Midwest Research Institute

Structural Modification Studies of 3-Piperonylsydnone I. Synthesis of Piperonyl-substituted Pyrazoles, Isoxazoles, Triazoles, Oxadiazoles and Thiadiazoles (1)

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As a structural modification study of the antimalarial compound 3-piperonylsydnone, a number of pyrazoles, isoxazoles, 1,2,4-triazoles, ψ-1,2,4-triazoles, 1,3,4-oxadiazoles, 1,3,4-thiadiazoles and their intermediates all of which contain the piperonyl moiety have been synthesized. The antimalarial activity of these compounds was found to be less than that of the original sydnone. With the exception of 2,4-diamino-5-piperonylpyrimidine, among the compounds tested, those which showed survival time of eleven days or over all possess a N-N linkage.

3-Piperonylsydnone (I) has recently been shown to possess antimalarial activity against *Plasmodium berghei* in mice (2). Since the mode and site of action of I as an antimalarial agent is still not known, structural modification studies of I may contribute some information toward the understanding of the activity of this mesoionic compound.

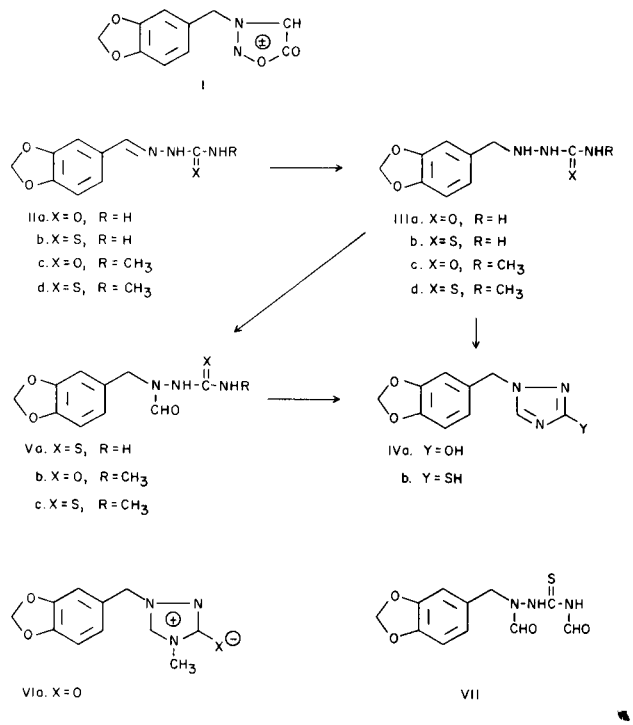
Prior to the present study, modification of the length of the $-CH_2-$ chain linking the phenyl and the 5-membered mesoionic ring system was studied. However, neither 3-homopiperonylsydnone nor 3-(3,4-methylenedioxy)phenylsydnone displayed comparable activity (2).

Modification of the substituents on the phenyl ring resulted in the preparation and evaluation of the following compounds: 3-(*p*-methoxybenzyl)sydnone (3), 3-(3,4-dimethoxybenzyl)sydnone, 3-(3,4,5-trimethoxybenzyl)sydnone and 3-(2,4-dichlorobenzyl)-sydnone. Among these, the *p*-methoxy analog possesses about half as much activity against *P. berghei* but is about twice as toxic; the trimethoxy analog, which is not toxic at the dose of 1.28 g./kg., has similar activity as that of 3-phenylsydnone (2,4). The dimethoxy and dichloro analogs are inactive (see Table I).

When the 4-position of the mesoionic ring in I is substituted with either a methyl or a chloro group, the resulting compounds (2) no longer retain the original antimalarial activity. The structure-activity relationship of the corresponding sydnone imines is somewhat reversed: 3-piperonylsydnone imine (2) is inactive as an antimalarial agent, whereas 3-piperonyl-4-methylsydnone imine (2) possesses activity comparable to that of 3-(*p*-methoxybenzyl)-sydnone.

It was found that 2,4-diamino-5-piperonylpyrimidine, prepared according to the method of Stenbuck, Baltzly and Hood (5), possesses "Day 14" activity against *P. berghei* at a dose of 640 mg./kg. The present study was centered on the preparation of compounds containing a piperonyl group attached to a five-membered heterocyclic ring.

