medicated broth: *T. mentagrophytes* and *M. canis* were grown on Sabouraud's dextrose agar slants at 28° for 7–10 days. Surface growth from an agar slant culture was taken up into 5 ml of sterile H_2O, homogenized, and dild 500-fold with sterile H_2O. *C. neoformans* was grown on Sabouraud's dextrose agar slants at 22° for 2 days. The surface growth from an agar slant culture was taken up into 5 ml of sterile H_2O, homogenized, and dild 25-fold with sterile H_2O. *H. capsulatum* was grown in Salvin's Y-P semifluid medium at 22° for 7 days; 0.5 ml of medium containing surface growth was uniformly suspended in 25 ml of sterile H_2O.

Minimum inhibitory concns (MICs), which are considered to be the min concns of the test compds in micrograms per milliliter which prevent grossly detectable growth of the test organisms, were detd after inoculated tubes were incubated for a suitable period of time at the desired temp. In the case of *T. mentagrophytes* and *M. canis*, this was 5 days at 28°, while *C. neoformans* and *H. capsulatum* were incubated for 2 and 4 days, respectively, at 37°.

Insect Chemosterilants. 10. Substituted Dithiobiurets[1a,b]

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Sexual sterilization of female insects can be achieved with many compounds of different structural types.[2] Apparently, the complex biochemical processes in oogenesis can be interrupted or modified at several points with the same ultimate effects, *i.e.*, the female does not produce eggs or the eggs are infertile. Fertility of male insects, on the other hand, is not as easily affected by chemicals and only 3 well-defined classes of male chemosterilants are known: alkylating agents,[3] phosphoramides,[4] and *s*-triazines.[5]

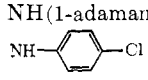
In this communication we wish to describe a new class of male insect chemosterilants, derivatives of dithiobiuret (Table I). Compounds **2** through **20** were synthesized according to Scheme I. Dialkylthiocarbamoyl chlorides were converted to the corresponding thiocarbamoyl isothiocyanates[6a] with KSCN in Me_2CO; the rather unstable[6b] thiocarbamoyl isothiocyanates were then treated, without isolation, with amines to provide the dithiobiurets.

SCHEME I

$$R_2R_1NCSCl \xrightarrow{KSCN} R_2R_1NCSNCS \xrightarrow[R_3R_4NH]{} R_2R_1NCSNHCSNR_3R_4$$

Several of the 1,1,5,5-tetrasubstituted dithiobiurets, particularly the unsymmetrically substituted ones, were unstable. Although all but **8**, **12**, and **14** were crystalline, **8**–**12** and **14** tended to decompose on attempted purification or on prolonged standing at room temperature, and satisfactory elemental analyses were not obtained; the compounds were characterized by their ir and nmr spectra. An extreme example was 1,1,5,5-tetraethyldithiobiuret (too unstable for biological test-

