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.

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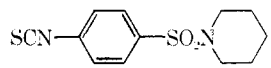
Several types of compounds containing the thiocarbonyl group have been shown to possess fungistatic properties. For example, thiosemicarbazones[2] and dithiosemicarbazones[3] have been shown to be effective against the cellulolytic microorganism *Chaetomium globosum*. In addition, it has been found[4]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

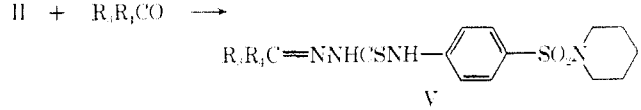
(1) Issued as NRCC No. 10726.

(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

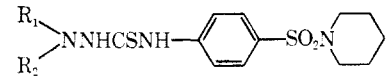


V

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-BENZENESULFONPIPERIDIDE)THIOSEMICARBAZIDES

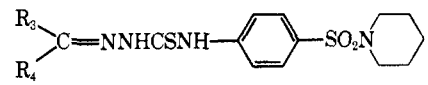


No.	R_1	R_2	Yield, %	Mp, °C	Formula[c]
1	Me	Me	84[a]	172	$C_{14}H_{22}N_4O_2S_2$
2	CH_2CH_2OH	H	61[b]	165	$C_{14}H_{22}N_4O_3S_2$
3	C_6H_5	H	56[b]	169	$C_{18}H_{22}N_4O_2S_2$
4	$C_6H_5SO_2$	H	75[b]	195	$C_{18}H_{22}N_4O_4S_3$
5	3-Hydroxy-2-naphthoyl	H	89[b]	201	$C_{23}H_{24}N_4O_4S_2$

[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	Anisaldehyde	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[c]	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	$C_{16}H_{22}N_4O_2S_2$	C, H, N, S
17	2-Butanone	65[a]	165	$C_{17}H_{24}N_4O_2S_2$	C, H, N, S
18	2-Heptadecanone	90[d]	74	$C_{29}H_{56}N_4O_2S_2$	C, H, N, S

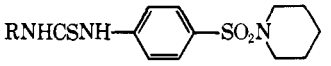
[a] Recrystallized from Me_2CO–H_2O. [b] Recrystallized from DMF–H_2O. [c] Recrystallized from dioxane–H_2O. [d] Recrystallized from EtOH–H_2O.

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.

TABLE III
SUBSTITUTED THIOUREAS



No.	R	Yield, %	Mp, °C	Formula[d]
19	Me	89[a]	175	$C_{13}H_{19}N_3O_2S_2$
20	Et	91[a]	173	$C_{14}H_{21}N_3O_2S_2$
21	Bu	85[a]	183	$C_{16}H_{25}N_3O_2S_2$
22	*i*-Pr	89[a]	187	$C_{15}H_{23}N_3O_2S_2$
23	Pr	95[b]	158	$C_{15}H_{23}N_3O_2S_2$
24	Octyl	89[c]	99	$C_{20}H_{33}N_3O_2S_2$
25	Dodecyl	91[c]	93	$C_{24}H_{41}N_3O_2S_2$
26	Octadecyl	84[a]	84	$C_{30}H_{53}N_3O_2S_2$
27	Ph	65[a]	177	$C_{18}H_{21}N_3O_2S_2$
28	β-Naphthyl	79[a]	188	$C_{22}H_{23}N_3O_2S_2$

[a] Recrystallized from Me_2CO–H_2O. [b] Recrystallized from C_6H_6. [c] Recrystallized from C_6H_6–C_6H_{12}. [d] Analyzed for C, H, N, S.[5]

pounds **2** and **7** were effective at 10 ppm, and (b) **4** and **16** were effective at 100 ppm. None was effective against *Aspergillus niger* at concentrations below 1000 ppm. Since the influence of molecular size and chemical structure on antifungal activity is not well understood, no specific explanation can be given to account for these data. It may be pointed out, however, that the antifungal effectiveness of **2** and **7** against *Chaetomium globosum* is equivalent to that of a number of dithiosemicarbazones and the copper complexes of some of them[3] as well as of a commercial formulation of copper 8-hydroxyquinolinate and of dihydroxydichlorodiphenylmethane.[2] These latter compounds have also been shown to be ineffective against *Aspergillus niger* at concentrations below 1000 ppm.

Experimental Section

The reagents and solvents used in the syntheses described in this paper were the purest grade obtainable from commercial sources. Melting points were measured with a Fisher-Johns apparatus and are corrected. Elemental analyses were performed at the microanalytical laboratory of Drs. Weiler and Strauss in Oxford, England. Ir spectra of the new compounds described in this work were obtained from KBr pellets with a Model 21 Perkin-Elmer double-beam spectrophotometer (NaCl prism) over the frequency range 3500–700 cm^{-1}.

