H-3'), 4.10 (t, 2 H, J = 6.2 Hz, CH_2N), 3.98 (br s, 1 H, H-4'), 3.63 (t, 5 H, J = 6.2 Hz, CH_2-5' and CH_2Cl), 2.34 (m, 2 H, H-2'), 1.79 (s, 3 H, CH_3-5). Anal. ($C_{13}H_{18}ClN_5O_6$) C, H, N.

3'-(3-Methylureido)-3'-deoxythymidine (9). Methyl isocyanate (0.13 g, 2.2 mmol) was added slowly to a solution of 7 (0.48 g, 2.0 mmol) in 15 mL of MeOH. The solution was stirred at 0 °C for 1 h, during which period white crystals precipitated out. The product was collected by filtration, washed with cooled MeOH, and dried to give 0.54 g (90%). The compound softened at 114 °C and effervesced at 120 °C: TLC R_f 0.38 ($CHCl_3$–EtOH, 4:1); NMR δ 11.29 (s, 1 H, NH-3), 7.75 (s, 1 H, H-6), 6.39 (d, 1 H, J = 7.5 Hz, NH-3'), 6.13 (t, 1 H, J = 6.6 Hz, H-1'), 5.74 (q, 1 H, J = 4.4 Hz, CH_3NH), 5.07 (t, 1 H, J = 4.4, OH-5'), 4.15 (m, 1 H, H-3'), 3.71 (m, 1 H, H-4'), 3.64 (dd, 1 H, J_{gem} = 12.4 Hz, H-5''), 3.53 (dd, 1 H, J_{gem} = 12.4 Hz, $J_{5',OH\text{-}5'}$ = 4.4 Hz, H-5'), 2.55 (d, 3 H, J = 4.4 Hz, CH_3N), 2.12 (m, 2 H, H-2'), 1.78 (s, 3 H, CH_3-5). Anal. ($C_{12}H_{18}N_4O_5$) C, H, N.

3'-(3-Methyl-3-nitrosoureido)-3'-deoxythymidine (11). Sodium nitrite (0.15 g, 2.2 mmol) was added slowly to an ice-cooled solution of **9** (0.48 g, 1.6 mmol) in 15 mL of 80% aqueous acetic acid. The reaction mixture was stirred at 0 °C for 5 h and then treated with AG 50W-X8 (H^+) resin (3 g). The mixture was stirred for another 30 min and then filtered. The filtrate was evaporated to dryness in vacuo below 35 °C to yield a residue which was crystallized from EtOH. The product was isolated by filtration, washed with cooled EtOH and ether, and dried to afford 0.28 g (53%) of pale yellow crystals. Upon heating the compound changed into a white crystalline mass around 135 °C and then decomposed at 159 °C: UV λ_{max} (EtOH) 265 nm (ϵ 12000); UV λ_{min} (EtOH) 238 nm; IR (KBr) ν_{max} 1528 cm^{-1} with shoulder at 1510 cm^{-1} (NH bending and C–NO stretching); NMR δ 11.31 (s, 1 H, NH-3), 9.14 (d, 1 H, J = 8.0 Hz, NH-3'), 7.81 (s, 1 H, H-6), 6.26 (t, 1 H, J = 6.6 Hz, H-1'), 5.11 (t, 1 H, J = 4.9 Hz, OH-5'), 4.57 (m, 1 H, H-3'), 3.99 (m, 1 H, H-4'), 3.69 (m, 2 H, H-5'), 3.09 (s, 3 H, CH_3N), 2.34 (m, 2 H, H-2'), 1.80 (s, 3 H, CH_3-5). Anal. ($C_{12}H_{17}N_5O_6$) H; C: calcd, 44.04; found, 42.94. N: calcd, 21.40; found, 20.91.

Probably due to the thermal instability of the compound, a satisfactory elemental analysis has not been obtained. However, the UV, IR, and NMR spectroscopic data are consistent with the assigned structure, and TLC indicated homogeneity in three solvent systems: (1) R_f 0.78 ($CHCl_3$–EtOH, 4:1), (2) R_f 0.88 (AcOEt–EtOH, 4:1), (3) R_f 0.25 ($CHCl_3$–i-PrOH, 6:1).