TABLE I
DITHIOBIURET CHEMOSTERILANTS
$R_1CSNR_2CSR_3$

Compd	R_1	R_2	R_3	Mp, °C	Formula[a]	% hatch[b] at injected dose 5 μg/♂[f]	10 μg/♂[f]
1	NH_2	H	NH_2	189–191[c]	$C_2H_5N_3S_2$	94 (0)	91 (0)
2	$N(CH_3)_2$	H	NH_2	126–127[d]	$C_4H_9N_3S_2$	92 (60)	(100)
3	$N(CH_3)_2$	H	$NHCH_3$	123–124	$C_5H_{11}N_3S_2$	70 (90)	(100)
4	$N(CH_3)_2$	H	NHC_2H_5	81–82	$C_6H_{13}N_3S_2$	79 (50)	(100)
5	$N(CH_3)_2$	H	NH(1-adamantyl)	144–145	$C_{14}H_{23}N_3S_2$	93 (0)	78 (0)
6	$N(CH_3)_2$	H		103–105	$C_{10}H_{12}ClN_3S_2$	90 (4)	82 (90)
7	$N(CH_3)_2$	H	$N(CH_3)_2$	112–115	$C_6H_{13}N_3S_2$	15 (10)	1 (80)
8	$N(CH_3)_2$	H	$N(C_2H_5)_2$	Oil[e]	$C_8H_{17}N_3S_2$	15 (70)	(100)
9	$N(CH_3)_2$	H	Pyrrolidyl	95–105[d]	$C_8H_{15}N_3S_2$	59 (10)	44 (40)
10	$N(CH_3)_2$	H	Piperidyl	103–128[d]	$C_9H_{17}N_3S_2$	28 (25)	(100)
11	$N(CH_3)_2$	H	Morpholinyl	163–165[d]	$C_8H_{15}N_3OS_2$	14 (50)	(100)
12	$N(CH_3)_2$	H	$N(CH_3)CH_2CH_2OH$	Oil[e]	$C_7H_{15}N_3OS_2$	41 (0)	17 (8)
13	$N(CH_3)_2$	H	$N(CH_2CH_2OH)_2$	96–100 dec	$C_8H_{17}N_3O_2S_2$	92 (0)	81 (0)
14	$N(CH_3)_2$	H	$N(CH_3)C_6H_5$	Oil[a]	$C_{11}H_{15}N_3S_2$	(100)[g]	(100)
15	Pyrrolidyl	H	Pyrrolidyl	147–153 dec	$C_{10}H_{17}N_3S_2$	24 (0)	20 (20)
16	Piperidyl	H	Piperidyl	133–138	$C_{12}H_{21}N_3S_2$	93 (0)	87 (10)
17	Morpholinyl	H	Morpholinyl	161–163 dec	$C_{10}H_{17}N_3O_2S_2$	29 (40)	13 (90)
18	Pyrrolidyl	H	Piperidyl	125–130 dec	$C_{11}H_{19}N_3S_2$	45 (0)	26 (20)
19	Pyrrolidyl	H	Morpholinyl	137–141	$C_{10}H_{17}N_3OS_2$	54 (0)	36 (20)
20	Piperidyl	H	Morpholinyl	138–144 dec	$C_{11}H_{19}N_3OS_2$	18 (10)	47 (80)
21	$N(CH_3)_2$	CH_3	$N(CH_3)_2$	Oil	$C_7H_{15}N_3S_2$	88 (60)	95 (70)
22	$N(CH_3)_2$	C_6H_5	$N(CH_3)_2$	130	$C_{12}H_{17}N_3S_2$	94 (0)	90 (10)

[a] New compds analyzed satisfactorily for C, H, N, S, except where indicated. [b] Average hatch among controls was 95 ± 5%. [c] Commercial sample (American Cyanamid). [d] J. S. Davidson, *J. Chem. Soc. C*, 2069 (1966). [e] Unstable, not obtd anal. pure. [f] Values in parentheses indicate per cent mortality in 48 hr. [g] At 1 and 2 μg, the hatch was 55 and 42%, respectively.

(1) (a) Paper 9: P. H. Terry and A. B. Bořkovec, *J. Med. Chem.*, **13**, 782 (1970); (b) mention of a pesticide does not constitute a recommendation by the U. S. Department of Agriculture.

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ing): recrystallization from Me_2CO or EtOH gave a white solid, mp 89–94°. Upon standing overnight in a desiccator at room temp the entire sample decomposed to a red oil.

The nature of the decomposition has not been studied in detail, but a likely pathway is disproportionation of the dithiobiurets to thiocarbamoyl isothiocyanates and amines. These isothiocyanates can undergo dimerization and other reactions;[6b] furthermore, in the case of unsymmetrical dithiobiurets, 2 isothiocyanates and 2 amines can result, and random recombination could provide 3 dithiobiurets (Scheme II). This idea

SCHEME II

$$R_2NCSNHCSNR_2' \longrightarrow R_2NCSNCS + R_2'NH + R_2'NCSNCS + R_2NH \longrightarrow \text{other products}$$

$R_2NCSNHCSNR_2$, etc.

is supported by the fact that repeated recrystallization of the dimethylaminopiperidino compound **10** from *i*-PrOH, then MeCN, resulted in a poor yield of the bis(piperidino)dithiobiuret **16**.

