2′-(Benzylthio)cinnamanilide.—A solution of 64.5 g (0.30 mole) of 2-(benzylthio)aniline[11] and 30.3 g (0.30 mole) of Et_3N in 100 ml of $CHCl_3$ was added dropwise to a cold solution (10–20°) of 50.0 g (0.3 mole) of cinnamoyl chloride in 300 ml of $CHCl_3$. This mixture was refluxed for 1 hr, cooled, washed with H_2O (100 ml) (five times), and dried ($MgSO_4$). After evaporation of the solvent the residue was triturated with 300 ml of hexane to give 96.2 g of material, mp 139–142°. Following crystallization from 420 ml of MeCN, the nearly colorless material weighed 90.3 g (87%), mp 141–143°. *Anal.* ($C_{29}H_{25}NOS$) N, S.

Acknowledgments.—We are indebted to Dr. J. Bernstein for his interest and encouragement during this investigation and to Mr. J. Alicino and his associates for the analyses reported herein.

Notes

3-Phenylrhodanines as Potential Antimalarial Agents[1]

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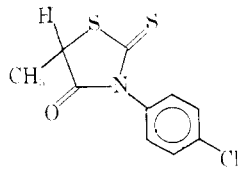
Received September 29, 1967

3-(*p*-Chlorophenyl)-5-methylrhodanine (**1**) was reported to exhibit antimalarial activity in preliminary screening against *Plasmodium berghei* in mice.[2] Therefore, an authentic sample of I and several related com-



I

pounds (Table I) were synthesized for antimalarial evaluation.

The majority of the rhodanines were prepared by the method of Brown and co-workers[3] (method A). A substituted aniline was converted to the corresponding aryldithiocarbanilic acid salt by treatment with ammonium hydroxide and carbon disulfide. Subsequent reaction with the required α-haloacetic or propionic acid in base, followed by acidification and brief heating, gave the desired rhodanines. The method failed with *o*- and *p*-nitroaniline, *o*-bromoaniline, and *o*- and *m*-trifluoromethylaniline. However, the α,α,α-trifluoro-*m*-tolylrhodanines (**9**–**11**, Table I) were obtained by using sodium hydride in tetrahydrofuran in place of ammonium hydroxide in the formation of the dithiocarbanilic acid (method C). The sodium hydride procedure was unsuccessful with *o*-trifluoromethylaniline. 3-Phenyl-5-methylrhodanine (**8**, Table I) was prepared by the condensation of thiolactic acid and phenyl isothiocyanate in ethanol (method B).[4] An attempt to extend this method to *m*-fluorophenyl isothiocyanate yielded only the ethyl ester of *m*-fluorophenylthiocarbanilic acid, and this procedure was not examined further.

Discrepancy was noted between the melting points we obtained and those reported[5] for **13**–**15** and **17**, although the microanalytical results were in agreement with the structures proposed. Comparison of the ir, uv, and nmr spectra of these materials with those of **6** which was prepared similarly and whose melting point agrees with the literature[5] value confirms their basic structural similarity. The difference in the melting points remains unexplained.

The 3-phenylrhodanine derivatives (Table I) were initially administered subcutaneously in a single dose to mice infected with *P. berghei*.[6,7] None of the compounds caused a significant prolongation of the mean survival time of mice even at the highest dose level employed, namely 640 mg/kg. However, when representative compounds (**1**, **3**, **7**, **12**, **17**) were administered in the diet for 6 days to mice infected with another strain of *P. berghei* in daily doses ranging from 87 to 354 mg/kg, a significant reduction in parasitemia (63–99%) was noted among each treated group.[8] It can thus be concluded that certain phenylrhodanine derivatives exhibit weak, but demonstrable, antimalarial properties.

Representative phenylrhodanine derivatives were also tested against other parasites in mice including *Syphacia obvelata*, *Nematospiroides dubius*, *Hymenolepis nana*, *Trypanosoma cruzi*, and *Schistosoma mansoni*, and against the bacteria *Staphylococcus aureus* (UC-76), *Pseudomonas aeruginosa* (No 28), *Mycobacterium tuberculosis* ($H_{37}Rv$), *Escherichia coli* (Vogel), *Proteus mirabilis* (MGH-1), *Salmonella typhimurium* (V-31), and *Shigella sonnei* (C-10) *in vitro*. Among them, **12** was active against *N. dubius* in mice when administered in a poorly tolerated regimen of 125 mg/kg daily by gavage for 2 days followed by 68 mg/kg daily by drug diet for 6 days. *In vitro* compounds **1** and **4** were active against *S. typhimurium* (V-31) at a concentration of 20 μg/ml, while **3** was active against *E. coli* (Vogel) at the same concentration.