Acknowledgment. The authors wish to express their appreciation to Ms. Jung Ja Lee and Mrs. C. Chai for their excellent technical assistance. We thank Dr. H. B. Wood of the Drug Development Branch, Division of Cancer Treatment, National Cancer Institute, for supplying a sample of 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) for test purposes in this work. This research was supported by U.S. Public Health Service Research Grant CA-05262 from the National Cancer Institute. We wish to acknowledge the support of the Southern New England High Field NMR Facility made possible by a grant from the Biotechnology Resources Program of the National Institutes of Health (RR-798).

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Modifications of Primaquine as Antimalarials. 2. 5-Phenylthio and 5-Anilino Derivatives of Primaquine

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Received July 13, 1977

A number of 5-phenylthio and 5-anilino derivatives of primaquine have been prepared which are less toxic but less active than primaquine itself in murine and monkey antimalarial screens. It is apparent that the toxicity of primaquine can be diminished by introduction at position 5 of phenylthio, anilino, or phenoxy groups. However, the best hope for concomitant retention of high activity would seem to reside with the phenoxy moieties.

The first paper[1] in this series described a group of 5-phenoxyprimaquines. Concurrently with the phenoxy derivatives, as part of an accelerated program which precluded the wait for antimalarial screening data, we prepared the 5-phenylthio and 5-anilino analogues discussed in the present paper.

Chemistry. The preparative route (Scheme I) was similar to that described in paper 1 and its various stages are tabulated in Table I and exemplified in the Experimental Section.

Biology. Table II compares primaquine with some of its 5-phenylthio and 5-anilino derivatives in the radical curative antimalarial screen (*Plasmodium cynomolgi*, rhesus monkey). All of the phenylthio primaquines (**11a–h**) were curative. However, the best of these (**11c** and **11g**), with cures at 1 mg/kg, were less active than

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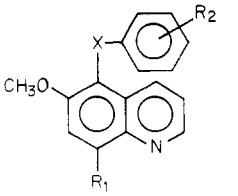
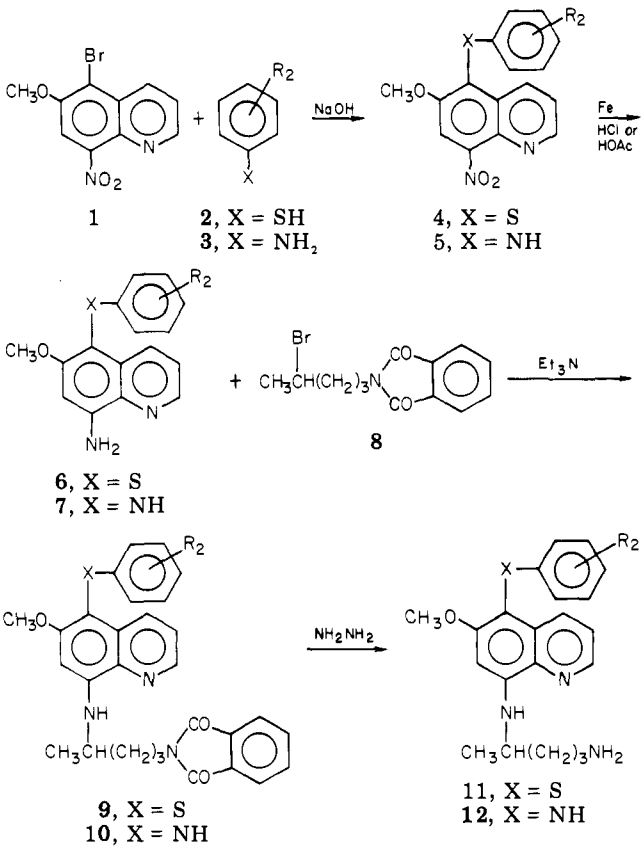
Table I. 5-Substituted Primaquines and Their Precursors