The pentasubstituted compounds **21** and **22** were prepared by treating $MeNH_2$ and $PhNH_2$, respectively, with 2 equiv of *N,N*-dimethylthiocarbamoyl chloride. The biological activity of **21** is uncertain because the compound decomposes in H_2O.

Biological Activity.—The compounds were tested as chemosterilants in male house flies, *Musca domestica* L., by the procedure of Chang and Bořkovec.[7] Briefly, groups of 10 newly emerged male flies were injected each with 5 and 10 μg of the test compound in DMSO–Me_2CO (1:1) and the treated males were crossed with untreated virgin females. The hatchability of eggs laid by the mated females is shown in Table I. Because the hatch in control experiments was 90–100%, the sterilizing activity of **3–6**, **13**, **16**, and **21** was only marginal and possibly insignificant. All the active compounds (**7–12**, **14**, **15**, **17–21**) were 1,1,5,5-tetrasubstituted; however, since the dose–response relationship was apparently affected by the instability of the compounds, structure–activity correlations within the series of active compounds cannot be reliably deduced from the present data. Nevertheless, it is apparent that a decrease in substitution (**1–6**) as well as a substitution of the 3-N (**21**, **22**) sharply reduces or destroys the sterilizing effect of dithiobiurets.

Experimental Section[8]

Thiocarbamoyl Chlorides.—*N,N*-Dimethylthiocarbamoyl chloride was purchased from Aldrich Chemical Co. Diethyl-, pyrrolidino-, piperidino-, and morpholinothiocarbamoyl chlorides were prepd from $CSCl_2$ and the appropriate amine as described by von Braun and Stechele.[9]

Dithiobiurets 2–20.—A thiocarbamoyl chloride (0.10 mole) and KSCN (0.105 mole) were combined in Me_2CO (90 ml). The mixt was stirred and refluxed for 15 min and then chilled, and the KCl was removed by filtration. The yellow filtrate was treated with 0.10 mole of the desired amine at 0°, then the ice bath was removed, and the soln was allowed to warm to room temp. The solvent was evapd, and the residue was recrystd from EtOH or MeCN.

Pentasubstituted Dithiobiurets 21 and 22.—The primary amines ($MeNH_2$ and $PhNH_2$) were treated with 2 equiv of *N,N*-dimethylthiocarbamoyl chloride in C_6H_6 containing 2 equiv of Et_3N. $MeNH_2$ reacted rapidly at room temp; $PhNH_2$ required a 2-hr reflux period. The solns were filtered to remove $Et_3N \cdot HCl$, washed with aq $NaHCO_3$ and aq NaCl, dried, and evapd; **21** was obtained as a clear oil (mp near room temp) that decompd upon attempted distn or upon standing in H_2O. It was therefore used without purification; **22** was obtd as an oily solid that was purified by recrystn from MeOH.

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Vitamin B_6 Analogs. An Improved Synthesis of 3-Hydroxypyridine-4-carboxaldehyde[1]

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3-Hydroxypyridine-4-carboxaldehyde (VIII) has been used as a model for pyridoxal 5′-phosphate in studies of imine formation and transamination with amino acids.[3–14] Unfortunately the tedious and inefficient synthesis[7,15,16] of VIII has limited the availability of this compound. We have now devised a simple synthesis of VIII.

The starting point for our synthesis of VIII is *N*-oxide I, which is treated with Ac_2O to form a mixt of acetates II and III. This reaction is well known and has been the subject of considerable study.[17–32] The acetates II and III were not sepd, but were oxidized

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