Syntheses and Pharmacological Activity of Compounds Related to the Antidepressant, 5-(2-Dimethylaminoethyl)-2,3-dihydro-2-phenyl-1,5-benzothiazepin-4(5H)-one (Thiazesim). III[1,2]

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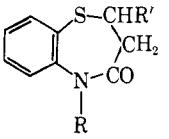
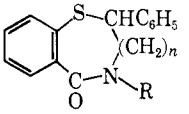
The resolution of thiazesim and the preparation of several piperazinopropyl analogs are reported. The syntheses of basically substituted derivatives of 2,3-dihydro-2-propenyl-1,5-benzothiazepin-4(5H)-one, 3,4-dihydro-2-phenyl-2H-1,4-benzothiazepin-5-one, 2,3-dihydro-2-phenyl-4H-1,3-benzothiazin-4-one, and 2'-(benzylthio)-acetanilide ("open-ring" analog of thiazesim) are described. These compounds were tested for their ability to inhibit the mouse-killing response of selected rats (antimuricide test). Of the 20 compounds of this series, two were slightly more active than thiazesim in this test procedure.

As part of our program to determine a structure–activity correlation in a series of compounds related to the antidepressant, 5-(2-dimethylaminoethyl)-2,3-dihydro-2-phenyl-1,5-benzothiazepin-4(5H)-one hydrochloride (Ia),[3] we wish to report the syntheses and



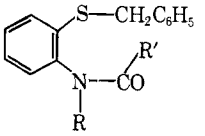
Ia, R = $(CH_2)_2N(CH_3)_2$·HCl; R′ = C_6H_5

pharmacological activity of an additional 20 compounds (Table I) which are divided into four classifications. Products of type I are represented by the optical isomers of Ia, as well as analogs containing a substituted-piperazinopropyl side chain and related compounds having a propenyl group in the 2 position. Compounds of type II are 1,4-benzothiazepin-5-ones, materials of type III are 1,3-benzothiazin-4-one analogs of type II,



II, $n = 1$
III, $n = 0$

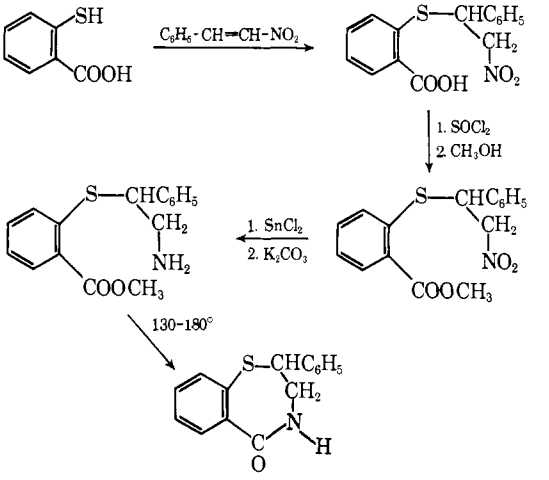
and type IV products represent "open-ring" modifications of type I.



IV

Most of the compounds of Table I were obtained by treatment of the intermediates of types I, II, and IV (R = H) with sodamide and the appropriate basically substituted alkyl halide. The new precursors (R = H) for the compounds were obtained in the following manner: I, by reaction of 2-aminobenzenethiol with sorbic acid; II, by a four-step procedure (Chart I) involving

CHART I



the interaction of thiosalicylic acid with nitrostyrene, conversion of the resulting 2-{[α-(nitromethyl)benzyl]-thio}benzoic acid to its methyl ester, reduction of the nitro group to the corresponding amine, followed by thermal cyclization; and IV, by acylation of 2-benzylthioaniline. Most of the products represented by type III were obtained by heating thiosalicylic acid with a benzal derivative of the appropriate diamine. In the preparation of **16**, the product from thiosalicylic acid and 3-(benzylideneamino)propanol was treated with thionyl chloride, sodium iodide, and dimethylamine successively. Resolution of the optical isomers of Ia was carried out using (+)-tartaric acid. In the preparation of **3** and **4**, the intermediate of type I [R = $(CH_2)_3Cl$, R′ = C_6H_5] was obtained and then treated with sodium iodide and the appropriate substituted piperazine. Compound **5** was obtained as the product of the reaction of the epoxy intermediate with N-methylpiperazine.