Compd	R_1	X	R_2	Mp, °C (solvent)	Yield, %	Formula[a]
4a	NO_2	S	2-Cl	183-184 (Me_2CO-MeOH)	63	$C_{16}H_{11}ClN_2O_3S$
4b	NO_2	S	3-Cl	129-130 (Me_2CO-MeOH)	90	$C_{16}H_{11}ClN_2O_3S$
4c	NO_2	S	4-Cl	160-161.5 (MeOH-Me_2CO)	87	$C_{16}H_{11}ClN_2O_3S$
4d	NO_2	S	3,4-Cl_2	159.5-160.5 (EtOH)	92	$C_{16}H_{10}Cl_2N_2O_3S$
4e	NO_2	S	2,5-Cl_2	232-234 (C_6H_6)	97	$C_{16}H_{10}Cl_2N_2O_3S$
4f	NO_2	S	4-CH_3O	123-124 (C_6H_6)	82	$C_{17}H_{14}N_2O_4S$
4g	NO_2	S	3-CF_3	141-142.5 (EtOH)	81	$C_{17}H_{11}F_3N_2O_3S$
4h	NO_2	S	3,4-Benzo	168-170 (C_6H_6)	89	$C_{20}H_{14}N_2O_3S$
5a	NO_2	NH	4-Cl	196-198 (EtOH)	71	$C_{16}H_{12}ClN_3O_3$
5b	NO_2	NH	3-CF_3	187-189 (MeOH)	97	$C_{17}H_{12}F_3N_3O_3$
6a	NH_2	S	2-Cl	157-159 (MeOH)	60[c]	$C_{16}H_{13}ClN_2OS$
6b	NH_2	S	3-Cl	125-126 (MeOH)	76[c]	$C_{16}H_{13}ClN_2OS$
6c	NH_2	S	4-Cl	110-111 (MeOH)	74[c]	$C_{16}H_{13}ClN_2OS$
6d	NH_2	S	3,4-Cl_2	147.5-148.5 (C_6H_6-hexane)	73[b]	$C_{16}H_{12}Cl_2N_2OS$
6e	NH_2	S	2,5-Cl_2	173-175 (C_6H_6-hexane)	45[b]	$C_{16}H_{12}Cl_2N_2OS$
6f	NH_2	S	4-CH_3O	91-92 (hexane)	86[b]	$C_{17}H_{16}N_2O_2S$
6g	NH_2	S	3-CF_3	98-99 (MeOH-H_2O)	70[c]	$C_{17}H_{13}F_3N_2OS$
6h	NH_2	S	3,4-Benzo	190-191 (C_6H_6)	72[b]	$C_{20}H_{16}N_2OS$
7a	NH_2	NH	4-Cl	166-167 (Et_2O-MeOH)	90[c]	$C_{16}H_{14}ClN_3O$
7b	NH_2	NH	3-CF_3	179-180 (MeOH)	90[c]	$C_{17}H_{14}F_3N_3O$
9a	$CH_3CH(NH\text{-})(CH_2)_3N(CO)_2$$C_6H_4$	S	2-Cl	134-136 (ligroine)	62	$C_{29}H_{26}ClN_3O_3S$
9b	$CH_3CH(NH\text{-})(CH_2)_3N(CO)_2$$C_6H_4$	S	3-Cl	113.5-115 (ligroine)	26	$C_{29}H_{26}ClN_3O_3S$
9c	$CH_3CH(NH\text{-})(CH_2)_3N(CO)_2$$C_6H_4$	S	4-Cl	147-147.5 (ligroine)	26	$C_{29}H_{26}ClN_3O_3S$
