Synthesis of Sulfonates of 4-Chloro-3,5-dimethylphenol and 5-Chloro-7-iodo-8-quinolinol

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Abstract □ Seven sulfonates of 4-chloro-3,5-dimethylphenol and seven sulfonates of 5-chloro-7-iodo-8-quinolinol were synthesized, characterized, and evaluated for antimalarial activity. None of the sulfonates was effective against *Plasmodium berghei*.

Keyphrases □ Sulfonates—of substituted phenols and quinolinols, synthesized and evaluated for antimalarial activity □ Phenols, substituted—sulfonates synthesized and evaluated for antimalarial activity □ Quinolinols, substituted—sulfonates synthesized and evaluated for antimalarial activity □ Antimalarial activity—sulfonates of substituted phenols and quinolinols evaluated □ Structure–activity relationships—sulfonates of substituted phenols and quinolinols evaluated for antimalarial activity

The sulfonation of quinoline occurs more readily than that of pyridine but less readily than that of naphthalene. Sulfonation with 30% sulfuric acid at approximately 80° yields 8-quinolinesulfonic acid (54% recovered after isolation) and possibly some 5- and 7-quinolinesulfonic acid as well (1). With mercury as a catalyst, however, 5-quinolinesulfonic acid is the sole reaction product (2). Sulfonation of quinoline with sulfur trioxide in the presence of mercury as a catalyst at 180° leads to a mixture of the 5- and 8-quinolinesulfonic acids (3). The velocity constant of sulfonation is influenced only by the temperature of the reaction and varies considerably.

The methyl group in either the 2- or 4-position to the hydroxyl group has the effect of retarding the speed of sulfonation at all temperatures from 20 to 80°. The methyl group in the 3-position both accelerates and retards the speed of sulfonation according to reaction temperature. Phenol is sulfonated at 2.11 times the rate of 4-methylphenol and 2.21 times the rate of 2,4-dimethylphenol at 40°. The esters, carbonates, and sulfonates of clopidol (3,5-dichloro-2,6 dimethyl-4-pyridinol) were prepared by treating the sodium salt of clopidol suspended in dimethylformamide with the corresponding alkyl or aryl chlorides (4, 5).

This study reports the synthesis of sulfonates of 4-chloro-3,5-dimethylphenol and 5-chloro-7-iodo-8-quinolinol. Sulfonation was carried out with different sulfonyl chlorides in the presence of sodium hydride and dimethylformamide at 3° (4). These sulfonates were evaluated for their antimalarial activity against *Plasmodium berghei* and toxicity in albino mice.

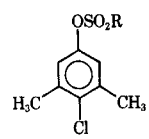


Table I—Sulfonates of 4-Chloro-3,5-dimethylphenol

Compound	R	Melting Point	Molecular Formula	Analysis, % Calc.	Analysis, % Found	IR[a], cm^{-1}	UV[b] λ_{max} ($CHCl_3$)	Toxicity[c] Test
I	p-$C_6H_4CH_3$	95°	$C_{15}H_{15}ClO_3S$	C 57.78 H 4.81 N 11.39	57.90 4.92 11.49	925 (s), 1017 (s), 1225 (b), 1424 (w)	241, 274	—
II	$C_6H_4NHCOCH_3$	148°	$C_{16}H_{16}ClNO_4S$	C 54.31 H 4.52 N 10.04	54.13 4.65 9.86	927 (s), 1018 (s), 1224 (b), 1418 (w)	261	—
III	α-$H_2CC_6H_4$	102°	$C_{15}H_{15}ClO_3S$	C 57.97 H 4.83 N 11.43	57.87 4.95 11.26	924 (s), 1022 (s), 1232 (b), 1430 (w)	236, 239	Nontoxic
IV	$C_6H_3(CH_3)_2$	78°	$C_{16}H_{17}ClO_3S$	C 59.16 H 5.23 N 10.93	59.21 5.34 10.87	922 (s), 1019 (s), 1227 (b), 1420 (w)	241, 278, 286	Nontoxic
V	C_6H_4Cl	110°	$C_{14}H_{12}Cl_2O_3S$	C 50.75 H 3.62 N 21.45	50.74 3.74 21.36	923 (s), 1019 (s), 1226 (b), 1428 (w)	240	Nontoxic
VI	C_6H_5	64°	$C_{14}H_{13}ClO_3S$	C 56.66 H 4.38 N 11.97	56.79 4.47 12.08	922 (s), 1016 (s), 1230 (b), 1415 (w)	241, 259, 266, 273	—
VII	o-$C_6H_4CH_3$	58°	$C_{15}H_{15}ClO_3S$	C 57.78 H 4.81 N 11.39	57.87 4.99 11.31	926 (s), 1025 (s), 1233 (b), 1418 (w)	241, 271, 280	—

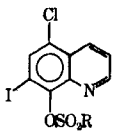
[a] Baird atomic IR recording spectrophotometer; s = strong, b = broad, and w = weak. [b] Beckman Acta CIII spectrophotometer. [c] The mortality observed after administration of 5 g/kg of III, IV, and V was 10, 30, and 10%, respectively, during 14 days. Gross necropsies performed in mice after administration of III–V showed normal pathology.