In our previous studies,[1,4] the compounds were tested for their ability to calm a septal rat. Because of the difficulty in preparing such animals and their short period of usefulness, it was desirable to develop a simplified test procedure for screening further members of this series of compounds. Studies in the cat showed that Ia affected the amygdala area of the brain.[5] Since neurological lesioning of the amygdala of the rat

(1) Paper II of this series: J. Krapcho and C. F. Turk, *J. Med. Chem.*, **9**, 191 (1966).

(2) Presented in part before the 3rd International Meeting of Chimie Therapeutique, Paris, July 1967.

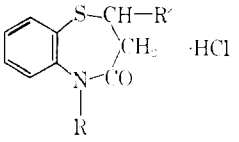
(3) Thiazesim hydrochloride, Altinil®.

(4) J. Krapcho, E. R. Spitzmiller, and C. F. Turk, *J. Med. Chem.*, **6**, 544 (1963).

(5) Z. P. Horovitz, A. R. Furgiuele, L. J. Brannick, J. C. Burke, and B. N. Craver, *Nature*, **200**, 369 (1963).

TABLE I

SUBSTITUTED 2,3-DIHYDRO-1,5-BENZOTHIAZEPIN-4(5H)-ONES AND RELATED COMPOUNDS



No.	Class	R	A or R′	Mp, °C[a]	Yield, %[b]	Formula[c]	Antimuricide[d] ED_{50}, mg/kg	Rotarod[d] ED_{50}, mg/kg	Rotarod/antimuricide ratio
1		$(CH_2)_2N(CH_3)_2$ (+)	C_6H_5	249–251	57	$C_{19}H_{23}ClN_2OS$	17.5	34	1.9
2		$(CH_2)_2N(CH_3)_2$ (−)	C_6H_5	249–251	70	$C_{19}H_{23}ClN_2OS$	18	39	2.2
3		$(CH_2)_3NC_4H_8NCH_2CH_2OH$[e]	C_6H_5	212–214	34	$C_{24}H_{33}Cl_2N_3O_2S$[g]	45	120	2.7
4		$(CH_2)_3NC_4H_8NC_6H_4$-2-(OCH_3)[e]	C_6H_5	165–167	7	$C_{25}H_{34}ClN_3O_2S\cdot 0.5H_2O$[f]	23	28	1.2
5		$ClCH(OH)CH_2NC_4H_8NCH_3$[e]	C_6H_5	235–237	4	$C_{23}H_{31}Cl_2N_3O_2S$[g]	45	114	2.5
6		$(CH_2)_2N(CH_3)_2$	$CH{=}CHCH_3$	141–143	64	$C_{18}H_{24}N_2O_3S$[g]	35	71	2.0
7		$(CH_2)_2N(C_2H_5)_2$	$CH{=}CHCH_3$	95–100	68	$C_{24}H_{34}N_2O_3S$[h]	28	65	2.3
8		$(CH_2)_3NC_4H_8NCH_3$[e]	$CH{=}CHCH_3$	176–178	49	$C_{20}H_{31}Cl_2N_3OS$[i]	22	47	2.1
9	II	$(CH_2)_2N(CH_3)_2$	1	271–273	37	$C_{19}H_{23}ClN_2OS$[j]	10.2	18.5	1.8
10	II	$(CH_2)_2N(C_2H_5)_2$	1	213–215	60	$C_{21}H_{27}ClN_2OS$	12.7	23.5	1.9
11	II	$(CH_2)_3N(CH_3)_2$	1	280–282	80	$C_{20}H_{25}ClN_2OS$	19.8	38.5	1.9
12	II	$(CH_2)_3NC_4H_8NCH_3$[e]	1	265–267	41	$C_{23}H_{31}Cl_2N_3OS$[i]	25	45	1.8
13	III	$(CH_2)_2N(CH_3)_2$	0	201–203	83	$C_{18}H_{21}ClN_2OS$	17.5	45	2.6
14	III	$(CH_2)_2N(C_2H_5)_2$	0	191–193	22	$C_{20}H_{25}ClN_2OS$	24.8	43	1.7
15	III	$(CH_2)_2NC_4H_8O$[e]	0	130–135	88	$C_{20}H_{23}ClN_2O_2S\cdot H_2O$[f]	>50	[k]	
16	III	$(CH_2)_3N(CH_3)_2$	0	206–208	83	$C_{19}H_{23}ClN_2OS$	25	55	2.2
17	IV	$(CH_2)_2N(CH_3)_2$	CH_3	182–184	49	$C_{19}H_{23}ClN_2OS$	19	23.5	1.2
18	IV	$(CH_2)_3N(CH_3)_2$	CH_3	143–145	54	$C_{20}H_{27}ClN_2OS$	35	[k]	
19	IV	$(CH_2)_2N(CH_3)_2$	C_2H_5	179–181	65	$C_{20}H_{27}ClN_2OS$	25	21.5	0.8
20	IV	$(CH_2)_3N(CH_3)_2$	$CH{=}CHC_6H_5$	154–156	46	$C_{27}H_{31}ClN_2OS$	23	40	1.7