9d	$CH_3CH(NH\text{-})(CH_2)_3N(CO)_2$$C_6H_4$	S	3,4-Cl_2	99-101 (EtOH)	20	$C_{29}H_{25}Cl_2N_3O_3S$
9e	$CH_3CH(NH\text{-})(CH_2)_3N(CO)_2$$C_6H_4$	S	2,5-Cl_2	129-132 (Et_2O)	33	$C_{29}H_{25}Cl_2N_3O_3S$
9f	$CH_3CH(NH\text{-})(CH_2)_3N(CO)_2$$C_6H_4$	S	4-CH_3O	126-128 (ligroine)	57	$C_{30}H_{29}N_3O_4S$
9g	$CH_3CH(NH\text{-})(CH_2)_3N(CO)_2$$C_6H_4$	S	3-CF_3	154-157 (EtOH-ligroine)	53	$C_{30}H_{27}ClF_3N_3O_3S$[d]
9h	$CH_3CH(NH\text{-})(CH_2)_3N(CO)_2$$C_6H_4$	S	3,4-Benzo	105-109 (Et_2O)	37	$C_{33}H_{29}N_3O_3S$
10a	$CH_3CH(NH\text{-})(CH_2)_3N(CO)_2$$C_6H_4$	NH	4-Cl	127-129 (MeOH)[i]	40	$C_{29}H_{27}ClN_4O_3$
10b	$CH_3CH(NH\text{-})(CH_2)_3N(CO)_2$$C_6H_4$	NH	3-CF_3	168-169 (MeOH-Me_2CO)	34	$C_{30}H_{27}F_3N_4O_3$
11a	$CH_3CH(NH\text{-})(CH_2)_3NH_2$	S	2-Cl	118-121[e]	80	$C_{21}H_{24}ClN_3OS$
11b	$CH_3CH(NH\text{-})(CH_2)_3NH_2\cdot H_2O$	S	3-Cl	67-70 (Et_2O)	98	$C_{21}H_{26}ClN_3O_2S$
11c	$CH_3CH(NH\text{-})(CH_2)_3NH_2\cdot H_2O$	S	4-Cl	73-75[e]	64	$C_{21}H_{26}ClN_3O_2S$[h]
11d	$CH_3CH(NH\text{-})(CH_2)_3NH_2\cdot H_2O$	S	3,4-Cl_2	65-67[f]	72	$C_{21}H_{25}Cl_2N_3O_2S$
11e	$CH_3CH(NH\text{-})(CH_2)_3NH_2$	S	2,5-Cl_2	115-117 (Et_2O)	90	$C_{21}H_{23}Cl_2N_3OS$
11f	$CH_3CH(NH\text{-})(CH_2)_3NH_2\cdot$citrate	S	4-CH_3O	Indefinite (EtOH)	35	$C_{28}H_{35}N_3O_9S$
11g	$CH_3CH(NH\text{-})(CH_2)_3NH_2\cdot 0.5H_2O$	S	3-CF_3	84-89[g]	87	$C_{22}H_{25}F_3N_3O_{1.5}S$
11h	$CH_3CH(NH\text{-})(CH_2)_3NH_2\cdot H_2O$	S	3,4-Benzo	120-125 (Et_2O)	78	$C_{25}H_{29}N_3O_2S$
12a	$CH_3CH(NH\text{-})(CH_2)_3NH_2$	NH	4-Cl	101-103 (petr ether)	82	$C_{21}H_{25}ClN_4O$
12b	$CH_3CH(NH\text{-})(CH_2)_3NH_2\cdot 2H_3PO_4\cdot H_2O$	NH	3-CF_3	268-271 (EtOH)	86	$C_{22}H_{33}F_3N_4O_{10}P_2$

