**carboxamide (21).**—Propionyl isocyanate (2.2 g, 0.024 mole) in 5 ml of THF was added dropwise to a suspension of 4.3 g (0.02 mole) of 1-(5-nitro-2-thiazolyl)piperazine[9] in 50 ml of THF, and the mixture was stirred at room temperature for 45 min. The solid was collected and recrystallized from EtOH to give the product.

**1-(Chloroacetyl)-4-(5-nitro-2-thiazolyl)piperazine (13).**—Chloroacetyl chloride (1.13 g, 0.01 mole) in 5 ml of THF was added dropwise to a mixture of 1-(5-nitro-2-thiazolyl)piperazine[9] (2.14 g, 0.01 mole) and $Et_3N$ (1.38 ml, 0.01 mole) in 45 ml of THF at 0°. The mixture was stirred for 3 hr at room temperature, and the solid was collected, washed with $H_2O$, and recrystallized from EtOH.

**{*o*-[(5-Nitro-2-thiazolyl)amino]phenyl}acetic Acid (17).**—To a solution of 6.3 g (0.05 mole) of 2-bromo-5-nitrothiazole in 250 ml of MeOH was added 5.0 g (0.03 mole) of $Et_3N$ and 80 ml (1 equiv) of a $H_2O$ solution of sodium *o*-aminophenylacetate. The reaction was exothermic. The mixture was allowed to stir for 4 hr, poured into about 3 l. of iced $H_2O$, and acidified with concentrated HCl. The pale green solid which formed was removed by filtration and dried. This material (3.6 g) had a broad melting point and could not be purified. The filtrate upon standing deposited a yellow solid. This material was dried (1.7 g) and recrystallized from *i*-PrOH to give 1.0 g (12%) of the product, mp 166–168° dec.

**Sodium *o*-Aminophenylacetate.**—To 1 l. of $H_2O$ vigorously stirred was added 38 g (0.306 mole) of $Na_2CO_3 \cdot H_2O$. *o*-Nitrophenylacetic acid (100 g, 0.56 mole), was added portionwise (4 drops of 2-octanol was added to suppress foam). The solution was hydrogenated over 1 g of 20% Pd–C at 24° for 16 hr. The mixture was filtered through Supercel, the yellow solution was diluted to 1475 ml, and aliquots were used as needed.

**1-(5-Nitro-2-thiazolyl)-4-(piperidinoacetyl)piperazine (28).**—Piperidine (1.63 g, 0.0192 mole) was added dropwise to 2.9 g (0.01 mole) of 1-(chloroacetyl)-4-(5-nitro-2-thiazolyl)piperazine in 45 ml of THF at 0°, and the mixture was stirred for 1 hr at room temperature. The mixture was filtered, and the filtrate was evaporated to dryness. The residue was recrystallized from EtOH.

**Benzyl ({[4-(5-Nitro-2-thiazolyl)-1-piperazinyl]carbonyl}methyl)carbamate (31).**—A solution of 2.1 g (0.01 mole) of dicyclohexylcarbodiimide in 5 ml of THF was added to a solution of 2.14 g (0.01 mole) of 1-(5-nitro-2-thiazolyl)piperazine[9] and 2.1 g (0.01 mole) of benzyloxycarbonylglycine in 30 ml of THF, and the mixture was stirred for 1 hr at room temperature. The solid was collected, washed with $Et_2O$, and recrystallized from EtOH.

**1,1′-(Sulfonyldiethylene)bis[4-(5-nitro-2-thiazolyl)piperazine] (32).**—A solution of 1.22 g (0.0103 mole) of divinyl sulfone in 12 ml of EtOH was added dropwise to a suspension of 4.4 g (0.0206 mole) of 1-(5-nitro-2-thiazolyl)piperazine in 25 ml of EtOH, and the mixture was stirred for 4 hr at room temperature. The mixture was allowed to remain at room temperature overnight and then heated under reflux for 1 hr. The product was removed by filtration and recrystallized from DMF.

**Acknowledgments.**—The authors express their appreciation to Dr. Paul E. Thompson and coworkers of these laboratories for the antiparasitic evaluation of these compounds. We also thank Dr. J. M. Vandenbelt and coworkers for the spectral studies, and Mr. Charles E. Childs and associates for the microanalyses.

## Antimalarials. Some Quinuclidine Derivatives of 7-Chloro-4-aminoquinoline and 6-Methoxy-8-aminoquinoline

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Quinuclidine is an important moiety of cinchona alkaloids. The recent availability of quinuclidinone (Aldrich) and the facile preparation of 2-methylene-3-quinuclidinone, reported earlier from our laboratories,[1] put at our disposal the suitable starting materials. These were used to incorporate this important feature of quinine as a side-chain amine in the ring systems of two well-known antimalarial drugs, chloroquine and primaquine.