EXPERIMENTAL[1]

Preparation of Sulfonates—To a slurry of 10.8 g of sodium hydride (0.22 mole, 50% mixture in oil) in 100 ml of dimethylformamide was added 0.20 mole of 4-chloro-3,5-dimethylphenol or 5-chloro-7-iodo-8-quinolinol.

[1] Melting points were taken in open capillary tubes and are uncorrected. All compounds were analyzed for carbon, hydrogen, and nitrogen content by M.H.W. Laboratories, Garden City, MI 48135.

Table II—Sulfonates of 5-Chloro-7-iodo-8-quinolinol



Compound	R	Melting Point	Molecular Formula	Analysis, % Calc.	Analysis, % Found	IR, cm^{-1}	UV λ_{max} ($CHCl_3$)	Toxicity[a] Test
VIII	C_6H_4Cl	116–117°	$C_{15}H_8Cl_2INO_3S$	C 37.57 H 1.67 N 2.92	37.65 1.56 2.87	920 (s), 1020 (s), 1232 (b), 1414 (w)	241	—[b]
IX	p-$C_6H_4CH_3$	139–140°	$C_{16}H_{11}ClINO_3S$	C 41.78 H 2.39 N 3.04	41.73 2.42 2.96	926 (s), 1022 (s), 1230 (b), 1416 (w)	242	Nontoxic
X	o-$C_6H_4CH_3$	110°	$C_{16}H_{11}ClINO_3S$	C 41.78 H 2.39 N 3.04	41.82 2.43 2.96	918 (s), 1026 (s), 1224 (b), 1410 (w)	242.5	—
XI	$C_6H_4NHCOCH_3$	160°	$C_{17}H_{12}ClIN_2O_4S$	C 40.59 H 2.38 N 5.57	40.49 2.45 5.63	922 (s), 1025 (s), 1234 (b), 1408 (w)	454.5	—[b]
XII	α-$CH_2CH_6H_4$	86–87°	$C_{16}H_{11}ClINO_3S$	C 41.78 H 2.39 N 3.04	41.68 2.47 3.10	920 (s), 1021 (s), 1228 (b), 1405 (w)	258	—[b]
XIII	$C_6H_3(CH_3)_2$	125–126°	$C_{17}H_{13}ClINO_3S$	C 43.08 H 2.74 N 2.95	43.17 2.84 3.03	930 (s), 1025 (s), 1232 (b), 1407 (w)	242	Nontoxic
XIV	C_6H_5	98–99°	$C_{15}H_9ClINO_3S$	C 40.04 H 2.00 N 3.11	39.96 2.09 3.16	923 (s), 1026 (s), 1224 (b), 1407 (w)	241	—

[a] The mortality observed after administration of 5 g/kg of VIII, IX, XI, XII, and XIII was 90, 40, 100, 100, and 30%, respectively, during 14 days. Gross necropsies performed in mice treated with VIII, IX, and XI–XIII showed congested lungs of varying degree; advanced autolysis was found in mice treated with VIII and XI–XIII. [b] Due to mortality, classification of toxicity cannot be made because the compound may be highly toxic.

The mixture was cooled to 3° and added to the desired sulfonyl chloride (0.22 mole) dissolved in 75 ml of dimethylformamide. The reaction mixture was stirred for 1.5 hr, filtered, and washed with chloroform. The filtrate was partially concentrated under reduced pressure and, on cooling, gave the desired product. The analytical product was purified by two recrystallizations from ethanol. The sulfonates of 4-chloro-3,5-dimethylphenol and 5-chloro-7-iodo-8-quinolinol are recorded in Tables I and II, respectively.

Antimalarial Activity—All sulfonates were evaluated[2] for antimalarial activity (6) against *P. berghei* in mice. They were inactive at dose levels of 40, 160, and 640 mg/kg.

Toxicity Studies[3]—The acute oral toxicity was determined by oral administration of sulfonates by stomach tube to 10 albino mice[4], 12–20 g, kept on an *ad libitum* diet. Each sulfonate was administered as a 50% (w/v) suspension in corn oil[5] at a dose of 5 g/kg. The mice were kept in two cages of five animals each and starved for 18 hr prior to the sulfonate administration. The animals were observed closely, and their mortality was recorded. Gross necropsies were performed on the mice that died during the 14-day period. The surviving mice were weighed and then sacrificed by cervical dislocation, and gross necropsies were performed.

[2] Evaluated by Dr. Leo Rane, University of Miami, Miami, Fla., and furnished by Dr. E. A. Stack, Walter Reed Army Institute of Research, Washington, D.C.
[3] Hill Top Research Laboratory, Miamiville, OH 45147 [by using Federal Hazardous Substances Act (Revised), Federal Register, Sept. 17, 1964].
[4] Laboratory Supply Company, Indianapolis, IN 46241.
[5] Mazola.

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