Structural Modification Studies of 3-Piperonylsydnone. III. (1) Some Analogs of 3-Piperonylsydnone and 2,4-Diamino-5-piperonylpyrimidine

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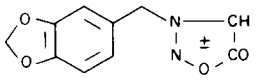
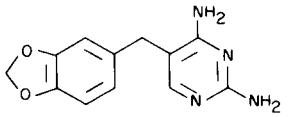
In a continued structural modification study of the antimalarial compounds 3-piperonylsydnone and 2,4-diamino-5-piperonylpyrimidine, the related piperonyl derivatives of ψ-1,2,3;4-oxatriazole, ψ-1,3,5-oxadiazole, pyrazole, tetrazole, 1,2,4-triazine, pyrrolidine, amino- and sulfamoyl-1,2,4-triazole, as well as some sydnones and diaminopyrimidines with side chains other than the piperonyl group have been synthesized. 3-(3,4-Ethylenedioxyphenyl)sydnone was found to double the survival time of *Plasmodium berghei* infected mice. The other compounds are not as active.

Two piperonyl-containing heterocyclic compounds, 3-piperonylsydnone (2) (I) and 2,4-diamino-5-piperonylpyrimidine (3) (II), possess excellent antimalarial activity against *Plasmodium berghei* in mice (2,4). Compound II is also active against *P. gallinaceum* in chicks (treated animals have mean survival time of 18.6 days at 120 mg./kg., compared to 3.8 days mean survival time of the control animals) (5). Although compound II is a typical antifolic compound which effectively inhibits the growth of *Streptococcus faecalis*, *Lactobacillus casei* and *Pediococcus cerevisiae* (5), its pattern of action was found to be different (6) from that of a closely related compound, trimethoprim (7-9). In connection with the structure-activity relationship study of compounds of this type and our continued interest in studying compounds containing the methylenedioxy moiety (2,4,10,11), some analogs of I and II were prepared.

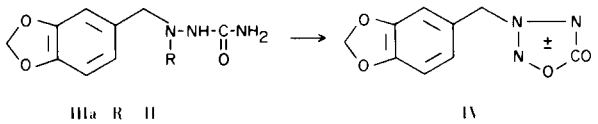


I



II

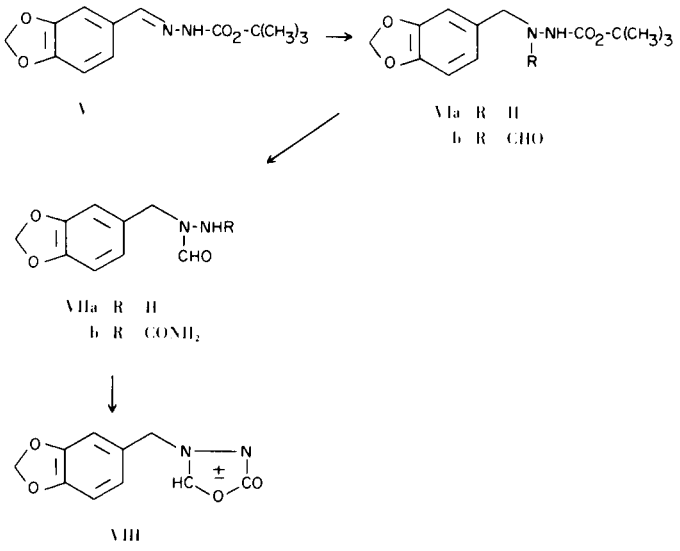
Anhydro-5-hydroxy-3-piperonyl-1,2,3,4-oxatriazolium hydroxide (IV, pseudo-5-oxo-3-piperonyl-3,5-dihydro-1,2,3,4-oxatriazole), the 4-aza analog of 3-piperonylsydnone (I), was prepared by the reaction of 1-*N*-piperonylsemicarbazide (4) (IIIa) with sodium nitrite and hydrochloric acid according to the general procedure of Boyer and Canter (12) or preferably, by the treatment of 1-*N*-nitroso-1-*N*-piperonylsemicarbazide (IIIb) with nitrosyl chloride.



IIIa R = H
b R = NO

IV

Preparation of anhydro-2-hydroxy-4-piperonyl-1,3,5-oxadiazolium hydroxide (VIII, pseudo-2-oxo-4-piperonyl-2,4-dihydro-1,3,5-oxadiazole) was also realized, albeit in very low yield, from *N*-formyl-*N*-piperonylhydrazine (VIIa). Compound VIIa was in turn obtained from *t*-butyl 3-piperonylidenecarbazate (V) *via* intermediates VIa and VIb. Attempted preparation of VIII from the formylated semicarbazide VIIb was not successful in our hands.



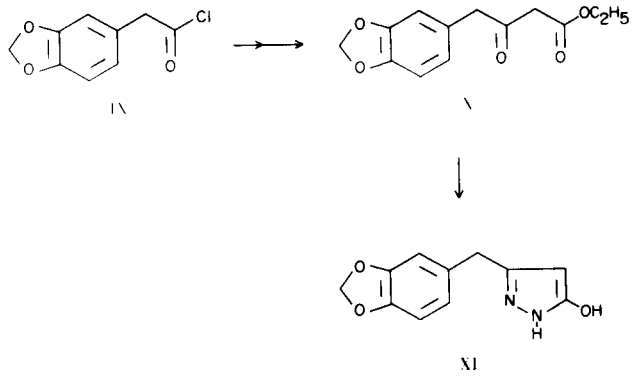
V

VIa R = H
b R = CHO

VIIa R = H
b R = $CONH_2$

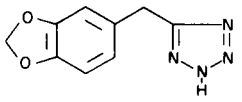
VIII

Preparation of some 1- and 4-piperonylpyrazole derivatives were reported previously (4). A 3-piperonylpyrazole derivative XI was prepared as follows. Homopiperonyloyl chloride (IX), prepared by chlorination of homopiperonylic acid (4) with thionyl chloride, was treated with the sodio derivative of benzyl ethyl malonate. The resulting intermediate was debenzylated and decarboxylated to give ethyl 3-oxo-3-piperonylpropionate (X). Cyclization of the keto ester with hydrazine readily yielded 3-piperonyl-5-hydroxypyrazole (XI).



IX X XI

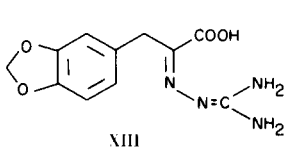
Since quite a number of piperonyl derivatives possessing antimalarial activity were found to contain a *N-N* linkage (4), a piperonyltetrazole XII was prepared by treatment of homopiperonyl nitrile with sodium azide according to the general procedure of Finnegan, *et al.* (13).