**Pharmacology.**—The compounds were tested for their antimalarial activity against *Plasmodium berghei* in mice. The screening was carried out by Dr. L. Rane of the University of Miami, Miami, Fla., by the screening procedure described previously.[2] Two compounds, **1** and **2**, were found to be curative. Compound **1** cured two mice at 160 mg/kg and all five in the test at 640 mg/kg. Compound **2** showed slight activity at 160 and 320 mg/kg and cured all five mice at 640 mg/kg. All other compounds were inactive and toxic.

### Experimental Section

All melting points were determined in open capillary tubes in a Thomas–Hoover Unimelt and are uncorrected. Reference should be made to Table I for relevant information.

**7-Chloro-4-(3-ketoquinuclidinyl-2-methyleneamino)quinoline (1).**—A mixture of 7-chloro-4-aminoquinoline[3] (2.0 g, 0.011 mol) and 2-methylene-3-quinuclidinone[1] (3.0 g, 0.022 mol) was heated at 80° with stirring for 1 hr. The reaction was cooled and diluted with 200 ml of MeOH when a white solid (1.0 g) precipitated.

**7-Chloro-4-(3-hydroxyquinuclidinyl-2-methyleneamino)quinoline (2).**—The quinuclidinone derivative **1** (2.0 g, 0.006 mol) was dissolved in 60 ml of MeOH at 0° and to this was added $NaBH_4$ (5.0 g) in small portions. The mixture was allowed to stand at room temperature for a few hours, and then worked up as usual to give 1.3 g of the product.

**7-Chloro-4-(3-quinuclidinylamino)quinoline (3).**—A mixture of 4,7-dichloroquinoline (25.0 g, 0.125 mol), 3-aminoquinuclidine dihydrochloride (25.0 g, 0.125 mol), NaOMe (12.0 g, 0.233 mol), and 100 ml of phenol was heated at 140° for 3 hr. Excess phenol was removed *in vacuo* and the residue was cooled, triturated with 30% NaOH, and extracted with $CHCl_3$. The $CHCl_3$ extract was dried ($Na_2SO_4$) and filtered and the product was converted to the hydrochloride with dry HCl; yield 5.58 g. It was crystallized several times from a large volume of EtOH until it melted at 330–335° dec. The HCl salt was extremely difficult to purify. The content of $H_2O$ appeared to depend on the degree of drying. This sample was dried at 100° (0.05 mm) for 20 hr.

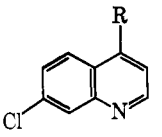
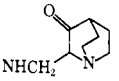
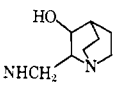
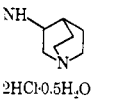
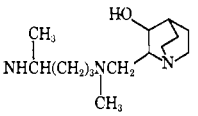
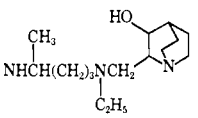
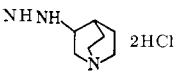
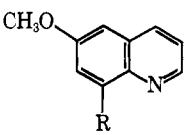
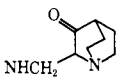
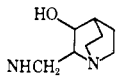
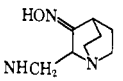
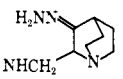
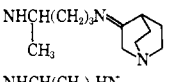
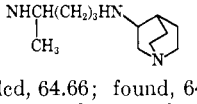
**7-Chloro-4-[1-methyl-4-N-methyl-(3-hydroxyquinuclidinyl-2-methylene)aminobutylamino]quinoline (4).**—A solution of 7-chloro-4-(1-methyl-4-methylaminobutylamino)quinoline[4] (12.5 g, 0.045 mol) and 2-methylene-3-quinuclidinone in 300 ml of MeOH was stirred at room temperature for 14 hr. The reaction was cooled in an ice bath, treated with $NaBH_4$ (15.0 g) in small portions over a period of 1 hr, and allowed to stand at room temperature for 2 hr. MeOH was evaporated off *in vacuo*, and the residue was treated with 500 ml of $H_2O$ and extracted with $C_6H_6$. The $C_6H_6$ extract was dried ($K_2CO_3$) and evaporated to give a glass which was passed through a basic alumina column (50 g of alumina to 1.0 g of material) in $C_6H_6$ solution. After eluting with 3 l. of $C_6H_6$ to wash off impurities, the product (12.5 g) was eluted with MeOH–$C_6H_6$ (1:19). It was still a glasslike material and melted over a wide range.

