CHEMOTHERAPY OF MALARIA

VI. Quinolylsulphones

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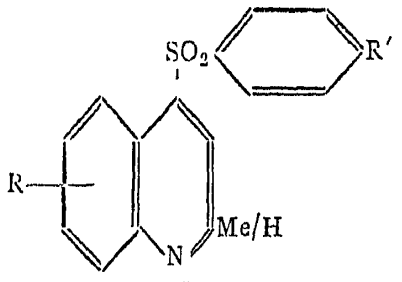
By heating 2-chloroquinoline with sodium arysulphinates, Troeger and Meinecke[1] synthesised the corresponding ary quinolyl sulphones. Surrey and Lindwall[2] prepared dipyridyl and diquinolyl sulphides and sulphones. Bambas[3] synthesised a series of 4-amino-phenylsulphones with a heterocyclic ring system attached to the sulphone group and of these the thiazole analog, "promizole" once received a great deal of attention. That derivatives of diamino-diphenylsulphone show antimalarial activity was shown by Coggeshall.[4] In view of the above, we synthesised phenylquinolylsulphones of general formula (I) with the hope that they may show antimalarial activity and also possess action against the exoerythrocytic forms of the plasmodia since many 4-hydroxyquinolines show this property.



(I)

The method of synthesis of the quinolylsulphones consisted of reacting 4-chloroquinoline derivatives with the substituted sulphinic acids which were used as sodium salts or in the presence of potassium acetate. In this work, 4:7-dichloroquinoline, 2-methyl-4:6-dichloroquinoline (4:6-dichloroquinaldine), 2-chloro-4-methyl-6-methoxyquinoline, 2-methyl-4-chloro-6-methoxyquinoline (4-chloro-6-methoxyquinaldine) and 2-chloro-4:6-dimethylquinoline were employed to condense them individually with the alkali metal salts of 4-acetaminobenzene sulphinic acid, 4-aminobenzenesulphinic acid, 4-acetaminomethylbenzenesulphinic acid, 4-chlorobenzenesulphinic acid and 2:5-dichlorobenzenesulphinic acid. The condensation of the 4-chloroquinolines with sulphinic acid salts proceeded with great ease when refluxed in ethanol solution; a small quantity of water was found to be essential for the reaction. The 2-chloroquinolines chosen for comparative study did not

condense under these conditions but the reaction proceeded at a higher temperature when heated in propylene glycol.

In the case of the dichloroquinolines that the 4-chlorine atom participates in the condensation has been shown by the fact that the sulphones obtained, on heating with acids, furnished the 4-hydroxy-quinolines. It has been found that the 4-quinoline sulphones readily undergo hydrolysis to the 4-hydroxy-quinolines.

The twenty-one compounds prepared have been presented in the table. They were tested for prophylactic antimalarial activity by feeding to mosquitoes infected with *Plasmodium gallinaceum* with negative results. Full details of these experiments will be reported elsewhere.

Experimental

The intermediate chloroquinolines were prepared by the standard methods of Knorr, Conrad and Lampach,[5] by the interaction of the requisite arylamines with ethylacetoacetate followed by cyclisation and the final conversion of the hydroxy to the chloroquinolines.

The sulphinic acids were prepared from the sulphochlorides by reduction with sodium sulphite.

4-(*p-Acetaminobenzenesulphonyl*)-7-*chloroquinoline* (*No.* 21).—4 : 7-Dichloroquinoline (5 g.), *p*-acetaminobenzenesulphinic acid (5 g.) and potassium acetate (2·5 g.) were refluxed in ethanol (100 c.c.) for 15–20 minutes. The reaction product that separated on cooling was filtered and washed with water (yield, 7·3 g., m.p. 222–24°). On crystallisation from ethanol it separated in long needles, m.p. 225°.

The above acetyl compound (5 g.) was refluxed with 12% hydrochloric acid (50 c.c.) for 15 to 20 minutes. From the solution a product m.p. 270° was isolated which was identified to be 4-hydroxy-7-chloroquinoline.

4-(*p-Aminobenzenesulphonyl*)-7-*chloroquinoline* (*No.* 22).—*p*-Aminobenzenesulphinic acid (5 g.) was taken up with potassium acetate (3 g.) and 4 : 7-dichloroquinoline (5 g.) in ethanol (150 c.c.), the mixture refluxed for about 2 hours and then kept aside. Next day, the solid that had separated was filtered, washed with water and dried (yield, 6·5 g. pale yellow needles, m.p. 233–35°). On recrystallisation from acetone, it had m.p. 233–6°. On acetylation, it furnished the acetamino compound described above (No. 21).

