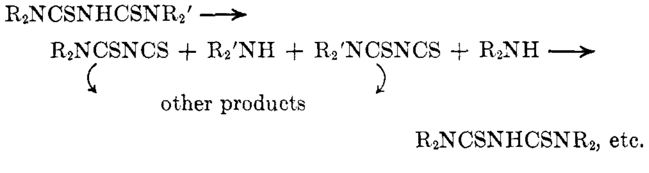
ing): recrystallization from Me_2CO or EtOH gave a white solid, mp 89–94°. Upon standing overnight in a desiccator at room temp the entire sample decomposed to a red oil.

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 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**.

SCHEME II



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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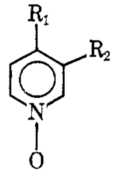
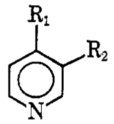
directly to the *N*-oxides IV and V. Because the phenolic acetate is much more labile than the benzylic acetate, acid-catalyzed hydrolysis of III, but not of II, occurs during the oxidation. The solubilities of the products IV and V are quite different, rendering them easily separable. The overall yield of V from I is only 12%, but the starting material is readily available, and the transformation can be carried out on a large scale. Reaction of V with Ac_2O yields the diacetate VI, which is hydrolyzed to the diol VII and oxidized to the desired aldehyde VIII.



I, $R_1 = CH_3$; $R_2 = H$
IV, $R_1 = CH_2OAc$; $R_2 = H$
V, $R_1 = CH_3$; $R_2 = OH$



II, $R_1 = CH_2OAc$; $R_2 = H$
III, $R_1 = CH_3$; $R_2 = OAc$
VI, $R_1 = CH_2OAc$; $R_2 = OAc$
VII, $R_1 = CH_2OH$; $R_2 = OH$
VIII, $R_1 = CHO$; $R_2 = OH$

Experimental Section

Melting points were detd on a Thomas Hoover Uni-Melt and are uncor. Satisfactory uv, ir, and nmr spectra were obtd for all compds.

4-Pyridinemethanol Acetate (II) and 3-Acetoxy-4-methylpyridine (III).—A soln of 81.6 g (0.74 mole) of I in 125 ml of C_6H_5Cl was refluxed under N_2 and 250 ml (2.64 moles) of Ac_2O was slowly added (this reaction is exothermic and caution is required). After a 2-hr reflux the soln was distd and 41.7 g (37.2%) of a yellow oil, bp 70–79° (0.03 mm), which was identified by vpc and nmr as a mixt of 64.5% II and 36.5% III, was obtained.

3-Hydroxy-4-methylpyridine *N*-Oxide (V).—The mixt of acetates II and III (41.7 g, 0.28 mole) was dissolved in 100 ml of HOAc at 70–80° under N_2 and 28.2 g (0.248 mole) of 30% H_2O_2 was added. After 3 hr an addl 18.8 g (0.136 mole) of 30% H_2O_2 was added and heating was contd for another 9 hr. The reaction mixt was cooled and fractionated on a rotary evaporator. To insure the removal of remaining AcOH and H_2O_2, the residual oil was dissolved in 100 ml of H_2O and the H_2O was removed on a rotary evaporator. This process was repeated, taking care to remove the last trace of H_2O at the end. The residual oil was dissolved in 300 ml of $CHCl_3$ and slow addn of 400 ml of anhyd Et_2O yielded 13.9 g of impure V, mp 155–175°. The yellow crystals were washed (Me_2CO), resulting in 10.8 g (86%) of white crystals of V, mp 188–193°.

3-Acetoxy-4-pyridinemethanol Acetate (VI).—In 100 ml of Ac_2O 5.0 g (0.04 mole) of V was refluxed under N_2. The excess Ac_2O was removed and the product was distd: yield 3.34 g (40%); bp 108–109° (0.2 mm).

3-Hydroxy-4-pyridinemethanol (VII).—The diacetate VI (3.34 g, 0.016 mole) was added dropwise with stirring to 50 ml of 4% aq NaOH and heated under N_2 at 80° for 2 hr. After cooling, the pH was adjusted to 8.5 with 1 *M* H_3PO_4 and H_2O was removed on a rotary evaporator. The product was extd from the resultant solid with 50 ml of abs EtOH. Evapn of solvent yielded 4.26 g of a cream-colored solid which was a mixt of 43% VII (90%) and 57% NaOAc.

3-Hydroxypyridine-4-carboxaldehyde (VIII).—The mixt of NaOAc and diol VII (1.0 g, contg 0.0034 mole of VII) was dissolved in 75 ml of H_2O and extd three times with 75 ml of $CHCl_3$ to remove unhydrolyzed pyridine acetates. The aq soln was mixed with 200 ml of $CHCl_3$, the 2-phase system was brought to reflux under N_2, 3.0 g (0.035 mole) of activated MnO_2 (Sterwin Chemicals, Inc.) was added, and the mixt was refluxed 10 min. Then 5 ml of 0.14 *M* H_2SO_4 was added and refluxing was contd. After 45 min another 20 ml of the same H_2SO_4 soln was added over a 15-min period.

After cooling, the mixt was extd with $CHCl_3$. The $CHCl_3$ was treated with 5 g of $NaHCO_3$ and 5 g of Na_2SO_4. The solvent was removed below 40°, leaving 0.167 g (40%) of a yellow solid, mp 112–123°. After sublimation the compd melted at 132–133° and had ir, uv, and nmr spectra identical with those reported.[16,33,34]

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