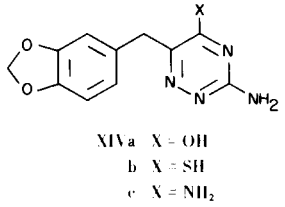
XII

It is of interest to note that although compound II possesses good antimalarial activity, a closely related homolog, 2,4-diamino-6-methyl-5-piperonylpyrimidine (14), was found to be inactive against *P. berghei* (15). In view of the close structural and possible biological relationships of diaminopyrimidines, diamino-1,2,4-triazines and guanazoles (16), 3,5-diamino-6-piperonyl-1,2,4-triazine (XIVc) and 3,5-diamino-1-piperonyl-1,2,4-triazole (XVI) were prepared.

Our synthetic approach to compound XIVc was based on a reaction sequence of Ueda and Furukawa (17) for the preparation of 6-alkyl-3-amino-5-hydroxy-1,2,4-triazines. The intermediate guanylhydrazone XIII was readily prepared from 3,4-methylenedioxyphenylpyruvic acid (18,19). Treatment of compound XIII with potassium carbonate gave 3-amino-5-hydroxy-6-piperonyl-1,2,4-triazine (XIVa). The desired compound XIVc was obtained by thiation of XIVa (to give XIVb) followed by amination.

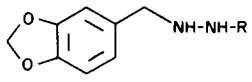


XIII

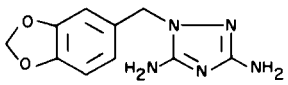


XIVa X = OH
b X = SH
c X = NH_2

For the synthesis of the diaminotriazole XVI, the intermediate piperonylhydrazine (XVb) was prepared from ethyl 2-piperonylcarbazate (XVa) rather than from piperonal azine by the Curtius' method (2,20). The latter method was found to be rather lengthy and the yield was unsatisfactory. The guanazole XVI was obtained by the treatment fo XVb with cyanoguanidine.

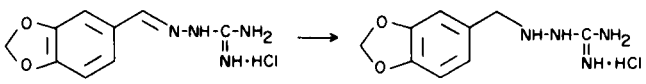


XVa R = COC_2H_5
b R = H

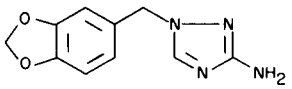


XVI

A corresponding monoaminotriazole XIX was prepared by the following sequence of reactions. Piperonylideneaminoguanidine hydrochloride (XVII) was prepared by condensation of piperonal and aminoguanidine hydrochloride. This substituted guanidine salt was readily reduced to XVIII, which, on treatment with formic acid, was cyclized to give XIX.

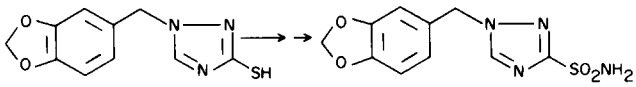


XVII XVIII



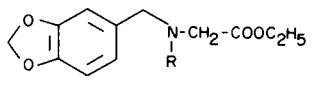
XIX

The fact that many *N*-unsubstituted sulfonamides are carbonic anhydrase inhibitors (21-25) and that these inhibitors, in general, have substantial degrees of affinity for erythrocytes (26-32) suggested the preparation of compounds such as 1-piperonyl-3-sulfamoyl-1,2,4-triazole (XXI). This compound was prepared by the oxidative chlorination of 3-mercapto-1-piperonyl-1*H*-1,2,4-triazole (4) (XX) followed by treatment of the resulting intermediate sulfonyl chloride with ammonia.

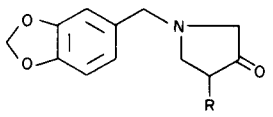


XX XXI

An *N*-substituted pyrrolidone XXIIIb was synthesized by the following procedure: the ethyl ester of *N*-piperonylglycine (XXIIa) was treated with ethyl acrylate to yield the diethyl ester XXIIb. Intramolecular Claisen condensation of XXIIb furnished the pyrrolidone ester XXIIIa in good yield. The latter was decarboxylated in acid to give 1-piperonyl-3-pyrrolidone (XXIIIb).

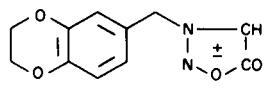


XXIIa R = H
b R = CH_2-CH_2-$COOC_2H_5$

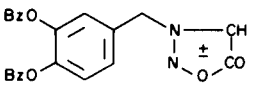


XXIIIa R = $COOC_2H_5$
b R = H

Modification of the methylenedioxyphenyl portion of compounds I and II have also been studied. 3-(3,4-Ethylenedioxybenzyl)sydnone (XXIV) and 3-(3,4-dibenzyloxybenzyl)syndnone (XXV) were prepared in several steps from 1,4-benzodioxan-6-carboxaldehyde (33,34) and 3,4-benzyloxybenzaldehyde, respectively, in a fashion similar to that for preparation of I.

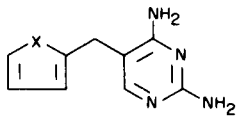


XXIV

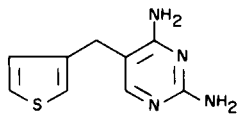


XXV

2,4-Diamino-5-furfurylpyrimidine (XXVIa), 2,4-diamino-5-(2-thenyl)pyrimidine (XXVIb) and 2,4-diamino-5-(3-thenyl)pyrimidine (XXVII) were prepared from a mixture of guanidine, 3-methoxypropionitrile and the appropriate carboxaldehyde according to the general procedure for the synthesis of 5-benzylpyrimidines (3).



XXVIa X = O
b X = S



XXVII

Available antimalarial screening results indicated that, at either 320 or 640 mg./kg., 3-(3,4-ethylenedioxybenzyl)-sydnone (XXIV) doubled the survival time of noninbred ICR/Ha Swiss mice infected with *P. berghei*. Both compound XXIV and 1-formyl-1-piperonylsemicarbazide (VIIb) at concentrations of 0.1% in sucrose solution, caused complete suppression of sporozoite (*P. gallinaceum*) development in the salivary glands of *Aedes aegypti*.

EXPERIMENTAL

Melting points were taken on a Thomas-Hoover melting point apparatus. The ultraviolet absorption spectra were determined with a Beckman DK-2 spectrophotometer. The infrared spectra were taken with a Perkin-Elmer Infracord.

Anhydro-5-hydroxy-3-piperonyl-1,2,3,4-oxatriazolium Hydroxide (Pseudo-5-oxo-3-piperonyl-3,5-dihydro-1,2,3,4-oxatriazole, IV).

Method A.

A slurry of 6.3 g. (0.03 mole) of 1-*N*-piperonylsemicarbazide (4) (IIIa) in 40 ml. of 6*N* hydrochloric acid was treated with 50 ml. of 10% aqueous sodium nitrite (0.07 mole) at 0-5° over a period of 40 minutes. The mixture was then stirred in a water bath at 50° for 30 minutes and cooled. The solid was collected by filtration, washed with water, methanol, ether, and air dried. This material (4 g.), on extraction with boiling benzene, afforded an insoluble residue (2.2 g.), m.p. 144-145°, which was identified as 1-*N*-nitroso-1-*N*-piperonylsemicarbazide (IIb, 32% yield). The benzene-soluble extract, upon cooling, yielded 1.4 g. of tan crystals, m.p. 116-118°. Another 0.2 g. portion of material melting at 113-115° was obtained by concentration of the filtrate. These were combined and recrystallized from ethanol to give 1.2 g. (18% yield) of IV, m.p. 117-118°. An analytical sample was prepared by recrystallization from a mixture of benzene and hexane to yield pale yellow crystals, m.p. 118-119°. The infrared spectrum showed no N-H absorption in the 2.8-3.2 μ region. A C=O bond was present at 5.62 μ, a characteristic feature for mesoionic compounds which was noted previously (4); λ max (ethanol) 239 mμ (ϵ, 5,100), 281 mμ (ϵ, 4,400).