4-Isothiocyanatobenzenesulfonpiperidide (I) was obtained from a commercial source and was recrystallized repeatedly from benzene–hexane. The thiosemicarbazide of it (II) was prepared by adding dropwise hydrazine hydrate, 99–100% purity (0.1 mole), in EtOH (50 ml) to a solution of I (0.1 mole) in EtOH (250 ml). The mixture was heated on a steam bath for 30 min. The light brown precipitate which formed was separated by filtration, washed (H_2O, EtOH), dried, and purified by repeated crystallization from DMF–H_2O; yield 85%, mp 191°. *Anal.* ($C_{12}H_{18}N_4O_2S_2$) C, H, N, S. An ir absorption band observed at 1635 cm^{-1}, for II but none of the other compounds, is attributable to δ (NH_2).[6]

General Preparation for 1-Substituted 4-(4-Benzenesulfonpiperidide)thiosemicarbazides (III) (Table I).—Substituted hydrazine (0.01 mole), dissolved in warm H_2O or EtOH (50 ml), was added dropwise to a solution of I (0.01 mole) in EtOH (50 ml). The mixture was heated on a steam bath for 45 min, then cooled. The precipitate which formed was collected by filtration, washed (EtOH), dried, and recrystallized to constant melting point; ir absorptions: **2**, 3440 (OH); **5**, 3440 (OH), 1650 (C=O).

General Preparation for 4-(4-Benzenesulfonpiperidide)thiosemicarbazones (V) (Table II).—A solution of 4-(4-benzenesulfonpiperidide)thiosemicarbazide (II) (0.01 mole) in DMF (25 ml) was prepared. To this was slowly added a solution of aldehyde or ketone (0.01 mole) in EtOH (50 ml) containing 1 ml of glacial AcOH. The mixture was heated on a steam bath for 20 min; H_2O was then added until incipient precipitation. The precipitate which formed on cooling was collected by filtration, washed with cold 50% H_2O–EtOH, dried, and recrystallized to constant melting point; ir absorptions: **9**, **12**, **14**, 3440 (OH); **10**, 1630 (C=C); **11**, 1255 (COC).

General Preparation for Substituted Thioureas (IV) (Table III).—A solution of a primary amine (0.01 mole) in H_2O or EtOH (50 ml) was slowly added to a solution of I (0.01 mole) in EtOH (50 ml). The mixture was heated on a steam bath for 45 min, then cooled. The precipitate which formed was collected by filtration, washed (cold 50% H_2O–EtOH), dried, and recrystallized to constant melting point.

It is reported[7] that alcohols react with isothiocyanates to yield thiourethans. Nevertheless, the syntheses described above produce higher yields of the desired products when the reactions are carried out in EtOH than when either $CHCl_3$ or Et_2O is used as solvent.

The antimicrobial activity of all the compounds prepared in this work toward two microorganisms was determined by screening procedures involving the tube dilution method described previously.[2] The test organisms used in the screening experiments were *Chaetomium globosum* strain USDA 1042.4, and *Aspergillus niger* strain USDA 215–5373.16. Concentrations of the compounds being tested of 10, 100 and 1000 ppm were employed; the criterion of effectiveness was simply the absence of fungal growth after a 2-week incubation period (*C. globosum*) or after 48 hr (*A. niger*).

Acknowledgments.—The authors are grateful to Miss G. Colin for screening the new compounds for antifungal activity and to R. Ironside and V. Boyko for recording the infrared spectra.

(6) D. M. Wiles and T. Suprunchuk, *Can. J. Chem.*, **47**, 1087 (1969).

(7) S. J. Assony in "Organic Sulphur Compounds," Vol. 1, N. Kharasch, Ed., Pergamon Press, New York, N. Y., 1961, p 333.

Synthetic Penicillins Derived from Cycloheptatrienecarboxylic Acids

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A common feature in the majority of the medicinally important synthetic penicillins[2] is the aromatic nature of the acyl group attached to the 6-aminopenicillanic acid. With the commercial availability of this compound,[3] a great number of semisynthetic penicillins[4,5] have been prepared in an effort to obtain clinically effective products. From the vast number of examples which are available in the literature, it is evident that minor changes in the nature and position of substituents on the aromatic ring or a side chain in the vicinity of the acyl carbonyl group causes profound changes in the biological activity. Thus, the quest for newer synthetic penicillins having a broader spectrum of biological activity continues.

To the best of our knowledge, the preparation of penicillins containing the cycloheptatrienecarbonyl moiety has not been reported. We now wish to describe

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(2) J. O. Klein and M. Finland, *New Engl. J. Med.*, **269**, 1019, 1074, 1129 (1963).

(3) F. R. Batchelor, F. P. Doyle, J. H. C. Nayler, and G. N. Rolinson, *Nature*, **183**, 257 (1959).

(4) For leading references see Y. G. Perron, W. F. Minor, L. B. Crast, A. Gourevitch, J. Lein, and L. C. Cheney, *J. Med. Pharm. Chem.*, **5**, 1016 (1962).

(5) F. P. Doyle, J. H. C. Nayler, H. R. J. Waddington, J. C. Hanson, and G. R. Thomas, *J. Chem. Soc.*, 497 (1963).