[a] All compounds were analyzed for C, H, and N. [b] Method A, Experimental Section. [c] Method B, Experimental Section. [d] Isolated as the hydrochloride. [e] Purified by trituration with Et_2O. [f] Purified by trituration with Et_2O-petroleum ether (bp 20-40 °C). [g] Purified by trituration with petroleum ether (bp 20-40 °C). [h] C: calcd, 60.05; found, 60.66. [i] A dimorph (10a′), mp 118-120 °C, was isolated from EtOH (C, H, N).

Scheme I



primaquine with 10/12 cures at 0.5 mg/kg. The anilino derivative **12b** permitted early relapses at 1 and 10 mg/kg.

With the exception of the 4-$CH_3OC_6H_4S$ compound (**11f**), all of the derivatives were nontoxic and inactive, at the highest level tested (640 mg/kg), in the schizonticidal screen (*Plasmodium berghei*, mouse).[1] Compound **11f** combined nontoxicity with weak activity at 320 and 640 mg/kg. By contrast, primaquine caused toxic deaths at 160 mg/kg.

It is apparent that the toxicity of primaquine can be diminished by introduction at position 5 of phenylthio, anilino, or phenoxy groups. However, the best hope for concomitant retention of high activity would seem to reside with the phenoxy moieties.

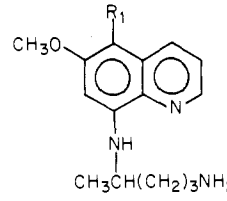
Experimental Section

Melting points were determined in capillary tubes in an electrically heated Thiele-Dennis apparatus and are uncorrected. Elemental analyses (Micro-Analysis, Inc., Wilmington, Del.) were within ±0.4% of the theoretical values unless otherwise noted. Satisfactory IR spectra were obtained for all compounds as Nujol mulls on a Perkin-Elmer 137B Infracord. The starting material, 3-trifluoromethylbenzenethiol, was provided by Dr. R. E. Strube of WRAIR. The remaining starting materials (**2** and **3**) were commerically available.

5-(3,4-Dichlorophenylthio)-6-methoxy-8-nitroquinoline (4d). A suspension of 23 g (0.081 mol) of **1**[3] in 100 mL of EtOH was stirred under reflux while a solution of 14.5 g (0.08 mol) of 3,4-dichlorothiophenol, 50 mL of EtOH, 3.5 g (0.087 mol) of NaOH, and 15 mL of H_2O was added rapidly. After stirring for an additional hour under reflux, the suspension was cooled to 0 °C and filtered. The solid was washed with warm H_2O, in a Waring blendor, and dried to give 28.5 g of **4d**, mp 155.5–158 °C.

5-(3-Trifluoromethylanilino)-6-methoxy-8-nitroquinoline (5b). A stirred mixture of **1**[3] (30 g, 0.1 mol) and 3-trifluoromethylaniline (50 g, 0.31 mol) was heated at a bath temperature of 120 °C for 3 h and allowed to cool. The resulting orange solid was stirred with MeOH (150 mL) to give 36 g of **5b**, mp 183–185 °C.

Table II. Radical Curative Antimalarial Activity (*P. cynomolgi*, Rhesus)[a]



Compd[b]	R_1	R_2	Cures/(no. of animals) or day of relapse[c] 0.5 mg/kg	1 mg/kg	10 mg/kg
Primaquine	H	$2H_3PO_4$	10/12		
11a	2-ClC_6H_4S			15	1/1
11b	3-ClC_6H_4S	H_2O		12	1/1
11c	4-ClC_6H_4S	H_2O	0/3	1/5	2/2
11d	3,4-$Cl_2C_6H_3S$	H_2O		20	1/1
11e	2,5-$Cl_2C_6H_3S$			12	1/1
11g	3-$CF_3C_6H_4S$	$0.5H_2O$	30	1/1	
11h	2-Naphthyl-S	H_2O		27	1/1
12b	3-$CF_3C_6H_4NH$	$2H_3PO_4 \cdot H_2O$		7	8

[a] Tests were carried out by Dr. L. H. Schmidt, Southern Research Institute, Birmingham, Ala., using sporozoite induced, *P. cynomolgi* infected rhesus monkeys.[2] Test data were supplied by Drs. E. A. Steck, R. E. Strube, and T. R. Sweeney of Walter Reed Army Institute of Research. [b] No data available for compounds **11f** and **12a**. [c] Monkeys that do not relapse in 90 days are considered cured.

8-Amino-5-(2,5-dichlorophenylthio)-6-methoxyquinoline (6e) (Method A). A mixture of 17 g (0.045 mol) of **4e**, 500 mL of 95% EtOH, 20 g of Fe filings, and 2 mL of concentrated HCl was heated under reflux for 44 h and filtered hot. The filtrate was concentrated in vacuo to give 7 g of **6e** as yellow crystals, mp 172–175 °C.