Anal. Calcd. for $C_9H_7N_3O_4$: C, 48.87; H, 3.19; N, 19.00. Found: C, 49.07; H, 2.89; N, 19.20.

Method B.

A fine suspension of 9.2 g. (0.044 mole) of IIIa in 36 ml. of 6*N* hydrochloric acid was cooled to 0°. To the stirred mixture was added dropwise 90 ml. (0.13 mole) of 10% aqueous sodium nitrite. After the addition was complete, the mixture was stirred for 2 hours at 0° and filtered. The solid product, after washing with water and drying *in vacuo*, weighed 11.0 g., m.p. 138-140°. Recrystallization of the product from ethyl acetate gave 4.5 g. (47% yield) of analytically pure IIIb as white rosettes, m.p. 148-150°.

Anal. Calcd. for $C_9H_{10}N_4O_4$: C, 45.38; H, 4.23; N, 23.52. Found: C, 45.60; H, 4.41; N, 23.40.

Three and one-half g. (0.014 mole) of IIIb was dissolved in 20 ml. of warm 2-methoxyethanol. The solution was diluted with 200 ml. of chloroform. To the resulting solution was added in one portion, a solution of 1.0 g. (0.015 mole) of nitrosyl chloride in 25 ml. of chloroform. After the initial gas evolution had subsided, the mixture was heated at 60° for 2 minutes and cooled. The reaction mixture was extracted successively with a saturated sodium bicarbonate solution and water. The remaining organic layer was dried over anhydrous sodium sulfate and the solvent was removed *in vacuo* to yield a solid residue. This was recrystallized from a mixture of benzene and hexane to give 1.6 g. (49% yield) of IV, m.p. 117-119°. The product was found to be identical with that prepared by Method A.

t-Butyl 3-Piperonylidenecarbazate (V).

A solution of 15 g. (0.1 mole) of piperonal and 13.2 g. (0.1 mole) of *t*-butyl carbazate in 200 ml. of ethanol was refluxed for 1 hour. Ethanol was then distilled until the volume of the reaction mixture was *ca.* 100 ml. The product, which crystallized on cool-

ing, was collected by filtration. The filtrate, upon being evaporated to one-half of its original volume, deposited a second crop of product to give a total of 22 g. (84% yield) of V as white needles, m.p. 159-161°. An analytical sample was prepared by recrystallization from methanol, m.p. 159-161°.

Anal. Calcd. for $C_{13}H_{16}N_2O_4$: C, 59.08; H, 6.10; N, 10.60. Found: C, 59.33; H, 6.15; N, 10.40.

t-Butyl 3-Piperonylcarbazate (VIa).

A suspension of 13.2 g. (0.05 mole) of V and 1 g. of 5% palladium-on-charcoal in 150 ml. of ethanol was hydrogenated at 50 psig. Hydrogen uptake was completed after 1 hour. The catalyst was removed by filtration and the filtrate evaporated *in vacuo* to dryness. The resulting syrupy residue crystallized when triturated with cold methanol. The product was collected by filtration to give 9.5 g. (71% yield) of VIa as white plates, m.p. 78-79°. An analytical sample was prepared by recrystallization from hexane, m.p. 73-75°; I.R.: 3.10 μ (N-H), 5.95 μ (carbamate C=O).

Anal. Calcd. for $C_{13}H_{18}N_2O_4$: C, 58.63; H, 6.81; N, 10.52. Found: C, 58.34; H, 7.05; N, 10.40.

t-Butyl 3-Formyl-3-piperonylcarbazate (VIb).

To 13.3 g. (0.05 mole) of VIa was added 150 ml. of formic acid-acetic anhydride mixture (prepared by allowing 75 ml. of 98-100% formic acid and 100 ml. of acetic anhydride to stand at room temperature for 72 hours). The resulting solution was held at room temperature for 24 hours and then poured onto 500 g. of crushed ice. The product, which initially separated as an oil, gradually solidified on standing at 0°. After 3 hours the solid was collected by filtration and recrystallized from methanol to give 9.1 g. (62% yield) of VIb as white needles, m.p. 82-84°. Recrystallization from hexane gave an analytical sample, m.p. 83-84°; IR: 3.18 μ (N-H), 5.88 μ (carbamate C=O) and 6.10 μ (formamide C=O).

Anal. Calcd. for $C_{14}H_{18}N_2O_5$: C, 57.13; H, 6.17; N, 9.52. Found: C, 57.43; H, 6.05; N, 9.55.

N-Formyl-*N*-piperonylhydrazine (VIIa).

To 2.9 g. (0.01 mole) of VIb was added 30 ml. of nitromethane saturated with hydrogen chloride. The solid dissolved initially and within 30 seconds a solid precipitated from the reaction solution. The reaction mixture was allowed to stand at room temperature for 40 minutes and then evaporated *in vacuo* to dryness. The residue was cautiously treated with cold, saturated aqueous potassium bicarbonate until effervescence ceased. The resulting solution was extracted once with chloroform and three times with ether. The organic extracts were combined, dried (sodium sulfate), and evaporated. The oily residue was crystallized from carbon tetrachloride to afford 1.7 g. (89% yield) of VIIa as white needles, m.p. 69-70°. A second recrystallization from carbon tetrachloride gave an analytical sample, m.p. 70-71°; IR: 3.08-3.18 μ (doublet, primary N-H), 6.05 μ (formamide C=O).

Anal. Calcd. for $C_9H_{10}N_2O_3$: C, 55.67; H, 5.19; N, 14.43. Found: C, 55.89; H, 5.14; N, 14.66.

1-Formyl-1-piperonylsemicarbazide (VIIb).

A solution of 10.5 g. (0.05 mole) of 1-*N*-piperonylsemicarbazide (4) in 100 ml. of 98-100% formic acid was heated under reflux for 1 hour. The resulting solution was poured onto crushed ice and the mixture neutralized with 40% sodium hydroxide at < 20°. After standing overnight at 6°, the precipitated solid was collected by filtration. Recrystallization from 2-methoxyethanol gave 7.2 g. (61% yield) of VIIb as white needles, m.p. 204-205°; IR: 2.90 μ, 3.05 μ, 3.10 μ (N-H), 6.0 μ (amide C=O).

Anal. Calcd. for $C_{10}H_{11}N_3O_4$: C, 50.63; H, 4.67; N, 17.22. Found: C, 50.53; H, 4.47; N, 17.43.