(1) This investigation was supported by U. S. Army Medical Research and Development Command Contract DA-49-193-MD-2754.

(2) Private communication, Walter Reed Army Institute of Research.

(3) F. C. Brown, C. K. Bradsher, E. C. Morgan, M. Tetenbaum, and P. Wilder, Jr., *J. Am. Chem. Soc.*, **78**, 384 (1956).

(4) S. R. Andreasch and A. Zipser, *Monatsh.*, **25**, 159 (1901).

(5) B. K. Raval and J. J. Trivedi, *J. Indian Chem. Soc.*, **39**, 53 (1962).

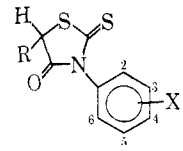
(6) The initial antimalarial screening was carried out by Dr. Leo Rane of the University of Miami, and test results were supplied through the courtesy of Dr. David P. Jacobus of the Walter Reed Army Institute of Research.

(7) For a description of the test method, see T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).

(8) Selected compounds were kindly evaluated by drug diet against *Plasmodium berghei* in mice by Dr. Paul E. Thompson and co-workers, Research Laboratories, Parke, Davis and Co., Ann Arbor, Mich.

TABLE I

PREPARATION OF 3-PHENYLRHODANINES



No.	X	R	Method	Yield purified, %	Mp, °C	Formula	Analyses[10]
1	4-Cl	H	A	7	124–125[b]	$C_9H_6ClNOS_2$	C, H, N, S
2	H	H	*a*		193–195[b]	$C_9H_7NOS_2$	C, H, N, S
3	3,4-Cl_2	CH_3	A	10	149–150	$C_{10}H_7Cl_2NOS_2$	C, H, N, S
4	3-Br	CH_3	A	6	98–100	$C_{10}H_8BrNOS_2$	C, H, N, S
5	4-Br	CH_3	A	26	149–151[c]	$C_{10}H_8BrNOS_2$	C, H, N, S
6	3-Cl	CH_3	A	48	105–107[c]	$C_{10}H_8ClNOS_2$	C, H, N, S
7	4-Cl	CH_3	A	55	120–122[d]	$C_{10}H_8ClNOS_2$	C, H, N, S
8	H	CH_3	B	16	117–119[e]	$C_{10}H_9NOS_2$	C, H, N
9	3-CF_3, 4-Br	CH_3	C	12	204–206	$C_{11}H_7BrF_3NOS_2$	C, H, N
10	3-CF_3, 4-Cl	CH_3	C	34	167–169	$C_{11}H_7ClF_3NOS_2$	C, H, N
11	3-CF_3	CH_3	C	29	109–111	$C_{11}H_8F_3NOS_2$	C, H, N
12	4-CF_3	CH_3	A	48	136–137	$C_{11}H_8F_3NOS_2$	C, H, N
13	3-CH_3	CH_3	A	64	99–100[c]	$C_{11}H_{11}NOS_2$	C, H, N, S
14	4-CH_3	CH_3	A	31	96–97[c]	$C_{11}H_{11}NOS_2$	C, H, N, S
15	2-OCH_3	CH_3	A	57	118–120[c]	$C_{11}H_{11}NO_2S_2$	C, H, N, S
16	3-OCH_3	CH_3	A	30	131–133	$C_{11}H_{11}NO_2S_2$	C, H, N, S
17	4-OCH_3	CH_3	A	33	130–132[c]	$C_{11}H_{11}NO_2S_2$	C, H, N, S

[a] Purchased from Eastman Kodak Co. [b] J. L. Garraway, *J. Chem. Soc.*, 3733 (1961), reports compound **1**, mp 125–127°; **2**, mp 195–197°. [c] Lit.[5] mp 145° (**5**), 108° (**6**), 124° (**13**), 196° (**14**), 137° (**15**), 178° (**17**). [d] J. T. Bashour, U. S. Patent 2,743,211 (1956), reports mp 116–117°. [e] Lit.[4] mp 118–119°.