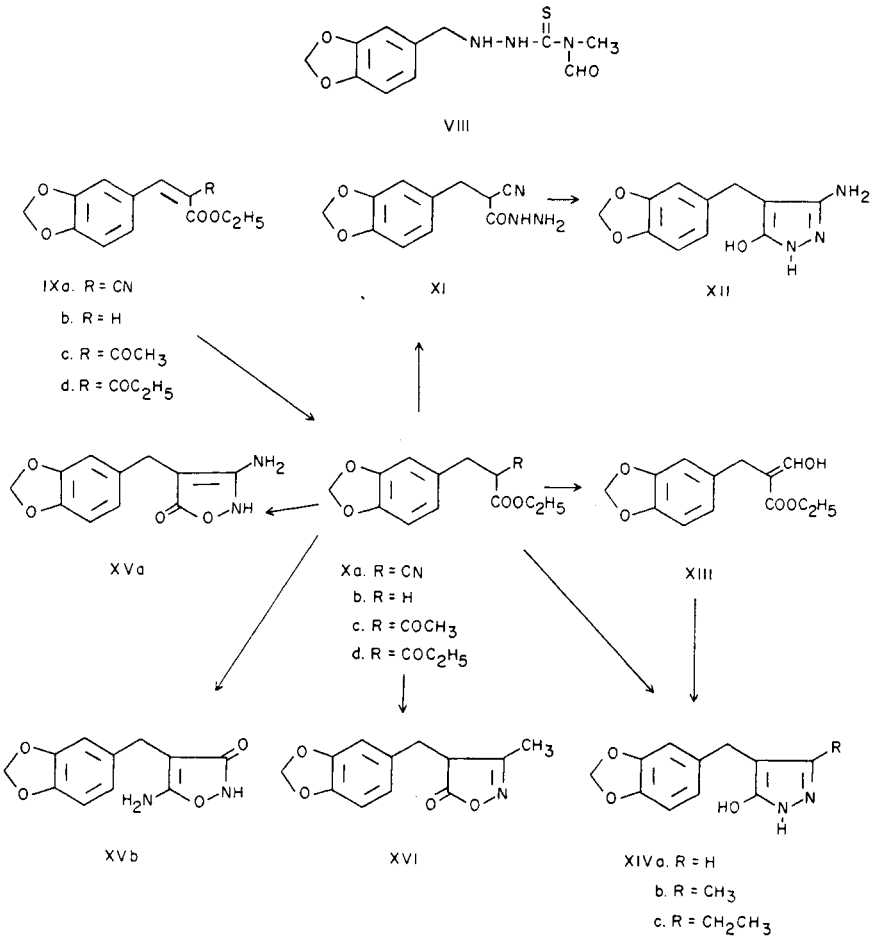
Piperonyl semicarbazone (6) (IIa) was prepared in quantitative yield by the treatment of piperonal with semicarbazide hydrochloride and sodium acetate in a methanol-water mixture, according to the method of Boyer and Canter (7). Reduction of IIa



to 1-*N*-piperonylsemicarbazide (IIIa) was found to be a rather capricious reaction. Catalytic hydrogenation was not considered to be appropriate as conditions vigorous enough to reduce the C=N grouping also may effect the hydrogenolytic cleavage of the resulting benzylamine. Sodium borohydride and acetic acid (8), a method used to reduce enamines, provided an oily substance which could not be purified. Lithium aluminum hydride also could not be used in this case due to a possible simultaneous reduction of the amide grouping. Pyridine borane has been used previously for the reduction of ketones (9) and Schiff bases (10). No mention has been made as to its effects upon amides; however, esters are not reduced by this reagent (10). Treatment of piperonal semicarbazone (IIa) with pyridine borane in acetic acid at room temperature gave a 90 percent yield of 1-*N*-piperonylsemicarbazide (IIIa). When compound IIIa was refluxed with ethyl orthoformate in xylene in the presence of *p*-toluenesulfonic acid (11), a 70 percent yield of 1-piperonyl-3-hydroxy-1,2,4-triazole (IVa) was obtained.

The corresponding 1-piperonyl-3-thio-1,2,4-triazole (IVb) was synthesized from piperonyl thiosemicarbazone (IIb) via 1-piperonylthiosemicarbazide (IIIb) and 1-formyl-1-piperonylthiosemicarbazide (Va). The latter was prepared by formylation of IIIb with formic-acetic anhydride at 6°. In a separate run, when the reaction temperature was maintained at 25°, a diformyl derivative (VII) was obtained.