Anhydro-2-hydroxy-4-piperonyl-1,3,5-oxadiazolium Hydroxide (Pseudo-2-oxo-4-piperonyl-2,4-dihydro-1,3,5-oxadiazole (VIII).

To a solution of 1.9 g. (0.01 mole) of VIIa in 25 ml. of chloroform there was added 10 g. of anhydrous potassium carbonate followed by 20 ml. of a saturated solution of phosgene in chloroform. The suspension was stirred for 2 hours at room temperature and then boiled for 30 minutes. The resulting mixture was filtered and the filtrate evaporated *in vacuo*. The gummy residue was extracted with hot benzene. The benzene extract was taken to dryness *in vacuo* and the residual oil extracted with boiling hexane. On standing at room temperature for 5 days, crystals slowly separated from the hexane solution. The solid was collected by filtration. Recrystallization of the crude product from benzene gave 32 mg. (1.5% yield) of VIII as pale yellow cubes, m.p. 92-93°. The infrared spectrum revealed an absence of N-H absorption in the 3 μ region. Characteristic C=O and C=N (mesoionic) absorption were noted at 5.55 μ and 5.70 μ; λ max (ethanol) 235 mμ (ε, 4,300), 285 mμ (ε, 3,900).

Anal. Calcd. for $C_{10}H_8N_2O_4$: C, 54.55; H, 3.66; N, 12.72. Found: C, 54.34; H, 3.48; N, 12.63.

Homopiperonyloyl Chloride (IX).

To a stirred solution of 80 ml. of thionyl chloride in 1 l. of benzene was added 72 g. (0.4 mole) of homopiperonylic acid (4). The mixture was stirred for 30 minutes at room temperature, refluxed for 2 hours and then cooled. Benzene and excess thionyl chloride were removed under reduced pressure and the residue was distilled to give 67 g. (83% yield) of IX, b.p. 142-144°/8 mm. n_D^{20} 1.5580; IR: 5.6 μ (C=O).

Anal. Calcd. for $C_9H_7ClO_3$: C, 54.43; H, 3.55; Cl, 17.85. Found: C, 54.25; H, 3.58; Cl, 17.67.

Ethyl 3-Oxo-3-piperonylpropionate (X).

A solution of 66.2 g. (0.3 mole) of benzyl ethyl malonate (35) in 250 ml. of ether was added in 50 minutes to a stirred mixture of 6.9 g. (0.3 g.-atom) of sodium pellets in 400 ml. of ether under nitrogen. The mixture was stirred and refluxed for 3 days. To the reaction mixture was added a solution of 30 g. (0.15 mole) of IX in 50 ml. of ether in 10 minutes with stirring. The resulting mixture was refluxed for 30 minutes. The insoluble solid was collected by filtration, washed with water, and decomposed by shaking with 800 ml. of ether with 200 ml. of 6*N* sulfuric acid. The ether layer was dried over calcium sulfate, filtered, and the filtrate evaporated. The residue was dissolved in 2-butanone and hydrogenated in a Parr hydrogenator in the presence of 3 g. of 5% palladium-on-calcium carbonate. The catalyst was removed by filtration and the filtrate was refluxed for 30 minutes. Removal of solvents followed by distillation of the residue *in vacuo* through a 20-cm. column gave 16.5 g. (44% yield) of X, b.p. 155-165°/0.6-0.8 mm., m.p. 19-21°, n_D^{20} 1.5274; IR: 5.75 μ (C=O), 5.85 μ (C=O), λ max (*p*H 11) 277 mμ (ε, 1,800).

Anal. Calcd. for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.69; H, 5.88.

3-Piperonyl-5-hydroxypyrazole (XI).

The general procedure of Sonn and Litten was used (36). One gram (0.02 mole) of hydrazine hydrate was mixed thoroughly with a solution of 5.0 g. (0.02 mole) of X in 20 ml. of ether. After 1 hour the precipitated white solid was collected by filtration and recrystallized from 50% ethanol to give 2.1 g. (48% yield) of XI, m.p. 213-215°; λ max (*p*H 1) 285 mμ (ε, 3,700); λ max (*p*H 11) 233 mμ (ε, 10,200), 285 mμ (ε, 3,700).

Anal. Calcd. for $C_{11}H_{10}N_2O_3$: C, 60.55; H, 4.62; N, 12.84. Found: C, 60.85; H, 4.57; N, 12.92.

5-Piperonyltetrazole (XII).

A mixture of 6.5 g. (0.04 mole) of homopiperonylnitrile (37), 2.9 g. (0.044 mole) of sodium azide, and 0.2 g. (0.044 mole) of ammonium chloride in 20 ml. of dimethylformamide was stirred and heated at 120° for 10 hours. To the cooled reaction mixture was added 30 ml. of water. The *p*H of the resulting solution was adjusted to 2 by the addition of concentrated hydrochloric acid. On cooling, 6.1 g. (74% yield) of crude solid product was obtained. Recrystallization from 50% ethanol gave 2.5 g. of analytically pure XII, m.p. 176-177°.

Anal. Calcd. for $C_9H_8N_4O_2$: C, 52.94; H, 3.95; N, 27.44. Found: C, 53.18; H, 3.94; N, 27.54.

3,4-Methylenedioxyphenylpyruvic Acid Guanylhydrazone (XIII).

A mixture of 7.4 g. of 3,4-methylenedioxyphenylpyruvic acid (18,19) and 50 ml. of water was added to a solution of aminoguanidine hydrochloride [prepared from 5.1 g. (0.38 mole) of aminoguanidine bicarbonate, 50 ml. of water and enough 10% hydrochloric acid to dissolve the bicarbonate]. The mixture was brought to boiling and enough ethanol was added to the boiling mixture to yield a clear solution, after which the solution was refluxed for 30 minutes and then was left at room temperature overnight. The product, which had then crystallized, was collected by filtration and washed successively with water, methanol, and ether, and dried. There was obtained 7 g. (70% yield) of XIII, m.p. 317-319°. The compound crystallized from 2-methoxyethanol as white needles with one molecule of solvent, m.p. 317-319°.

Anal. Calcd. for $C_{11}H_{12}N_4O_4 \cdot C_3H_8O_2$: C, 49.41; H, 5.92; N, 16.46. Found: C, 49.44; H, 5.88; N, 16.59.

3-Amino-5-hydroxy-6-piperonyl-1,2,4-triazine (XIVa).

A mixture of 10.6 g. (0.04 mole) of XIII, 8.3 g. (0.06 mole) of potassium carbonate and 120 ml. of water was refluxed for 3 hours (until nearly all solid has dissolved). The still-hot solution was freed from any suspended matter by filtration. The filtrate was cooled, acidified with glacial acetic acid, and the precipitated product was collected by filtration. It was washed with water, methanol and ether, and dried to give 8.2 g. (85% yield) of XIVa, m.p. > 300° dec. An analytical sample was obtained after two recrystallizations from dimethylformamide, m.p. 323-324° dec.