**7-Chloro-4-[1-methyl-4-N-ethyl-(3-hydroxyquinuclidinyl-2-methylene)aminobutylamino]quinoline (5)** was prepared from the corresponding N-ethyl compound[4] and purified in the same way as **4**.

**7-Chloro-4-[N′-(3-quinuclidinyl)hydrazino]quinoline (6).**—A solution of 7-chloro-4-hydrazinoquinoline[5] (3.86 g, 0.02 mol), 3-quinuclidinone (2.5 g, 0.02 mol), and 0.1 g of *p*-toluenesulfonic acid hydrate in 100 ml of MeOH was refluxed for 12 hr. The

(1) A. R. Hansen and H. Bader, *J. Heterocycl. Chem.*, **3**, 109 (1966).
(2) T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).
(3) R. C. Elderfield, W. J. Gensler, O. Birstein, F. J. Kreysa, J. T. Maynard, and J. Galbraith, *J. Amer. Chem. Soc.*, **68**, 1250 (1946).
(4) M. Carmack, O. H. Bullitt, Jr., G. R. Hendrick, L. W. Kissinger, and I. Von, *ibid.*, **68**, 1220 (1946).
(5) A. R. Surrey and R. A. Cutler, *ibid.*, **68**, 2570 (1946).

TABLE I

| No. | R | Yield, % | Mp or bp (mm), °C | Crystn solvent | Formula | Analyses |
|---|---|---|---|---|---|---|
| |  | | | | | |
| 1 |  | 29.0 | 225–227 | | $C_{17}H_{18}ClN_3O$ | H, N, Cl; C[a] |
| 2 |  | 38.0 | 240.5–242 | $C_6H_6$ | $C_{17}H_{20}ClN_3O$ | C, H, N |
| 3 |  | 12.0 | 330–335 dec | EtOH | $C_{16}H_{20}Cl_3N_3 \cdot 0.5H_2O$ | C, H, N, Cl(total), $Cl^-$, $H_2O$ |
| 4 |  | 60.0 | 65–110 | | $C_{23}H_{33}ClN_4O$ | C, H, N |
| 5 |  | 85.0 | 66–75 | | $C_{24}H_{35}ClN_4O$ | H, N; C[b] |
| 6 |  | 55.0 | 263.5–265 dec | MeOH–$Et_2O$ | $C_{11}H_{21}Cl_3N_4$ | H, N; C[c] |
| |  | | | | | |
| 7 |  | 75.0 | 120–122 | | $C_{18}H_{21}N_3O_2$ | C, H, N |
| 8 |  | 55.0 | 196–197 | | $C_{18}H_{23}N_3O_2$ | C, H, N |
| 9 |  | | 196–198 | $CH_2Cl$–petr ether | $C_{18}H_{22}N_4O_2$ | H, N; C[d] |
| 10 |  | | 98–102 | $Et_2O$–petr ether | $C_{18}H_{23}N_5O$ | C, H; N[e] |
| 11 |  | 17.7 | 150 (0.001) | | $C_{17}H_{21}N_3O$ | C, H, N |
| 12 |  | 77.0 | 210–222 (0.005) | | $C_{22}H_{30}N_4O$ | C, H, N |
| 13 |  | 80.0 | 210–220 (0.002) | | $C_{22}H_{32}N_4O$ | C, H, N |

[a] C: calcd, 64.66; found, 64.21. [b] C: calcd, 66.88; found, 66.43. [c] C: calcd, 51.15; found, 51.65. [d] C: calcd, 66.23; found, 65.78. [e] N: calcd, 21.52; found, 21.01.

solvent was evaporated off *in vacuo* and the hydrazone was dissolved in 100 ml of THF and added slowly to a mixture of LAH (5.7 g, 0.15 mol) in 250 ml of THF. After refluxing for 12 hr, the reaction mixture was cooled in an ice bath and carefully decomposed with 5.4 ml of $H_2O$ followed by 5.4 ml of a 15.0% NaOH solution and 16.2 ml of $H_2O$. After stirring for 3 hr, the inorganic salts were removed by filtration and washed with THF and the filtrate was concentrated to a green oil. It was converted to the dihydrochloride and crystallized to give 2.3 g of the salt.

**6-Methoxy-8-(3-ketoquinuclidinyl-2-methyleneamino)quinoline (7).**—A solution of 6-methoxy-8-aminoquinoline (34.8 g, 0.20 mol) and 2-methylene-3-quinuclidinone in 50 ml of MeOH was stirred and refluxed for 0.5 hr. On cooling the mixture to room temperature, 46.5 g of the product crystallized; it was filtered off and washed with MeOH.