Reaction of piperonal and 4-*N*-methylsemicarbazide (12) yielded IIc, which was reduced with pyridine borane to give 1-piperonyl-4-methylsemicarbazide (IIIc). Formic acid-acetic anhydride mixture converted IIIc to the corresponding formyl derivative Vb in 72% yield. This in turn yielded, in aqueous potassium carbonate, pseudo-1-piperonyl-3-oxo-4-methyl-1,3-dihydro-1,2,4-triazole (VIa, anhydro-1-piperonyl-3-hydroxy-4-methyl-1,2,4-triazolium hydroxide). Mesoionic compounds of this type have earlier been reported by Potts and co-workers (13) by the action of phosgene or thiophosgene on *N*-amino-*N*,*N*'-disubstituted benzamidine or by the ring



closure of 1,1,4-trisubstituted semicarbazide with sodium ethoxide.

1-Piperonyl-4-(methyl)thiosemicarbazide (IIId) was formylated in formic-acetic anhydride at 6° to give 1-formyl-1-piperonyl-4-(methyl)thiosemicarbazide (Vc). When the reaction was carried out at 25°, a different monoformylated derivative was obtained. Infrared studies suggested the product may be 1-piperonyl-4-formyl-4-(methyl)thiosemicarbazide (VIII). Since treatment of either the 1-formyl derivative (Vc) with aqueous potassium carbonate or treatment of the 4-formyl (VIII) derivative with acetic acid and methanol gave pseudo-1-piperonyl-3-thioxo-4-methyl-1,3-dihydro-1,2,4-triazole (VIb, anhydro-1-piperonyl-3-thio-4-methyl-1,2,4-triazolium hydroxide), the possibility of VIII being the 2-formyl derivative was ruled out.

Treatment of piperonal with ethyl cyanoacetate

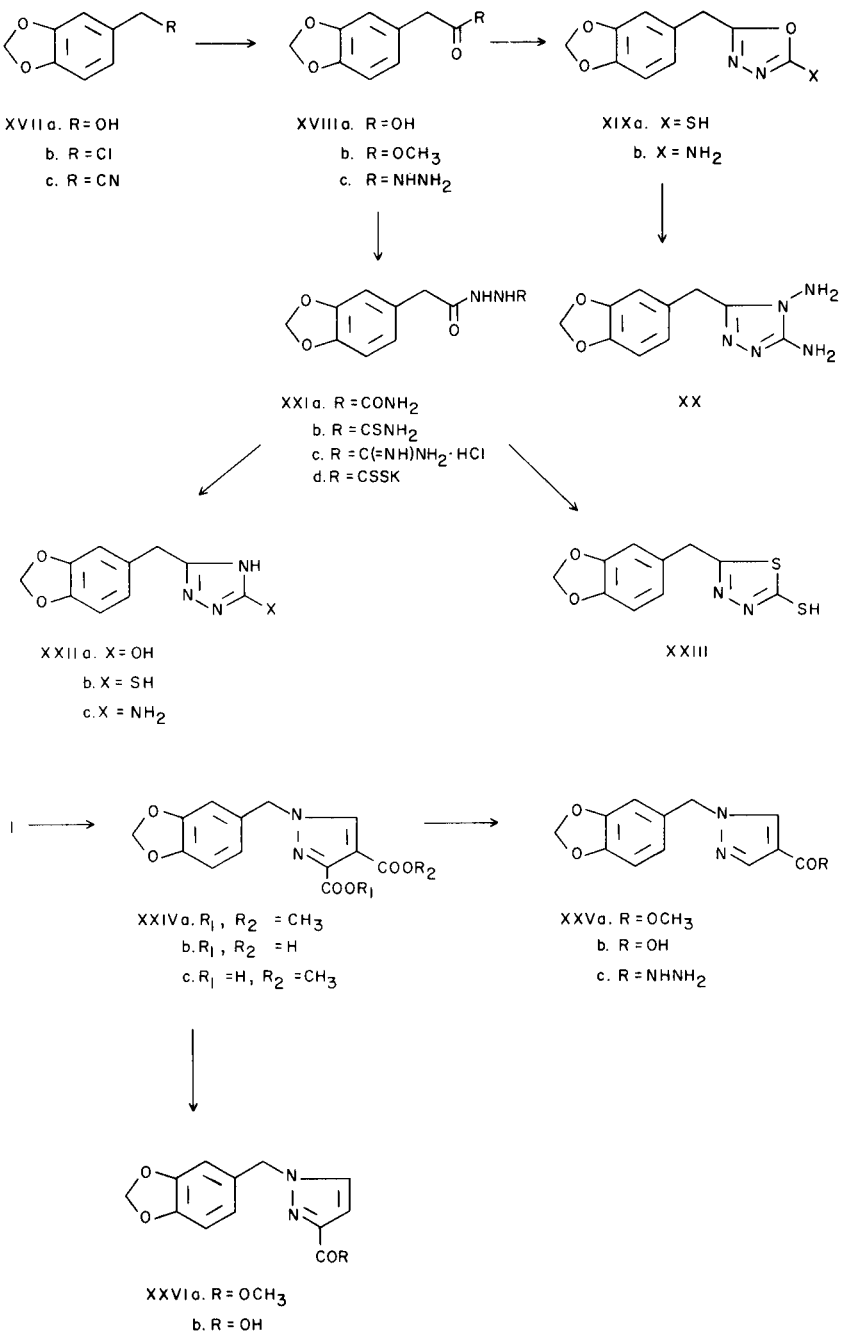
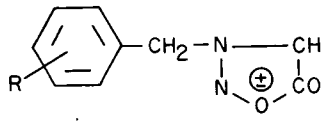