8-Amino-6-methoxy-5-(3-trifluoromethylphenylthio)-quinoline (6g) (Method B). A stirred mixture of 3.8 g (0.01 mol) of **4g**, 2.2 g of Fe filings, 30 mL of H_2O, 1 mL of HOAc, and 1 mL of dibutyl ether was heated at 100 °C for 17 h and filtered. The filtrate and the solid were thoroughly extracted with Et_2O and the combined extracts were dried and concentrated. Treatment of the concentrate with ethereal HCl gave 2.7 g of **6g** as its hydrochloride, mp 204–207 °C. Basification with NH_4OH provided **6g**.

5-(3-Chlorophenylthio)-6-methoxy-8-(1-methyl-4-phthalimidobutylamino)quinoline (9b). A stirred mixture of **6b** (6.35 g, 0.02 mol) and **8** (6 g, 0.02 mol) was heated at 155–160 °C while Et_3N (2.4 g, 0.02 mol) was added, dropwise, during 2 h. Stirring was continued at 155–160 °C for an additional 2.5 h and the mixture was allowed to cool, diluted with Me_2CO, and filtered to remove $Et_3N \cdot HBr$. The filtrate was concentrated in vacuo and the resulting thick oil was again diluted with Me_2CO to precipitate more $Et_3N \cdot HBr$. The filtrate was extracted with warm Et_2O and the extract was concentrated to 100 mL. On cooling and standing, the concentrate produced 2.7 g of **9b**, mp 113–114 °C.

An improved phthalimidoalkylation method was detailed in paper 1.[1]

8-(4-Amino-1-methylbutylamino)-5-(3-chlorophenylthio)-6-methoxyquinoline Hydrate (11b). A stirred mixture of **9b** (2.1 g, 0.0039 mol), 95% hydrazine (2.5 mL), EtOH (95 mL), and $CHCl_3$ (45 mL) was heated under reflux for 3 h and allowed to cool. Crystalline phthalhydrazide (0.6 g) was filtered and the filtrate was concentrated to dryness in vacuo. The residue was extracted with Et_2O, and the extract was washed with 30% KOH (2 × 50 mL) and H_2O (3 × 20 mL) and extracted with 20% HCl (3 × 50 mL) and H_2O (2 × 50 mL). The combined extracts were washed with Et_2O (2 × 100 mL) and basified with 30% KOH. The resulting yellow solid was extracted with Et_2O and the extract

was washed with H_2O and evaporated to near dryness. The oily residue was allowed to stand in a moist atmosphere until it solidified (ca. 1 h): yield 1.7 g. Purification was effected by twice dissolving in Et_2O (carbon) and concentrating.

Acknowledgment. We are grateful to Drs. E. A. Steck, R. E. Strube, and T. R. Sweeney of WRAIR for assistance, suggestions, and enthusiasm during the course of our research. This investigation was supported by the U.S. Army Medical Research and Development Command under Contract No. DADA 17-70-C-0101 and is Contribution No. 1470 from the Army Research Program on Malaria.

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[1-[3-(Phenothiazin-10-yl)propyl]-4-piperidinyl]phenylmethanones, a Novel Class of Long-Acting Neuroleptic Agents

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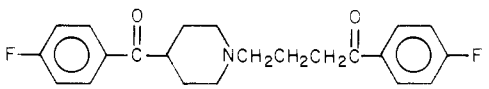
In previous studies the phenyl-4-piperidinylmethanone moiety was shown to be a neuroleptic pharmacophore. A short series of [1-[3-(phenothiazin-10-yl)propyl]-4-piperidinyl]phenylmethanones was prepared and tested for neuroleptic activity using the blockade of *d*-amphetamine lethality in aggregated mice and suppression of conditioned avoidance behavior as the end points. Most compounds were shown to be potent neuroleptic agents and two were found to possess a long duration of action.