**6-Methoxy-8-(3-hydroxyquinuclidinyl-2-methyleneamino)-quinoline (8).**—The ketone derivative **7** (10.0 g, 0.033 mol) was dissolved in EtOAc and hydrogenated at room temperature and atmospheric pressure using a $PtO_2$ catalyst. After the absorption of a little over 1 equiv of $H_2$, the catalyst was removed by filtration, and the filtrate was concentrated and allowed to crystallize to give 5.5 g of **8**.

**6-Methoxy-8-(3-quinuclidineamino)quinoline (11).**—A mixture of 6-methoxy-8-aminoquinoline (17.40 g, 0.01 mol), 3-quinuclidinone (12.50 g, 0.01 mol), *p*-toluenesulfonic acid (0.40 g), and 400 ml of $C_6H_6$ was refluxed for 18 hr using a Dean–Stark $H_2O$

separator. The reaction mixture was cooled to room temperature, stirred with anhydrous $K_2CO_3$ (15.0 g) for 0.5 hr, and filtered and the filtrate was evaporated to dryness. The crude Schiff base was reduced with $NaBH_4$ and distilled to give 5.0 g of **11**.

**6-Methoxy-8-[1-methyl-4-(3-quinuclidineimino)butylamino]-quinoline (12).**—A mixture of primaquine[6] (7.77 g, 0.03 mol), 3-quinuclidinone (3.75 g, 0.03 mol), *p*-toluenesulfonic acid (0.1 g), and 200 ml of PhMe was refluxed for 12 hr when 0.6 mol of $H_2O$ collected in the Dean–Stark separator. The clear solution was concentrated to a viscous oil and distilled to give 7.4 g of a yellow glasslike material.

**6-Methoxy-8-[1-methyl-4-(3-quinuclidineamino)butylamino]-quinoline (13).**—The Schiff base **12** (7.8 g, 0.021 mol) was dissolved in *i*-PrOH, cooled in an ice–$H_2O$ bath, and treated with 8.0 g of $NaBH_4$. The mixture was worked up as usual to give 6.5 g of a glasslike product.

**Acknowledgment.**—This work was supported by the U. S. Army Medical Research and Development Command through Research Contract No. DA-49-193-MD-2869 and is Contribution No. 488 from the Army Research Program on Malaria.

(6) R. C. Elderfield, H. F. Mertel, R. C. Mitch, I. M. Wempen, and I. Werbel, *ibid.*, 77, 4816 (1955).

## Some New Thiosemicarbazides, Thioureas, and Thiosemicarbazones from 4-Isothiocyanatobenzenesulfonpiperidide[1]

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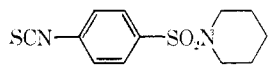
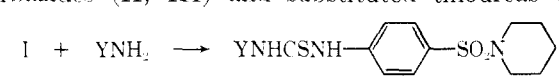
*Received December 9, 1968*

Several types of compounds containing the thiocarbonyl group have been shown to possess fungistatic properties. For example, thiosemicarbazones[2] and dithiosemicarbazones[3] have been shown to be effective against the cellulolytic microorganism *Chaetomium globosum*. In addition, it has been found[4] that 4-isothiocyanatobenzenesulfonpiperidide (I) has considerable value as a fungicide.



I

In the present work, three series of new compounds have been synthesized from I, their structures have been deduced from elemental analysis and ir absorption measurements, and the antifungal effectiveness of them has been evaluated against two microorganisms, *Chaetomium globosum* and *Aspergillus niger*. I reacts readily with hydrazine hydrate, substituted hydrazines, and amines to form the desired substituted thiosemicarbazides (II, III) and substituted thioureas (IV),



II, Y = $H_2N$
III, Y = $R_1R_2N$
IV, Y = R

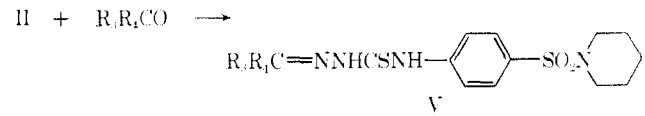
(1) Issued as NRCC No. 10726.

(2) B. G. Benns, B. A. Gingras, and C. H. Bayley, *Appl. Microbiol.*, 8, 353 (1960).

(3) D. M. Wiles, B. A. Gingras, and T. Suprunchuk, *Can. J. Chem.*, 45, 1735 (1967).