TABLE I

Comparison of Antimalarial Activity of 3-(Substituted benzyl)sydnones Against *Plasmodium berghei* in Mice (a, b)

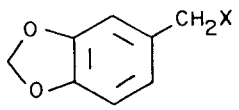


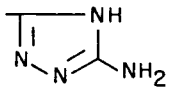
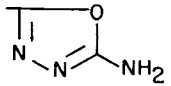
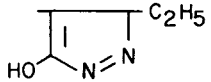
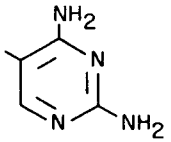
R-	Sex	Drug Dose (mg/kg)	Results of Tests (Daily Mortality) (Day/Number of Deaths)					Mean Survival Time, Treated	Mean Survival Time, Control	Toxic Deaths	Mean Survival Time of Toxic Deaths
3,4-O-CH_2-O-	F	1280	4/2	5/3				0.0	7.0	5	4.6
	F	640	5/1	18/2	27/1	28/1		22.8	7.0	1	5.0
	F	320	15/1	16/1	18/1	20/1	23/1	18.4	7.0	0	
	F	160	10/1	14/1	15/1	18/1	19/1	15.2	7.0	0	
	F	80	9/1	11/2	13/1	19/1		12.6	7.0	0	
p-CH_3O-	F	240	9/1	11/1	12/1	14/1	16/1	12.4	6.2	0	
	F	120	7/2	10/1	12/2			9.6	6.2	0	
	F	60	7/3	8/1	13/1			8.4	6.2	0	
	F	240	4/1	5/2	11/1	12/1		11.5	6.5	3	4.7
	F	120	7/2	8/1	14/2			10.0	6.5	0	
	F	60	6/2	7/1	10/1	12/1		8.2	6.5	0	
3,4-diCl-	F	240	5/5					0.0	6.2	5	5.0
	F	120	6/1	7/2	8/1	9/1		7.4	6.2	0	
	F	60	6/3	7/2				6.4	6.2	0	
3,4-diCH_3O-	M	640	4/3	9/1	10/1			9.5	7.7	3	0.0
	M	160	8/3	9/2				8.4	7.7	0	
	M	40	7/1	8/2	9/2			8.2	7.7	0	
3,4,5-triCH_3O-	F	1280	10/1	12/1	13/2	14/1		12.4	6.7	0	
	F	640	7/2	10/1	11/1	12/1		9.4	6.7	0	
	F	320	6/1	8/1	10/1	11/1	12/1	9.4	6.7	0	
	F	160	6/1	7/2	8/1	9/1		7.4	6.7	0	
	F	80	6/1	7/4				6.8	6.7	0	

(a) Test results were obtained by Dr. Leo Rane, University of Miami School of Medicine (Contract DA-49-193-MD-2218) and provided by the Division of Medicinal Chemistry, Walter Reed Army Institute of Research. (b) Mice are infected with a lethal dose of *P. berghei* three days prior to administration of the chemical (subcutaneously in oil) at each dose level. Five mice in each tast group.

TABLE II

Test Results of Some Piperonyl Derivatives Against *Plasmodium berghei* in Mice (a, b)