An earlier report from this laboratory[1] described the preparation and neuroleptic activity of a series of *N*-alkyl-4-benzoylpiperidines. The structure–activity data suggested that the benzoylpiperidine moiety is a potent neuroleptic pharmacophore comparable to a butyrophenone group. One of the compounds in the series, 1,[2] which combines both pharmacophores into a single molecule has proven to be a highly effective neuroleptic agent in clinical trials in man. These results prompted us to prepare and test a short series of phenothiazine derivatives (**2–6**) which coupled the benzoylpiperidine pharmacophore with the 10-phenothiazinylpropyl group.



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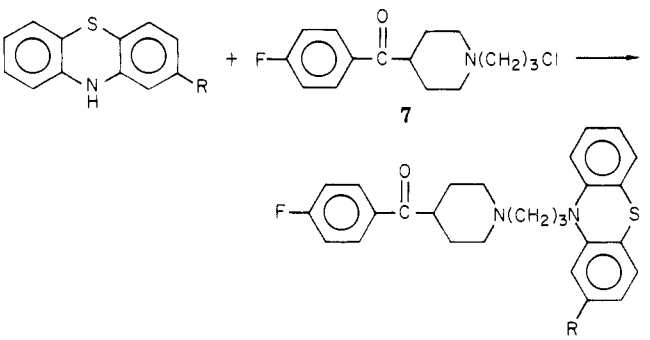
Chemistry. Compounds **2–5** (Table I) were prepared by reacting 1-(3-chloropropyl)-4-(4-fluorobenzoyl)piperidine (**7**) with the appropriately substituted phenothiazine (Scheme I). Compound **6** was prepared by reacting 2-chloro-10-(3-chloropropyl)phenothiazine (**8**) with 4-(3,4-dichlorobenzoyl)piperidine (**9**) (Scheme II). Column chromatography on Florisil, short-path distillation, or salt formation was used to purify compounds **2–6**. The intermediates **7** and **9** were prepared according to Schemes III and IV, respectively. The synthesis of **2** given in the Experimental Section is representative of the synthesis of compounds **2–6**. Compound **8** was prepared by a modification of a published synthesis of 3-chloro-10-(3-chloropropyl)phenothiazine.[3]

Compounds were tested for neuroleptic activity using blockade of *d*-amphetamine lethality in aggregated mice and suppression of conditioned avoidance behavior in trained mice as the end points. For the former method, groups of ten, adult, female mice (ICR–DUB strain) were given geometrically spaced doses of test compound at predetermined intervals (1 h to 7 days) prior to a dose of *d*-amphetamine (21 mg/kg ip) that was known to be lethal to 90% of the animals. Each group of animals was placed in a separate wire mesh cage (60 in.^{2} of floor space), and after 24 h the number of surviving animals was determined.

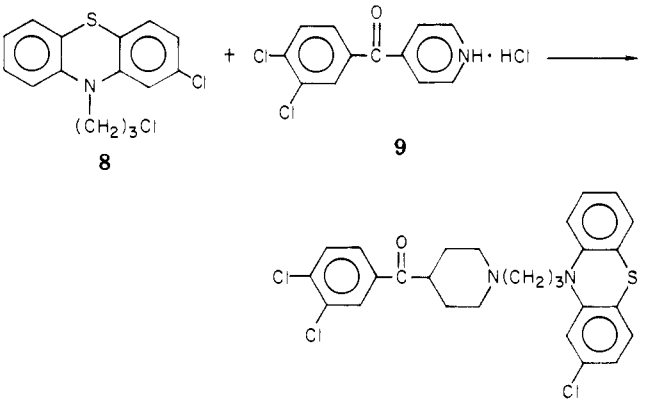
Scheme I



7

2-5

Scheme II



8

9

6

ED_{50} values were determined[4] and defined as the dose that prevented death in 50% of the mice.

Compounds **2** and **3** were as potent as the reference standards, haloperidol and chlorpromazine, when a 1-h pretreatment time was used (Table II). With longer pretreatment times, compound **2** retained its potency whereas the reference agents soon became ineffective. For example, with a 3-day pretreatment time, even doses of the reference agents approaching their LD_{50} values were

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