Anal. Calcd. for $C_{11}H_{10}N_4O_3$: C, 53.66; H, 4.09; N, 22.76. Found: C, 53.61; H, 3.72; N, 23.12.

3-Amino-5-mercapto-6-piperonyl-1,2,4-triazine (XIVb).

A mixture of 8.1 g. (0.033 mole) of XIVa, 25 g. of phosphorus pentasulfide and 100 ml. of pyridine was refluxed for 1 hour. The reaction mixture was concentrated to 50 ml., cooled, and poured into ice water. The resulting mixture was heated on a steam bath for 4 hours with occasional stirring and then was allowed to stand at room temperature overnight. The crude solid (7.5 g.) was collected by filtration and recrystallized from dimethylformamide and then from ethanol to give 6.0 g. (70% yield) of XIVb, m.p. >260° dec.; λ max 287 mμ (*p*H 1) (ε, 7,400), 322 mμ (ε, 8,900); λ max (*p*H 11) 286 mμ (ε, 6,300), 340 mμ (ε, 9,000).

Anal. Calcd. for $C_{11}H_{10}N_4O_2S$: C, 50.37; H, 3.84; N, 21.36. Found: C, 50.67; H, 3.86; N, 21.45.

3,5-Diamino-6-piperonyl-1,2,4-triazine (XIVc).

A mixture of 1.3 g. (0.005 mole) of XIVb and 200 ml. of saturated ethanolic ammonia was heated in an autoclave at 140-150° for 20 hours. The mixture was cooled and the crude solid product (1.1 g.) was isolated by filtration. Recrystallization from water gave 0.9 g. (75% yield) of analytically pure XIVc, m.p. 236° dec.; λ max (*p*H 11) 229 mμ (ε, 14,000), 291 mμ (ε, 8,400).

Anal. Calcd. for $C_{11}H_{11}N_5O_2$: C, 53.87; H, 4.52; N, 28.56. Found: C, 54.00; H, 4.72; N, 28.86.

Ethyl 2-Piperonylcarbazate (XVa).

Two g. of 5% palladium-on-charcoal was added to a solution of 11.8 g. (0.05 mole) of ethyl 2-piperonylidenecarbazate [prepared from piperonal and ethyl carbazate (38) m.p. 111-112°] in 200 ml. of 2-butanone. The mixture was shaken on a Parr hydrogenator at 50 psig of hydrogen for 2 hours. The catalyst was separated by filtration and the filtrate was evaporated under reduced pressure. The resulting residue was recrystallized from ethanol to give 8.7 g. (73% yield) of XVa, m.p. 99-101°; IR: 3.1 μ (NH), 6.0 μ (C=O); λ max (*p*H 1) 239 mμ (ε, 3,300), 284 mμ (ε, 2,600); λ max (*p*H 11) 235 mμ (ε, 4,100), 283 mμ (ε, 3,600).

Anal. Calcd. for $C_{11}H_{14}N_2O_4$: C, 55.46; H, 5.92; N, 11.76. Found: C, 55.77; H, 6.24; N, 12.04.

Piperonylhydrazine (XVb).

A mixture of 9.5 g. (0.04 mole) of XVa and 60 ml. of 6*N* sodium hydroxide was refluxed for 3 hours under nitrogen. The cooled solution was extracted with ether (4 x 100 ml.) and the extracts were evaporated to dryness under reduced pressure. The crude liquid product was immediately cooled to 10° and carefully treated with a slight excess amount of concentrated hydrochloric acid. The resulting salt was collected by filtration, washed with ether and recrystallized from ethanol to give 3.5 g. (43% yield) of the hydrochloride of XVb, m.p. 177-179° (lit (20) m.p. 173.5°).

3,5-Diamino-1-piperonyl-1*H*-1,2,4-triazole (XVI).

A mixture of 6.1 g. (0.03 mole) of XVb·HCl and 2.5 g. (0.03 mole) of cyanoguanidine in 15 ml. of water was stirred and refluxed for 2 hours. On cooling, a white precipitate was formed. This was collected by filtration, washed with water and cold ethanol, and dried to give 2.0 g. of solid. Recrystallization from 50 ml. of 50% ethanol afforded 1.5 g. (21% yield) of XVI, m.p. 209-211°. The infrared spectrum showed NH absorption at 3.05 μ and no C≡N absorption was observed; λ max (*p*H 1, 11) 284 mμ (ε, 3,500).

Anal. Calcd. for $C_{10}H_{11}N_5O_2$: C, 51.50; H, 4.75; N, 30.03. Found: C, 51.27; H, 4.54; N, 29.84.

Piperonylideneaminoguanidine Hydrochloride (XVII).

A stirred suspension of 40.8 g. (0.3 mole) of aminoguanidine carbonate in 150 ml. of water was carefully made acidic with concentrated hydrochloric acid to *p*H 2. After allowing to stand at room temperature for 30 minutes, the mixture was filtered. To the filtrate was added, with stirring, a solution of 45 g. (0.3 mole) of piperonal in 250 ml. of ethanol. The resulting solution was refluxed for 2 hours and was then kept at 5° overnight. The precipitated yellow product was collected by filtration, washed with ethanol and dried *in vacuo* to give 54 g. (73% yield) of XVII, m.p. 220-222°. Recrystallization from ethanol gave an analytically pure sample, m.p. 223-225°; λ max (*p*H 1) 285 mμ (ε, 15,100), 315 mμ (ε, 17,700); λ max (*p*H 11) 324 mμ (ε, 21,200).

Anal. Calcd. for $C_9H_{11}ClN_4O_2$: C, 44.54; H, 4.57; N, 23.09. Found: C, 44.79; H, 4.60; N, 23.13.

Piperonylaminoguanidine Hydrochloride (XVIII).

A mixture of 12.2 g. (0.05 mole) of XVII and 2 g. of 5% palladium-on-charcoal in 250 ml. of ethanol and 25 ml. of water was shaken in a Parr hydrogenator at 50 psig for 90 minutes. After removal of the catalyst by filtration, the solution was combined with the filtrate from another run of similar scale. The combined solution was evaporated to yield a colorless syrup which crystallized on standing to give 24 g. of white solid. Recrystallization from 50

ml. of ethanol gave 17 g. (70% yield) of XVIII, m.p. 140-142°; λ max (*p*H 1, 11) 284 mμ (ε, 3,400); λ max (*p*H 11) 234 mμ (ε, 4,200).

Anal. Calcd. for $C_9H_{13}ClN_4O_2$: C, 44.18; H, 5.36; N, 22.90. Found: C, 44.40; H, 5.28; N, 22.84.

3-Amino-1-piperonyl-1*H*-1,2,4-triazole (XIX).

A mixture of 4.9 g. (0.02 mole) of XVIII and 7 ml. of 98% formic acid was stirred and refluxed for 90 minutes. The solvent was removed under reduced pressure. Treatment of the residue with 30% cold sodium hydroxide to *p*H 9 gave a water-soluble pink oil. The water was removed *in vacuo* and the solid residue was recrystallized from 100 ml. of ethanol to give 2 g. (47% yield) of XIX as a white solid, m.p. 196-197°; λ max (*p*H 11) 234 mμ (ε, 6,900); λ max (*p*H 1, 11) 284 mμ (ε, 3,800).