[a] Crystallization solvents: EtOH, 1–**3** and **9**–**11**; MeCN, **8**, **13**, **14**, **16**, **17**, and **19**; *i*-PrOH, **5**, **6**, and **18**; butanone, **4** and **20**; EtOH–ether, **7**; MeOH, **12**; and H_2O, **15**. [b] These yields are the result of a single experiment. The alkylations were carried out in toluene using $NaNH_2$ and the basically substituted alkyl bromides (**6** at room temperature for 20 hr, **8** and **12** at 110° for 1 hr, **9** at 50–70° for 5 hr, and **11** at 110° for 3 hr) or the corresponding chlorides (**7** at 60–70° for 5 hr, and **10** and **17**–**20** at 110° for 3–5 hr). In the case of **5**, the alkylation with epibromohydrin was carried out at 35–40° for 6 hr and the resulting intermediate was heated with excess N-methylpiperazine for 8 hr. [c] Reference compounds (ED_{50} for antimuricide and rotarod and rotarod/antimuricide ratio): I (R′ = C_2H_5), R = $(CH_2)_2N(CH_3)_2$ (15, 32, 2.1), R = $(CH_2)_3N(CH_3)_2$ (19, 35, 1.8), and R = $(CH_2)_3NC_4H_8NCH_3$[d] (13, 44, 3.4). [d] NC_4H_8N = piperazino and NC_4H_8O = morpholino. [e] Dihydrochloride. [f] *Anal.* C, H. [g] Oxalic acid salt. *Anal.* C, H, N. [h] Citric acid salt. *Anal.* C, H, N, S. Prior to conversion to the citrate, the free base was distilled at 175–180° (0.3 mm). *Anal.* ($C_{18}H_{26}N_2OS$) N, S. [i] Base mp 125–127° (from hexane). *Anal.* N. [j] Product was previously crystallized from *i*-PrOH as a solvate, mp 114–118°. This material was obtained by evaporation of a 10% aqueous solution of the solvate to dryness under reduced pressure. [k] Compound was not evaluated. [l] All compounds except **6** and **7** were analyzed for Cl, N unless otherwise noted.

blocked the instinctive response of the animal to kill mice,[6] Ia was administered to rats showing this killing response and was found to block this action at nondebilitating doses.[7] Other antidepressants, such as imipramine and amitriptyline, and *d*-amphetamine produced the same inhibitory action.[8] Because depressant compounds would be expected to decrease or inhibit the killing response by impairing the mobility of the rat, the depressant effect of these compounds was measured in the rat using the rotarod procedure[8] and the ratio of the effective dose in the rotarod test to the effective dose inhibiting the mouse-killing response (antimuricide) was determined. A ratio significantly greater than 1.0 indicates a selective antimuricide response, whereas a ratio of less than one indicates a nonspecific antimuricide effect due to depressant activity. These test procedures were used for screening a series of potential antidepressants for candidate compounds for further pharmacological evaluation. The results of these tests are included in Table I. Two of these products, **9** and **10**, were slightly more active than Ia in the antimuricide test. Each of the optical isomers of Ia (**1** and **2**) had essentially the same antimuricide activity and toxicity as the racemic mixture.

Because of their structural similarity to the serotonin inhibitor, 2-(3-dimethylaminopropylthio)cinnamanilide,[9] **17**–**20** were tested by the isolated rat uterus procedure. Each of the four compounds exhibited antiserotonin activity but they were less active than the above reference material.

Experimental Section

Melting points are corrected. Optical rotations were measured on 1% aqueous solutions using a Perkin-Elmer 141 polarimeter. The infrared spectra of all of these compounds were in agreement with the assigned structures. Where analyses are indicated only by symbols of the elements analytical results obtained for those elements were within ±0.4% of the theoretical values.