(4) H. A. Stevenson, J. R. Marshall, and A. F. Hams, British Patent 840,122 (July 6, 1960).

respectively. Thiosemicarbazones V were prepared by treating a series of aliphatic and aromatic aldehydes

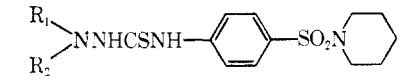


V

and aliphatic ketones with II. The yield, melting point, and formula for each of the new compounds of the types III–V are listed in Tables I–III.

TABLE I

SOME 1-SUBSTITUTED 4-(4-BENZENESULFONYLPERIDIDE)THIOSEMICARBAZIDES

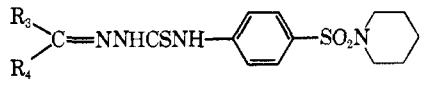


| No. | $R_1$ | $R_2$ | Yield, % | Mp, °C | Formula[c] |
|---|---|---|---|---|---|
| 1 | Me | Me | 84[a] | 172 | $C_{14}H_{22}N_4O_2S_2$ |
| 2 | $CH_2CH_2OH$ | H | 61[b] | 165 | $C_{14}H_{22}N_4O_3S_2$ |
| 3 | $C_6H_5$ | H | 56[b] | 169 | $C_{18}H_{22}N_4O_2S_2$ |
| 4 | $C_6H_5SO_2$ | H | 75[b] | 195 | $C_{18}H_{22}N_4O_4S_3$ |
| 5 | 3-Hydroxy-2-naphthoyl | H | 89[b] | 201 | $C_{23}H_{24}N_4O_4S_2$ |

[a] Recrystallized from $Me_2CO$. [b] Recrystallized from EtOH. [c] Analyzed for C, H, N, S.[5]

TABLE II

ALDEHYDE OR KETONE 4-(4-BENZENESULFONPIPERIDIDE)THIOSEMICARBAZONES



| No. | Aldehyde or ketone | Yield, % | Mp, °C | Formula | Analyses |
|---|---|---|---|---|---|
| 6 | Benzaldehyde | 93[a] | 228 | $C_{19}H_{22}N_4O_2S_2$ | C, H, N, S |
| 7 | *p*-Chlorobenzaldehyde | 75[a] | 235 | $C_{19}H_{21}N_4O_2S_2Cl$ | C, H, N, S, Cl |
| 8 | 2,4-Dichlorobenzaldehyde | 79[a] | 244 | $C_{19}H_{20}N_4O_2S_2Cl_2$ | C, H, N, S, Cl |
| 9 | *p*-Hydroxybenzaldehyde | 71[a] | 216 | $C_{19}H_{22}N_4O_3S_2$ | C, H, N, S |
| 10 | Cinnamaldehyde | 73[a] | 202 | $C_{21}H_{24}N_4O_2S_2$ | C, H, N, S |
| 11 | Anisaldebyde | 78[a] | 195 | $C_{20}H_{24}N_4O_3S_2$ | C, H, N, S |
| 12 | *o*-Hydroxybenzaldehyde | 61[b] | 217 | $C_{19}H_{22}N_4O_3S_2$ | C, H, N, S |
| 13 | 1-Naphthaldehyde | 79[a] | 217 | $C_{23}H_{24}N_4O_2S_2$ | C, H, N, S |
| 14 | 2-Hydroxy-1-naphthaldehyde | 81[a] | 201 | $C_{23}H_{24}N_4O_3S_2$ | C, H, N, S |
| 15 | Ferrocenecarboxaldehyde | 89[c] | 216 | $C_{29}H_{32}N_4O_2S_2Fe$ | C, H, N, S, Fe |
| 16 | Acetone | 75[a] | 169 | $C_{15}H_{22}N_4O_2S_2$ | C, H, N, S |
| 17 | 2-Butanone | 65[a] | 165 | $C_{16}H_{24}N_4O_2S_2$ | C, H, N, S |
| 18 | 2-Heptadecanone | 90[d] | 74 | $C_{29}H_{56}N_4O_2S_2$ | C, H, N, S |

[a] Recrystallized from $Me_2CO$–$H_2O$. [b] Recrystallized from DMF–$H_2O$. [c] Recrystallized from dioxane–$H_2O$. [d] Recrystallized from EtOH–$H_2O$.

It is necessary to obtain some direct evidence, in addition to the analytical data,[5] in support of the structures proposed for the new compounds reported here. In each case, the observation of particular ir absorption bands, characteristic of particular structural entities, verifies the structures shown in the tables.

The substituted thiosemicarbazides, the thiosemicarbazones, and the substituted thioureas were screened as potential fungicides by the tube dilution method.[2] The results of the effectiveness against *Chaetomium globosum* may be summarized as follows: (a) com-

(5) Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.