Anal. Calcd. for $C_{10}H_{10}N_4O_2$: C, 55.04; H, 4.62; N, 25.68. Found: C, 55.27; H, 4.79; H, 25.84.

1-Piperonyl-3-sulfamoyl-1*H*-1,2,4-triazole (XXI).

Through a stirred suspension of 4.7 g. (0.02 mole) of 3-mercapto-1-piperonyl-1*H*-1,2,4-triazole (4) (XX) in 100 ml. of 30% aqueous acetic acid cooled at 5° was bubbled a stream of chlorine gas at $<10°$ for 40 minutes. The solid thus obtained was collected by filtration, washed with ice water and added to 50 ml. of concentrated aqueous ammonia. The mixture was heated on a steam bath for 15 minutes and filtered. The filtrate was adjusted to *p*H 5 with glacial acetic acid. The solid was collected by filtration and extracted repeatedly with boiling methanol. The methanolic solution was evaporated and the residue was recrystallized three times from water to give 1.2 g. (22% yield) of XXI as buff plates, m.p. 183-185°. An analytical sample was prepared by recrystallization from ethanol, m.p. 185-186°.

Anal. Calcd. for $C_{10}H_{10}N_4O_4S$: C, 42.55; H, 3.57; N, 19.85. Found: C, 42.12; H, 3.30; N, 19.52.

Longer reaction or higher reaction temperature yielded 1-(6-chloropiperonyl)-3-sulfamoyl-1,2,4-triazole as tan plates, m.p. 204-205° (from 2-methoxyethanol).

Anal. Calcd. for $C_{10}H_9ClN_4O_4S$: C, 39.92; H, 2.86; N, 17.69. Found: C, 38.01; H, 3.09; N, 17.55.

Ethyl *N*-Piperonylglycinate (XXIIa).

To a refluxing solution of 50 g. (0.33 mole) of piperonylamine and 33.4 g. (0.33 mole) of triethylamine in 250 ml. of benzene was added, with stirring, 55 g. (0.33 mole) of ethyl bromoacetate. The mixture was stirred and refluxed for 3 hours and the solid was filtered and washed with benzene. The combined filtrate and washings were evaporated under reduced pressure and the product was distilled *in vacuo* to give 62.5 g. (80% yield) of XXIIa, b.p. 136-139°/0.3 mm., n_D^{20} 1.5250.

Anal. Calcd. for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.99; H, 6.16; N, 6.13.

Ethyl *N*-Piperonyl-*N*-carbethoxyethylglycinate (XXIIb).

A mixture of 23.7 g. (0.1 mole) of XXIIa, 11 g. (0.11 mole) of ethyl acrylate and 0.1 ml. of benzyl trimethylammonium hydroxide (40% in methanol) was refluxed for 24 hours. Excess solvents were evaporated under reduced pressure and the product was distilled *in vacuo* to give 15 g. (44% yield) of XXIIb, b.p. 153-158°/0.2 mm.; n_D^{20} 1.5086; λ max (*p*H 1) 240 mμ (ε, 4,600); λ max (*p*H 1, 11) 285 mμ (ε, 3,400); λ max (*p*H 11) 235 mμ (ε, 3,600).

Anal. Calcd. for $C_{17}H_{23}NO_6$: C, 60.52; H, 6.87; N, 4.15. Found: C, 60.77; H, 7.00; N, 4.41.

3-Ethoxycarbonyl-1-piperonyl-1*H*-4-pyrrolidone (XXIIIa).

This compound was prepared by the general procedure of Jaeger and Biel (39). To a slurry of 5.60 g. (0.05 mole) of potassium *t*-butoxide in 75 ml. of toluene was added, at 5°, 16.9 g. (0.05 mole) of XXIIb in 30 minutes. The resulting mixture was stirred at 10° for 2 hours followed by 18 hours standing at 5°. It was then extracted twice with 25 ml. of cold water. The combined aqueous extracts were washed three times with ether and the *p*H of the aqueous solution was adjusted to 2. This was again washed three times with ether and finally neutralized with potassium carbonate. The separated oil was extracted with ether (3 x 50 ml.). The etheral extracts were dried and evaporated. The residual liquid was distilled at 80°/10 mm. to give 8.3 g. (57% yield) of XXIIIa, n_D^{20} 1.5276. The infrared spectrum showed two C=O absorptions at 5.70 and 5.85 μ; λ max (*p*H 1) 240 mμ (ε, 5,800), 284 mμ (ε, 4,100); λ max (*p*H 11) 236 mμ (ε, 5,500), 283 mμ (ε, 20,400).

Anal. Calcd. for $C_{15}H_{17}NO_5$: C, 61.84; H, 5.88; N, 4.81. Found: C, 62.09; H, 5.72; N, 4.72.

1-Piperonyl-1*H*-3-pyrrolidone (XXIIIb).

A mixture of 43.6 g. (0.15 mole) of XXIIIa, 15 ml. of concentrated hydrochloric acid and 400 ml. of water was refluxed with stirring for 2 hours. It was cooled and the *p*H was adjusted to 8 with potassium carbonate. The resulting oil was extracted with ether. The ethereal extract was dried and concentrated under reduced pressure. The residual oil was distilled *in vacuo* to give 13 g. (40% yield) of XXIIIb, b.p. 132-138°/0.2 mm. n_D^{20} 1.5553; IR: 5.75 μ (C=O); λ max (*p*H 1) 239 mμ (ε, 4,600); λ max (*p*H 1, 11) 234 mμ (ε, 4,400); λ max (*p*H 11) 284 mμ (ε, 4,100).

Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.91; H, 6.27; N, 6.35.

1,4-Benzodioxan-6-carboxaldoxime.

A mixture of 14.8 g. (0.09 mole) of 1,4-benzodioxan-6-carboxaldehyde (34), 7.0 g. (0.1 mole) of hydroxylamine hydrochloride, 3.6 g. (0.09 mole) of sodium hydroxide in 80 ml. of water and 50 ml. of ethanol was refluxed for 2 hours. The reaction mixture was then evaporated to two-thirds of its original volume whereupon the aqueous and the organic layers separated. The organic layer was isolated and concentrated under reduced pressure. It was then distilled to give 13.9 g. (86% yield) of a product, b.p. 130°/0.16 mm., m.p. 54-59°; λ max (*p*H 1) 266 mμ (ε, 12,400); λ max (*p*H 11) 270 mμ (ε, 13,400).

Anal. Calcd. for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.14; H, 4.94; N, 7.88.

6-Aminomethyl-1,4-benzodioxan Hydrochloride.

Method A.