Experimental Section[9,10]

3-Phenylrhodanines (Table I). Method A. 3-(*p*-Chlorophenyl)rhodanine (1).—To a mixture of 30 ml of concentrated NH_4OH and 18.9 g (0.24 mole) of CS_2 cooled to 0° was added slowly 25.5 g (0.2 mole) of *p*-chloroaniline. The mixture was stirred at 0° for 10 min and then allowed to stand overnight at room temperature. The solid *p*-chlorophenyldithiocarbanilic acid ammonium salt was collected, washed with ether, dried, and added to a cold solution of 23.3 g (0.2 mole) of sodium chloroacetate in 40 ml of H_2O made just basic with anhydrous Na_2CO_3. The mixture was allowed to come to room temperature and was treated with a warm solution of 60 ml of concentrated HCl and 26 ml of H_2O. This mixture was heated to 85–95° for 20 min and cooled. The solid which formed on cooling was collected and recrystallized from EtOH–H_2O to give 3.3 g (7%) of **1**.

3-(Substituted Phenyl)-5-methylrhodanines.—To a mixture of 30 ml of concentrated NH_4OH and 18.9 g (0.24 mole) of CS_2 cooled to 0° was added 0.2 mole of a substituted aniline. The mixture was stirred at 0° for 15–40 min and allowed to stand overnight at room temperature. The solid (substituted phenyl)-dithiocarbanilic acid ammonium salt was collected, washed with ether (in a few cases the material was ether soluble and this step was omitted), dried, and added at 10° to an aqueous solution of sodium α-bromopropionate, prepared by making a solution of 30.6 g (0.2 mole) of α-bromopropionic acid in 35 ml of H_2O just basic with 50% aqueous NaOH. The mixture was brought to room temperature and treated with a warm solution of 66 ml of concentrated HCl and 26 ml of H_2O. The resulting mixture was heated to 85–95° for 20 min to 1 hr and cooled. The solid which formed on cooling was collected and recrystallized from EtOH, except for **16** and **17** which were recrystallized from C_6H_6–petroleum ether (bp 30–60°), to give the pure 3-(substituted phenyl)-5-methylrhodanines in 10–65% yields.

Method B. 3-Phenyl-5-methylrhodanine.—A mixture of 10.6 g (0.1 mole) of thiolactic acid and 13.5 g (0.1 mole) of phenylisothiocyanate in EtOH was heated under reflux for 12 hr. The solvent was removed *in vacuo* and the solid residue was recrystallized twice from EtOH to give 3.5 g (16%) of 3-phenyl-5-methylrhodanine,[4] mp 117–119°.

***m*-Fluorophenylthiocarbanilic Acid Ethyl Ester.**[11]—A mixture of 10.6 g (0.1 mole) of thiolactic acid and 15.3 g (0.1 mole) of *m*-fluorophenyl isothiocyanate in 170 ml of EtOH was heated under reflux for 21 hr and cooled. Excess EtOH was removed *in vacuo* and the solid residue was recrystallized from EtOH–H_2O to give 9.3 g (47%) of the ester, mp 81–82° (lit.[11] mp 81–82°). *Anal.* ($C_9H_{10}FNOS$) C, H, N, S. Ir and nmr spectra also confirm this structure.

Method C. 3-(4-Bromo-α,α,α-trifluoro-*m*-tolyl)-5-methylrhodanine (9).—To a solution of 4.8 g (0.06 mole) of CS_2 and 12.0 g (0.05 mole) of 5-amino-2-bromobenzotrifluoride in 100 ml of THF was added slowly at room temperature 2.4 g (0.05 mole of a 50% suspension in mineral oil) of NaH. The mixture was stirred 3 days at room temperature. The solid formed was filtered and the filtrate was concentrated to obtain a second crop. The solid was washed with ether, dried, and added at 0° to an aqueous solution of 7.7 g (0.05 mole) of α-bromopropionic acid and 9 ml of H_2O made just basic with 50% aqueous NaOH. The mixture was allowed to warm gradually to room temperature, and to it was added 7 ml of H_2O and 16 ml of concentrated HCl. This mixture was heated under reflux for 1 hr and cooled. The solid formed was filtered and recrystallized from EtOH–H_2O to give 2.3 g (12%) of **9**.

Acknowledgments.—The authors are indebted to Dr. Leo Rane of the University of Miami and to Dr. Paul E. Thompson and Dr. M. W. Fisher of Parke, Davis and Company for the biological testing. We also wish to thank Mr. C. E. Childs and associates for the microanalyses, and Dr. J. M. Vandenbelt and coworkers for determination of the spectral data reported herein.

(9) Melting points (corrected) were taken in open capillary tubes in a Thomas–Hoover capillary melting point apparatus.

(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.

(11) D. Goeckeritz and R. Pohlouddek-Fabini, *Pharm. Zentralhalle*, **102**, 685 (1965).