Resolution of Thiazesim (Ia).—A solution of 326 g (1.0 mole) of the free base of Ia[1] in 600 ml of MeOH was treated with a solution of 150.0 g (1.0 mole) of (+)-tartaric acid in 600 ml of MeOH. After cooling the mixture for several days, the crystalline product was filtered and dried in a desiccator to give 340.0 g of material, $[\alpha]^{28}D$ +16°. Concentration of the filtrate gave 129.0 g of material, $[\alpha]^{28}D$ −82°. By repeated crystallizations

(6) P. Karli, *Behaviour* (Leiden), **10**, 81 (1956).

(7) Z. P. Horovitz, P. W. Ragozzino, and R. C. Leaf, *Life Sci.*, **4**, 1969 (1965).

(8) Z. P. Horovitz, J. J. Piala, J. P. High, J. C. Parke, and R. C. Leaf, *Intern. J. Neuropharmacol.*, **5**, 405 (1966).

(9) J. Krapcho, E. R. Spitzmiller, C. F. Turk, and J. Friel, *J. Med. Chem.*, **7**, 376 (1964).

of these solids from water (2 ml/g at 67°), from which the (−)-base (+)-tartrate crystallized as a hydrate, there was obtained 199 g of product, $[\alpha]^{28}D$ −312°. The latter was converted to the HCl salt (138 g) and purified by crystallization from 1.6 l. of EtOH to give 126 g of **2** as a colorless material, $[\alpha]^{28}D$ −446°.

After evaporation of the aqueous mother liquors at reduced pressure and trituration of the residues with EtOH, there was obtained 192.5 g of the (+)-base (+)-tartrate. This material was crystallized from 3.1 l. of MeOH to give 154 g of product, $[\alpha]^{28}D$ +340°. The latter was converted to the HCl salt (117 g) and purified by crystallization from 1.4 l. of EtOH to give 106 g of **1** as a colorless material, $[\alpha]^{28}D$ +449°.

5-(3-Chloropropyl)-2,3-dihydro-2-phenyl-1,5-benzothiazepin-4(5H)-one.—To a solution of K (8.0 g, 0.2 g-atom) in 500 ml of liquid NH_3 was added 55.0 g (0.22 mole) of finely divided 2,3-dihydro-2-phenyl-1,5-benzothiazepin-4(5H)-one.[9] The resulting pale yellow slurry was stirred for 1 hr and treated with 40.0 g (0.25 mole) of 1-bromo-3-chloropropane. This mixture was stirred for 3 hr in the cooling bath and the solvent was allowed to evaporate. The residue was triturated with ether and filtered from the solid (34 g; after trituration with H_2O, the recovered starting material weighed 12.0 g, mp 176–178°). The filtrate was concentrated under reduced pressure and the residue (64 g) crystallized from 20 ml of *i*-PrOH to give 30 g (54%, based on recovered starting material) of colorless product, mp 95–98°. The analytical sample, mp 102–104°, was recrystallized from *i*-PrOH. *Anal.* ($C_{18}H_{18}ClNOS$) Cl, N.

Conversion of this material to the corresponding iodo analog, followed by treatment with 1-(2-hydroxyethyl)- and 1-(*o*-methoxyphenyl)piperazine in the usual manner gave **3** and **4** of Table I.

Alkylation of the above nucleus with 3-dimethylaminopropyl bromide using $LiNH_2$ in liquid NH_3 in the above manner gave 5-(3-dimethylaminopropyl)-2,3-dihydro-2-phenyl-1,5-benzothiazepin-4(5H)-one as the only reaction product. The HCl salt melted at 204–206° (from MeCN). In our previous preparation[9] we obtained this material melting at 127–129° (from butanone). After recrystallization of the latter product from MeCN, it melted at 204–206°.

2,3-Dihydro-2-propenyl-1,5-benzothiazepin-4(5H)-one.—A mixture of 250.0 g (2.0 moles) of 2-aminobenzenethiol, 224.0 g (2.0 moles) of sorbic acid, 50 ml of DMF, and 1 l. of PhMe was stirred and refluxed for 12 hr (about 24 ml of H_2O was collected during this period). About 700 ml of solvent was then distilled, and the residue was cooled and washed (cold H_2O, dilute HCl, H_2O). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure, and the residue (398 g) was digested with 500 ml of hot hexane and cooled. The semisolid was then crystallized from 300 ml of $(i\text{-Pr})_2O$ to give 118 g of pale yellow product. Subsequent crystallizations from MeCN and from *i*-PrOH gave 71.0 g (16%) of nearly colorless product: mp 141–142°; λ_{max}^{Nujol} 3.35, 5.99 μ. *Anal.* ($C_{12}H_{13}NOS$) N, S.