A mixture of 18.0 g. (0.1 mole) of 1,4-benzodioxan-6-carboxaldoxime, 1.5 g. of 5% palladium-on-charcoal and 250 ml. of glacial acetic acid was hydrogenated at 50 psig. The catalyst was removed by filtration and the filtrate evaporated under reduced pressure. To the syrupy residue was carefully added 30 ml. of saturated ethanolic hydrogen chloride. The resulting mixture was evaporated to dryness. The residue was treated with 50 ml. of hot absolute ethanol and the insoluble secondary amine, formed as a by-product, was removed by filtration. The filtrate was again evaporated to dryness and the residue was recrystallized from butanol to give 8 g. (40% yield) of product, m.p. 196-198°; λ max (*p*H 1, 11) 281 mμ (ε, 3,200).

Anal. Calcd. for $C_9H_{11}NO_2 \cdot HCl$: C, 53.60; H, 6.00; N, 6.95. Found: C, 53.83; H, 5.83; N, 6.77.

Method B.

To a stirred mixture of 2.6 g. (0.07 mole) of lithium aluminum hydride in 35 ml. of anhydrous tetrahydrofuran was added, at 60°,

a solution of 9 g. (0.05 mole) of 1,4-benzodioxan-6-carboxaldoxime in 25 ml. of anhydrous tetrahydrofuran. The addition was conducted at such a rate as to cause gentle refluxing of the reaction mixture (*ca.* 30 minutes). After the addition was complete, the resulting mixture was refluxed for 2 hours and cooled. To the mixture was cautiously added 20 ml. of water. The insoluble solid was removed by filtration and washed with ether. The combined filtrate and washings were evaporated to dryness. The syrupy residue was dissolved in 50 ml. of ether, dried, diluted with a mixture of 50 ml. of anhydrous ether and 50 ml. of absolute ethanol, and saturated with dry hydrogen chloride. The precipitated amine salt was collected by filtration, washed with benzene, and dried at room temperature to give 10 g. of crude hydrochloride salt, m.p. 180-187°. Recrystallization from butanol gave 5.0 g. (50% yield) of 6-aminomethyl-1-4-benzodioxan hydrochloride, m.p. 199-201°. The product was found to be identical with that prepared by Method A.

N-(3,4-Ethylenedioxybenzyl)glycine Hydrochloride.

To a stirred mixture of 30.3 g. (0.15 mole) of 6-aminomethyl-1,4-benzodioxan hydrochloride and 30.2 g. (0.30 mole) of triethylamine in 150 ml. of benzene was added 25 g. (0.15 mole) of ethyl bromoacetate. The mixture was refluxed for 1 hour with stirring. It was cooled and extracted with ether to remove the unreacted ester. The aqueous solution was acidified with concentrated hydrochloric acid and cooled at 0° for 1 hour. The resulting precipitate was collected by filtration, washed with cold ethanol and dried. Recrystallization from ethanol gave 18 g. (48% yield) of product, m.p. 236-238° dec.

Anal. Calcd. for $C_{11}H_{13}NO_4 \cdot HCl$: C, 50.87; H, 5.43; N, 5.39. Found: C, 51.00; H, 5.33; N, 5.47.

N-(3,4-Ethylenedioxybenzyl)-*N*-nitrosoglycine.

A solution of 6.9 g. (0.1 g.-atom) of sodium nitrite in 20 ml. of water was added, at 5°, to a stirred solution of 20.4 g. (0.08 mole) of *N*-(3,4-ethylenedioxybenzyl)glycine hydrochloride and 0.8 ml. of concentrated hydrochloric acid in 350 ml. of water. The mixture was stirred at 5° for 3 hours and was extracted with 3 x 100 ml. of ether. The combined ether extracts were dried and evaporated to yield a yellow oil, which crystallized on standing. It was recrystallized from a mixture of ethyl acetate and petroleum ether (b.p. 60-90°) to give 10 g. (50% yield) of product, m.p. 114-115° dec.

Anal. Calcd. for $C_{11}H_{12}N_2O_5$: C, 52.38; H, 4.80; N, 11.11. Found: C, 52.39; H, 4.85; N, 11.13.

3-(3,4-Ethylenedioxybenzyl)sydnone (XXIV).

A warm (40°) solution of 5.8 g. (0.028 mole) of *N,N'*-dicyclohexylcarbodiimide in 75 ml. of benzene was added in 5 minutes to a hot (70°), stirred solution of 6.3 g. (0.025 mole) of *N*-(3,4-ethylenedioxybenzyl)-*N*-nitrosoglycine in 250 ml. of benzene. The mixture was stirred at 50° for 2 hours. The precipitated *N,N'*-dicyclohexylurea was removed by filtration. The benzene filtrate was evaporated to dryness under reduced pressure and the pale yellow residue was recrystallized from a 1:3 mixture of benzene and petroleum ether (b.p. 60-90°) to give 4.0 g. (68% yield) of XXIV, m.p. 102-104°; IR: 5.85 μ (C=O); λ max (*p*H 1, 11) 285 mμ (ϵ, 9,600).

Anal. Calcd. for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.30; N, 11.96. Found: C, 56.44; H, 4.48; N, 12.22.

3,4-Dibenzyloxybenzaldoxime.

To a stirred solution of 6.1 g. (0.88 mole) of hydroxylamine hydrochloride in 500 ml. of absolute ethanol was added 10 ml. of pyridine and 25.4 g. (0.08 mole) of 3,4-dibenzyloxybenzaldehyde (40). The mixture was stirred at room temperature for 30 minutes and then refluxed for 1 hour. It was then evaporated under reduced pressure to yield a brown syrup. This was taken up in ethyl acetate, washed successively with water, 0.5 *N* hydrochloric acid, and water. The organic layer was treated with charcoal and filtered. The filtrate was dried and evaporated to dryness. The residual liquid, which crystallized on standing, was recrystallized from a mixture (1:1) of benzene and petroleum ether (b.p. 60-90°) to give 19 g. (72% yield) of product, m.p. 86-87°.

Anal. Calcd. for $C_{21}H_{19}NO_3$: C, 75.66; H, 5.74; N, 4.20. Found: C, 75.22; H, 5.84; N, 4.12.

3,4-Dibenzyloxybenzylamine Hydrochloride.

To a stirred solution of 1.9 g. (0.05 mole) of lithium aluminum hydride in tetrahydrofuran (50 ml. of 1 *M* solution) under nitrogen was added during 20 minutes a solution of 16.7 g. (0.05 mole) of 3,4-dibenzyloxybenzaldoxime in 150 ml. of tetrahydrofuran. The resulting mixture was refluxed for 1 hour and decomposed with water and dilute sodium hydroxide. The granular salts were separated by filtration and washed several times with ether. The combined filtrate and washings were evaporated to dryness. The residual syrup was treated with ethereal hydrogen chloride and recrystallized from 2-propanol to give 13 g. (73% yield) of 3,4-dibenzyloxybenzylamine hydrochloride, m.p. 156-157°.

Anal. Calcd. for $C_{21}H_{21}NO_2 \cdot HCl$: C, 70.88; H, 6,23; N, 3.94. Found: C, 71.01; H, 6.00; N, 3.73.

