminophenyl) Sulfone (IV).—A suspension of 24.8 g (0.1 mole) of III and 25 g (0.35 mole) of $SOCl_2$ in 350 ml of PhMe was refluxed for 4.5 hr; most of the PhMe was distd off *in vacuo* and the residue was recrystd from PhMe to obtain 31.1 g (92%) of yellow product, mp 181–182°. When exposed to moisture it liberated SO_2. *Anal.* ($C_{12}H_8N_2O_4S_3$): C, H, N.

Ethyl *N*-[4-(*p*-Nitrophenyl)sulfonylphenyl]-*N*-acetylalaninate (XX) and *N*-[4-(*p*-Nitrophenyl)sulfonylphenyl]alanine (XXI).—A mixt of 73.8 g (0.3 mole) of 4-amino-4′-nitro(diphenyl sulfide), 55.0 g (0.3 mole) of ethyl α-bromopropionate, 42.0 g (0.3 mole) of $NaOAc \cdot 3H_2O$, and 10 ml of Carbitol was stirred for 30 hr at 150–155°. The cooled reaction mixt was poured in 1000 ml of 5% aq $NaHCO_3$ and extd (2 × 300 ml) with Et_2O. The Et_2O ext was washed with satd aq $NaHCO_3$, dried ($CaCl_2$), and evapd to obtain an oily residue which was extd with petr ether (bp 60–110°). The insol oil was subjected to vacuum (15 mm) for 30 min at 25–30° and refluxed for 2 hr with a mixt of 100 ml of glacial AcOH and 80 ml of AcOAc. A soln of 75 g of $KMnO_4$ in 700 ml of H_2O and 500 ml of AcOH was added and stirred for 1.5 hr at 35–45°. After addn of 110 g of $NaHSO_3$, the reaction mixt was poured in 800 ml of ice–water, and the resulting ppt was recrystd from C_6H_6-petr ether (bp 60–110°) to obtain 51.0 g (40%) of the acetylalaninate XX, mp 141–146°. *Anal.* ($C_{19}H_{20}N_2O_7S$): S, C, H.

A mixt of 21.0 g (0.05 mole) of XX, 50 ml of concd HCl, 20 ml of H_2O, and 200 ml of AcOH was refluxed for 4.5 hr and poured in 2 l. of H_2O. The solid product was recrystd from THF–petr ether (bp 60–110°) to obtain 13.8 g (79%) of the alanine XXI, mp 181–183°. *Anal.* ($C_{15}H_{14}N_2O_6S$): C, H, N.

Ethyl *N*-[*p*-(Phenylsulfonyl)phenyl]glycinate (XXIV).—A mixt of 10.0 g (0.042 mole) of the sulfone XXII, 7.2 g (0.043 mole) of ethyl α-bromoacetate, and 5.9 g (0.044 mole) of $NaOAc \cdot 3H_2O$ was refluxed for 7 hr, cooled, triturated with aq $NaHCO_3$, washed with H_2O, and recrystd from EtOH–petr ether (bp 60–110°) to obtain 7.3 g (53%) of XXIV, mp 112–114°. *Anal.* ($C_{16}H_{17}NO_4S$): C, H, N.

***N*-[*p*-(Phenylsulfonyl)phenyl]sydnone (XXV).**—A mixt of 8.0 g (0.025 mole) of the glycinate XXIV, 50 ml of concd HCl, 50 ml of H_2O, and 100 ml of AcOH was stirred and refluxed for 2 hr. A soln of 2.5 g (0.036 mole) of $NaNO_2$ in 15 ml of H_2O was added slowly to the reaction mixt at 25–35°. After 30 min at 20–25°, the mixt was poured in 500 ml of ice–water to isolate the crude *N*-nitroso-*N*-[*p*-(phenylsulfonyl)phenyl]glycine, mp 159–160° dec. It was dried (P_2O_5) at 80° *in vacuo* and refluxed for 1.5 hr in a mixt of 250 ml of Et_2O and 10 ml of $(CF_3CO)_2O$. The solid was filtered off and recrystd from acetone to obtain 5.5 g (72%) of XXV, mp 181–182° dec. *Anal.* ($C_{14}H_{10}N_2O_4S$): C, H, N.

***N*-[4-(*p*-Chlorophenyl)sulfonylphenyl]-*N*-nitrosoglycine (XXVI).**—A soln of 7.6 g (0.11 mole) of $NaNO_2$ in 15 ml of H_2O was added at 10° to 29.4 g (0.1 mole) of *N*-[4-(*p*-chlorophenyl)-sulfonylphenyl]glycine in 500 ml of AcOH and 75 ml of concd HCl and stirred for 2 hr at 10–20°. The reaction mixt was dild with 750 ml of ice–water and the ppt was recrystd from Me_2CO–petr ether (bp 60–110°) to obtain 26.6 g (77%) of XXVI, mp 158–159° dec. *Anal.* ($C_{14}H_{11}ClN_2O_5S$): C, H, N.

***N*-[4-(*p*-Chlorophenyl)sulfonylphenyl]sydnone (XXVII).**—A suspension of 14.2 g (0.04 mole) of the nitrosoglycine XXVI in 350 ml of Et_2O and 15 ml of $(CF_3CO)_2O$ was refluxed for 1.5 hr. The ppt was washed with Et_2O (3 × 75 ml) and recrystd from Me_2CO (Darco)–petr ether (bp 60–110°) to obtain 12.7 g (94%) of XXVII, mp 190° dec. *Anal.* ($C_{14}H_9ClN_2O_4S$): C, H, N, S.

4-Acetamidophenyl 4-aminobenzyl sulfone (XXVII), mp 200–201°, was obtained in 99% yield by the hydrogenation of the NO_2 analog XXXIX over Raney Ni in DMF at 4.2 kg/cm². The pure product pptd from the DMF soln upon dilution with H_2O. *Anal.* ($C_{15}H_{16}N_2O_3S$): C, H, N.

4-Aminophenyl 4-nitrobenzyl sulfone (XXXVIII), mp 292–293° (from 5:2 MeCN–DMF), was obtained in 96% yield by a 5-hr refluxing of XXXIX in 10% HCl. *Anal.* ($C_{13}H_{12}N_2O_4S$): C, H, N.

Analgetic and Anticonvulsant Activity of Some 2- and 4-Pyridyl Ketones[1]

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Previous investigations have shown that certain substituted 2,3-dihydro-4-quinolones[2] and their open chain analogs, the substituted β-aminopropiophenones,[3] possess analgetic activity. Compounds in the open chain series were more potent. With the hope that such simple compounds might provide information concerning structural requirements for analgetic activity, we wished to examine the biological activity of compounds in which the amino and carbonyl groups had a more

(1) This investigation was supported in part by the Institute of Arthritis and Metabolic Diseases, National Institute of Health, Public Health Service Grant AM 06432-05.

(2) M. Atwal, L. Bauer, S. Dixit, J. Gearien, and R. Morris, *J. Med. Chem.*, **8**, 566 (1965).

(3) M. Atwal, L. Bauer, S. Dixit, J. Gearien, M. Megahy, R. Morris, and C. Pokorny, *ibid.*, **12**, 994 (1969).