2-{[α-(Nitromethyl)benzyl]thio}benzoic Acid.—A mixture of 100 g (0.66 mole) of thiosalicylic acid, 100 g (0.66 mole) of β-nitrostyrene, and 150 ml of EtOH was heated and the resulting solution refluxed for 3 hr. The hot solution was diluted with 15 ml of H_2O and cooled, and the crystalline product was washed with cold 95% EtOH to give 167.7 g (84%) of colorless material, mp 150–152°. *Anal.* ($C_{15}H_{13}NO_4S$) N, S.

Methyl 2-{[α-(Nitromethyl)benzyl]thio}benzoate.—A suspension of 167.7 g (0.55 mole) of the above acid, 300 ml of $CHCl_3$, and 300 ml of $SOCl_2$ was refluxed for 3 hr. The bulk of the volatile material was distilled, and the remainder was removed under reduced pressure leaving 176.1 g of the intermediate acid chloride as a pale yellow solid, mp 89–91°. This material was heated with 600 ml of MeOH and the resulting solution was refluxed for 6 hr and cooled to give 162.8 g (93%) of colorless product, mp 100–102°. *Anal.* ($C_{16}H_{15}NO_4S$) N, S.

Methyl 2-{[α-(Aminomethyl)benzyl]thio}benzoate.—A mixture of 130.0 g (0.41 mole) of the above material, 350 g (1.5 moles) of $SnCl_2 \cdot 2H_2O$, 1 l. of MeOH, and 350 ml of AcOH was stirred and refluxed for 3 hr. The reaction mixture was then partly concentrated (500 ml collected), cooled, and treated portionwise with a cold solution of 700 g of K_2CO_3 in 1 l. of H_2O. Ether (600 ml) and $CHCl_3$ (200 ml) were added and the mixture was shaken. The layers were separated and the aqueous phase was extracted twice with the same Et_2O–$CHCl_3$ mixture. The organic phases were combined and dried ($MgSO_4$) and the solvents were removed under reduced pressure to give 110 g of residue. The latter was dissolved in 700 ml of ether (small quantity of insoluble oil was discarded) and treated with 300 ml of ether containing an equivalent quantity of HCl to give an oil. Trituration of this oil with fresh ether and removal of the remaining solvent under reduced pressure gave 98.5 g of the hydrochloride as a foamlike solid. A suspension of this material in 500 ml of ether was treated with a solution of 45 g of K_2CO_3 in 80 ml of H_2O to give 83.7 g (71%) of base. This material gave a crystalline salt with oxalic acid, mp 153–155° (from MeCN). *Anal.* ($C_{18}H_{19}NO_6S$) N, S; neut equiv: calcd, 189; found, 190.

3,4-Dihydro-2-phenyl-2H-1,4-benzothiazepin-5-one.—The above amine (68.6 g, 0.24 mole) was heated at 130–180° for 1 hr, 5 g of MeOH being collected during this period. The residue was rapidly distilled [bp 190–240° (0.2–0.5 mm)] and the syrupy orange distillate (50.4 g) was digested with 70 ml of *i*-PrOH to give 31.3 g of pale yellow product, mp 180–183°. After crystallization from 330 ml of MeCN, the colorless product weighed 28.2 g (46%); mp 186–188°; λ_{max}^{Nujol} 3.25, 5.95, 6.35 μ. *Anal.* ($C_{15}H_{13}NOS$) N, S.

N-Benzylidene-4-(2-aminoethyl)morpholine.—A mixture of 68.0 g (0.64 mole) of PhCHO, 83.5 g (0.64 mole) of 4-(2-aminoethyl)morpholine, and 150 ml of PhH was stirred and refluxed for 2 hr, 11 ml of H_2O being collected during this period. The solvent was distilled and the residue was fractionated to give 135.3 g (97%) of a pale yellow liquid, bp 118–123° (0.1 mm). *Anal.* ($C_{13}H_{18}N_2O$) N.

Interaction of equivalent quantities of PhCHO and 3-aminopropanol gave a 93% yield of N-benzylidene-3-aminopropanol, bp 127–128° (2 mm). *Anal.* ($C_{10}H_{13}NO$) N.