N-(3,4-Dibenzyloxybenzyl)glycine Hydrochloride.

To a hot, stirred mixture of 35.6 g. (0.1 mole) of 3,4-dibenzyloxybenzylamine hydrochloride and 20.2 g. (0.02 mole) of triethylamine in 300 ml. of benzene was added 16.7 g. (0.1 mole) of ethyl bromoacetate over a period of 30 minutes. The resulting mixture was refluxed for 4 hours. The solid salt was separated by filtration and washed with benzene. The combined filtrate and washings were evaporated under reduced pressure to an oily residue, which was refluxed with 25 ml. of 8 *N* sodium hydroxide for 2 hours. The mixture was diluted with 400 ml. of water and extracted with 2 x 50 ml. of ether. The ethereal extract was washed with water, dried and evaporated. The residue was then converted to the hydrochloride salt which, after recrystallization from propanol, gave 9.6 g. (23% yield) of the desired product, m.p. 187-188° dec.

Anal. Calcd. for $C_{23}H_{23}NO_4 \cdot HCl$: C, 66.74; H, 5.84; N, 3.38. Found: C, 66.86; H, 5.68; N, 3.28.

N-(3,4-Dibenzyloxybenzyl)-*N*-nitrosoglycine.

To a stirred mixture of 24.8 g. (0.06 mole) of *N*-(3,4-dibenzyloxybenzyl)glycine hydrochloride and 500 ml. of 30% acetic acid was added dropwise, at 5°, a solution of 5 g. (0.075 mole) of sodium nitrite in 25 ml. of water. Stirring was continued for 1 hour after addition. The supernatant liquid was removed by decantation and the gummy mixture was stirred with 500 ml. of warm ethyl acetate. The unreacted starting material was removed by filtration and the filtrate was evaporated under reduced pressure. The oily residue was induced to crystallization from a hot mixture (7:3) of benzene and petroleum ether (b.p. 60-90°) to give 14 g. (57% yield) of the nitrosoglycine as a white solid, m.p. 118-119°; λ max (*p*H 1, 11) 227 mμ (ϵ, 4,500); λ max (*p*H 11) 233 mμ (ϵ, 17,200).

Anal. Calcd. for $C_{23}H_{22}N_2O_5$: C, 67.97; H, 5.46; N, 6.89. Found: C, 68.03; H, 5.21; N, 6.89.

3-(3,4-Dibenzyloxybenzyl)sydnone (XXV).

A warm solution of 3.4 g. (0.0165 mole) of *N,N*-dicyclohexylcarbodiimide in 50 ml. of benzene was added during 10 minutes to a stirred, refluxing solution of 6.1 g. (0.015 mole) of *N*-(3,4-di-

benzyloxybenzyl)-*N*-nitrosoglycine in 200 ml. of benzene. After the addition was complete, the mixture was refluxed for an additional 2 hours and cooled. The urea was removed by filtration and the filtrate was evaporated under reduced pressure to give a colorless liquid, which crystallized on standing. Recrystallization of this material from a mixture (1:1) of benzene and petroleum ether (b.p. 60-90°) afforded 4.0 g. (69% yield) of XXV, m.p. 93-94°; IR: 5.65 μ, 5.8 μ and 6.6 μ; λ max (*p*H 11) 233 mμ (ϵ, 10,900); λ max (*p*H 1, 11) 283 mμ (ϵ, 10,000).

Anal. Calcd. for $C_{23}H_{20}N_2O_4$: C, 71.12; H, 5.19; N, 7.21. Found: C, 70.99; H, 5.44; N, 7.27.

2,4-Diamino-5-furfurylpyrimidine (XXVIa).

To a solution of 3.5 g. (0.15 g.-atom) of magnesium and 1.5 g. (0.06 g.-atom) of sodium in 200 ml. of methanol there was added 17.0 g. (0.2 mole) of 3-methoxypropionitrile and 16.0 g. (0.17 mole) of furfural. The mixture was heated to boiling and *ca.* 100 ml. of methanol was allowed to evaporate. The resulting reaction mixture was refluxed with stirring for 18 hours, after which the mixture was poured onto ice. To the icy mixture was added 150 ml. of 2*N* hydrochloric acid. The resulting mixture was filtered and the filtrate was extracted with 4 x 50 ml. of ether. The ethereal extract was dried and evaporated to give an oil. This oil was added to a methanolic guanidine solution [prepared by dissolving 29.5 g. (0.3 mole) of guanidine hydrochloride in 250 ml. of methanol followed by addition of a solution of 6.9 g. (0.3 g.-atom) of sodium in 250 ml. of methanol, and the precipitated sodium chloride was removed by filtration]. The resulting solution was refluxed for 24 hours, after which about one-half of the solvent was evaporated and the remaining solution allowed to stand at room temperature for two days with occasional scratching of the container with a glass rod. The resulting solid was collected by filtration and recrystallized from methanol and then from water. There was obtained 3.8 g. (12% overall yield) of XXVIa as buff plates, m.p. 177-178°; λ max (*p*H 1) 269 mμ (ϵ, 5,400); λ max (*p*H 11) 285 mμ (ϵ, 7,600).

Anal. Calcd. for $C_9H_{10}N_4O$: C, 56.83; H, 5.30; N, 29.46. Found: C, 56.59; H, 5.30; N, 29.68.

2,4-Diamino-5-(2-thenyl)-pyrimidine (XXVIb).

This compound was prepared from 17.0 g. (0.17 mole) of 3-methoxypropionitrile and 19.0 g. (0.17 mole) of 2-thiophenecarboxaldehyde (41) by a procedure similar to that described for the synthesis of XXVIa. The crude material was recrystallized twice from methanol to give 12.6 g. (36% yield) of XXVIb as light yellow plates, m.p. 176-178°. An analytical sample was prepared by recrystallization from water, m.p. 178-180°; λ max (*p*H 1) 232 mμ (ϵ, 18,100), 270 mμ (ϵ, 5,600); λ max (*p*H 11) 286 mμ (ϵ, 7,900).

Anal. Calcd. for $C_9H_{10}N_4S$: C, 52.40; H, 4.89; N, 27.16. Found: C, 52.37; H, 4.94; N, 27.16.

2,4-Diamino-5-(3-thenyl)pyrimidine (XXVII).

This compound was prepared by a procedure similar to that described for the synthesis of XXVIa from 17 g. (0.2 mole) of 3-methoxypropionitrile, 19 g. (0.17 mole) of 3-thiophenecarboxaldehyde (42) to give, after recrystallization from water, 12.2 g. (34% yield) of XXVII as buff plates, m.p. 182-184°; λ max (*p*H 1) 272 mμ (ϵ, 5,800); λ max (*p*H 11) 233 (ϵ, 16,500), 287 mμ (ϵ, 7,600).

Anal. Calcd. for $C_9H_{10}N_4S$: C, 52.40; H, 4.89; N, 27.16. Found: C, 52.20; H, 4.62; N, 27.16.

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