2-(*p-Acetaminobenzenesulphonyl*)-4-*methyl*-6-*methoxyquinoline* (*No.* 35).—2-Chloro-4-methyl-6-methoxyquinoline (4·15 g.) and potassium *p*-acetaminobenzenesulphinate (6 g.) were refluxed in a mixture of ethanol (30 c.c.) and

TABLE II

Sl. No.	Name of Compound	Formula	M. P.	Analysis	
				Found	Requires
					%
21	4-(*p*-Acetaminobenzenesulphonyl)-7-chloroquinoline	$C_{17}H_{13}O_3N_2ClS$	226° C.	Cl, 10·1 N, 7·7	9·8 7·8
22	4-(*p*-Aminobenzenesulphonyl)-7-chloroquinoline	$C_{15}H_{11}O_2N_2ClS$	235-36°	Cl, 11·4 N. 9·0	11·1 8·8
23	4-(*p*-Chlorobenzenesulphonyl)-7-chloroquinoline	$C_{15}H_9O_2NCl_2S$	147-48°	Cl, 21·1	21·0
24	4-(2′:5′-Dichlorobenzenesulphonyl)-7-chloroquinoline	$C_{15}H_8O_2NCl_3S$	158-59°	Cl, 28·4	28·6
25	4-(*p*-Acetaminomethylbenzenesulphonyl)-7-chloroquinoline	$C_{18}H_{15}O_3N_2ClS$	185-86°	Cl, 9·6	9·5
26	2-Methyl-4-(*p*-acetaminobenzenesulphonyl)-6 chloroquinoline	$C_{18}H_{15}O_3N_2ClS$	212°	Cl, 9·7	9·5
27	2-Methyl-4-(*p*-aminobenzenesulphonyl)-6-chloroquinoline	$C_{16}H_{13}O_2N_2ClS$	241-42°		
28	2-Methyl-4-(*p* chlorobenzenesulphonyl)-6-chloroquinoline	$C_{16}H_{11}O_2NClS$	192° d.	Cl, 20·1	20·1
29	2-Methyl-4-(2′:5′-dichlorobenzenesulphonyl)-6-chloroquinoline	$C_{16}H_{10}O_2NCl_3S$	165-66°	Cl, 28·0	27·6
30	2-Methyl-4-(*p*-acetaminomethylbenzenesulphonyl)-6-choroquinoline	$C_{19}H_{17}O_3N_2ClS$	213°	Cl, 8·9	9·15
31	2-Methyl-4-(*p*-acetaminobenzenesulphonyl)-6-methoxyquinoline	$C_{19}H_{18}O_4N_2S$	223-24°	N, 7·7	7·6
32	2-Methyl-4-(*p*-aminobenzenesulphonyl)-6-methoxyquinoline	$C_{17}H_{16}O_3N_2S$	237-38°	N, 8·4	8·5
33	2-Methyl-4-(*p*-chlorobenzenesulphonyl)-6-methoxyquinoline	$C_{17}H_{14}O_3NClS$	177-78°	Cl, 10·0	10·2
34	2-Methyl-4-(2′:5′-dichlorobenzenesulphonyl)-6 methoxyquinoline	$C_{17}H_{13}O_3NCl_2S$	183-84°	Cl, 18·9	18·6
35	2-(*p*-Acetaminobenzenesulphonyl)-4-methyl-6-methoxy-quinoline	$C_{19}H_{18}O_4N_2S$	259-60	N, 7·4	7·6
36	2-(*p*-Aminobenzenesulphonyl)-4-methyl-6-methoxyquinoline	$C_{17}H_{16}O_3N_2S$	221-22°	N, 8·6	8·5
37	2-(*p*-Chlorobenzenesulphonyl)-4-methyl-6-methoxyquinoline	$C_{17}H_{14}O_3NClS$	186-87°	Cl, 9·9	10·3
38	2-(*p*-Acetaminomethylbenzenesulphonyl)-4-methyl-6-methoxy-quinoline	$C_{20}H_{20}O_4N_2S$	264-65°	N, 7·2	7·3
39	2-(*p*-Acetaminobenzenesulphonyl)-4:6-dimethylquinoline	$C_{19}H_{18}O_3N_2S$	253-54°	N, 7·9	7·9
40	2-(*p*-Chlorobenzenesulphonyl)-4:6-dimethylquinoline	$C_{17}H_{14}O_2NClS$	177-78°	Cl, 10·8	10·7
41	2-(2′:5′-dichlorobenzenesulphonyl)-4:6-dimethylquinoline	$C_{17}H_{13}O_2NCl_2S$	196-98°	Cl, 19·6	19·4

water (10 c.c.) for 7 to 8 hours. The starting chloroquinoline was recovered back. On replacing ethanol by propyleneglycol and adding traces of copper bronze and iodine as catalysts the condensation product could be obtained (5·45 g. of white needles, m.p. 240–54°). On recrystallisation from a mixture ethanol and acetone, it had m.p. 259–60°.

On refluxing the above with 12% hydrochloric acid for about 30 minutes, the free amino derivative was obtained (No. 36), m.p. 221-2°.

SUMMARY

Twenty-one aryquinolylsulphones described in the table have been prepared by reacting the chloroquinolines with substituted arylsulphinic acids. The 4-chloroquinolines furnish the sulphones very readily and these sulphones are easily hydrolysed to the corresponding 4-hydroxyquinolines.

These compounds do not show any activity when tested for their prophylactic activity in mosquitoes against *Plasmodium gallinaceum* infection.

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