The benzylidene derivatives of dimethyl- and diethylaminoethylamines[10] were prepared in the same manner.

2,3-Dihydro-3-(morpholinoethyl)-2-phenyl-4H-1,3-benzothiazin-4-one.—A solution of 80.0 g (0.36 mole) of the above morpholine in 150 ml of xylene was added to a suspension of 56.0 g (0.35 mole) of thiosalicylic acid in 200 ml of xylene and the mixture was stirred and refluxed for 2 hr, 5.5 ml of H_2O being collected during this period. The mixture was cooled, diluted with 500 ml of $CHCl_3$, washed (H_2O, 5% $NaHCO_3$), and dried ($MgSO_4$). The solvent was evaporated and the residue was triturated with 200 ml of hexane to give 112.6 g of product. After crystallization from 300 ml of *i*-PrOH, the nearly colorless material weighed 108.3 g (87%), mp 131–133°, λ_{max}^{Nujol} 6.10 μ. *Anal.* ($C_{20}H_{22}N_2O_2S$) N. The HCl salt of this material is **15**.

The preparation of **13**, [bp 180–185° (0.2 mm)] was carried out in a similar manner. In the case of **14**, methyl thiosalicylate and the imine were heated at 175–180° for 1 hr and the free base then distilled at 175–185° (0.2 mm). The latter was purified as a citrate salt, mp 175–177° (from MeCN), and then converted to the HCl salt (**14**).

2,3-Dihydro-3-(3-hydroxypropyl)-2-phenyl-4H-1,3-benzothiazin-4-one.—A mixture of equivalent quantities of N-benzylidene-3-aminopropanol, thiosalicylic acid, and xylene was refluxed for 3 hr and diluted with $CHCl_3$, and the product was isolated as described above to give 53% yield of colorless material: mp 125–127° (from MeCN); λ_{max}^{Nujol} 2.94, 6.20 μ. *Anal.* ($C_{17}H_{17}NO_2S$) N, S.

3-(3-Chloropropyl)-2,3-dihydro-2-phenyl-4H-1,3-benzothiazin-4-one.—The above material was added to a solution of $SOCl_2$ in $CHCl_3$ and refluxed for 3 hr, and the solvent was evaporated under reduced pressure. The residue was triturated with hexane to give a 96% yield of product, mp 134–136°. The analytical sample was crystallized from MeCN; mp 134–136°. *Anal.* ($C_{17}H_{16}ClNOS$) Cl. This material was treated with NaI and $HN(CH_3)_2$ to give **16**.

2′-(Benzylthio)propionanilide.—A mixture of 40.0 g (0.18 mole) of 2-(benzylthio)aniline[11] and 80 ml of propionic anhydride was refluxed for 10 min. The propionic acid and excess anhydride were removed under reduced pressure and the residue was fractionated to give 60.0 g (77%) of nearly colorless liquid, bp 180–183° (0.2 mm). *Anal.* ($C_{16}H_{17}NOS$) N, S.

The acetyl derivative of 2-(benzylthio)aniline[11] was also prepared in the above manner. A small quantity of the diacetyl compound was isolated from the reaction, mp 88–90° (from *i*-Pr_2O). *Anal.* ($C_{17}H_{17}NO_2S$) C, H, N.

(10) A. R. Surrey, *J. Am. Chem. Soc.*, **71**, 3105 (1949).

(11) A. Sieglitz and H. Koch, *Ber.*, **58**, 78 (1925). We obtained this material by alkylation of the sodium salt of 2-aminobenzenethiol with benzyl chloride in *i*-PrOH.

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.* ($C_{22}H_{19}NOS$) 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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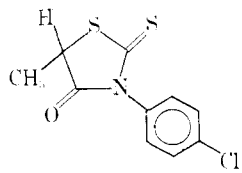
3-(*p*-Chlorophenyl)-5-methylrhodanine (**1**) was reported to exhibit antimalarial activity in preliminary screening against *Plasmodium berghei* in mice.[2] Therefore, an authentic sample of I and several related com-



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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. Wibler, Jr., *J. Am. Chem. Soc.*, **78**, 384 (1956).

(4) S. R. Andreasch and A. Zipser, *Monatsh.*, **25**, 159 (1904).

(5) B. K. Raval and J. J. Trivedi, *J. Indian Chem. Soc.*, **89**, 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.