-X	Sex	Drug Dose (mg/kg)	Results of Tests (Daily Mortality) (Day/Number of Deaths)				Mean Survival Time, Treated	Mean Survival Time, Control	Toxic Deaths	Mean Survival Time of Toxic Deaths
	F	640	3/1	4/2	5/2		0	6.3	5	4.2
-NH-NH-C(=S)-NH$_2$	F	160	7/1	8/1	9/2	14/1	9.4	6.3	0	
	F	40	6/1	8/2	9/1	10/1	8.2	6.3	0	
	F	640	7/1	8/2	10/1	11/1	8.8	6.4	0	
-N(CHO)-NH-C(=S)-NH-CHO	F	160	6/1	7/2	8/2		7.2	6.4	0	
	F	40	6/1	7/2	8/2		7.2	6.4	0	
	F	640	3/5				0	6.3	5	3.0
-C(=O)-NH-NH$_2$	F	160	3/5				0	6.3	5	3.0
	F	40	8/3	9/1	11/1		8.8	6.3	0	
-C(=O)-NH-NH-C(=$\oplus$NH$_2$ Cl$\ominus$)-NH$_2$	M	640	8/1	9/1	10/2	11/1	9.6	6.5	0	
	M	160	8/1	9/2	10/2		9.2	6.5	0	
	M	40	8/1	9/3	10/1		9.0	6.5	0	
	M	640	10/2	11/2	12/1		10.8	6.5	0	
	M	160	8/1	9/1	10/3		9.4	6.5	0	
	M	40	8/2	9/3			8.6	6.5	0	
	M	640	4/2	10/1	11/1	12/1	11.0	6.5	2	4.0
	M	160	9/2	10/2	12/1		10.0	6.5	0	
	M	40	8/2	9/2	11/1		9.0	6.5	0	
	M	640	9/2	10/2	12/1		10.0	6.8	0	
	M	160	8/2	9/2	10/1		8.8	6.8	0	
	M	40	6/1	7/1	8/3		7.4	6.8	0	
	M	640	11/1	14/1	16/1		>13.6	6.2	0	
	M	320	8/1	9/1	10/1	11/2	9.8	6.2	0	
	M	160	8/2	10/1	12/2		10.0	6.2	0	

(a) Test results were obtained by Dr. Leo Rane, University of Miami School of Medicine (Contract DA-49-193-MD-2218) and provided by the Division of Medicinal Chemistry, Walter Reed Army Institute of Research. (b) Mice are infected with a lethal dose of *P. berghei* three days prior to administration of the chemical (subcutaneously in oil) at each dose level. Five mice in each test group.

yielded ethyl piperonylidenecyanoacetate (IXa). Catalytic reduction of IXa readily gave ethyl piperonylcyanoacetate (Xa) which, in turn, was converted to the corresponding acid hydrazide XI. Heating of XI in triethylene glycol readily cyclized the acid hydrazide to 3-amino-4-piperonyl-5-hydroxypyrazole (XII) in excellent yield.

Ethyl piperonylideneacetate (IXb) was prepared by the Reformatsky reaction of piperonal with ethyl bromoacetate and zinc and a catalytic amount of mercuric bromide. Catalytic reduction (to give Xb) followed by formylation afforded the hydroxymethylene ester XIII. The latter was treated with hydrazine in aqueous ethanol to yield 3-hydroxy-4-piperonylpyrazole (XIVa). The corresponding 5-methyl homolog (XIVb) and 5-ethyl homolog (XIVc) were prepared in an analogous fashion starting with ethyl acetoacetate and ethyl propionylacetate.

Depending on the reaction conditions, either 3-amino-5-isoxazolones or the isomeric 5-amino-3-isoxazolones can be obtained by the reaction between α-cyano esters and hydroxylamine (14). Accordingly, both 3-amino-4-piperonyl-5-isoxazolone (XVa) and 4-piperonyl-5-amino-3-isoxazolone (XVb) were prepared from ethyl piperonylcyanoacetate (Xa).

Catalytic reduction of ethyl piperonylideneacetoacetate (15) (IXc) yielded ethyl piperonylacetoacetate (Xc) as a yellow viscous oil. Without further purification, compound Xc was refluxed with hydroxylamine to give 3-methyl-4-piperonyl-5-isoxazolone (XVI). A comparison of infrared spectra of compounds XVI with XIVa, b and c revealed that the isoxazole XVI exhibited a strong carbonyl absorption band at 5.9 μ whereas the isosteric pyrazole compounds XIVa, b, and c failed to have carbonyl absorption in this region. Instead, a strong OH absorption band at 3.7 μ was observed with the pyrazoles.

Piperonyl chloride (XVIIb) was prepared from piperonyl alcohol (XVIIa) by the method of Shepard and Noth (16). Subsequent treatment of XVIIb with sodium cyanide in dimethylsulfoxide (17) afforded homopiperonylnitrile (18) (XVIIc). Base hydrolysis of XVIIc gave homopiperonylic acid (19) (XVIIIa) in good yield. Boron trifluoride etherate and methanol readily converted XVIIIa into its methyl ester (20), XVIIIb, which was then treated with hydrazine hydrate to give homopiperonylic acid hydrazide (XVIIIc). Cyclization of XVIIIc to 2-piperonyl-1,3,4-oxadiazole-5-thione (XIXa, shown as the thiol form) was achieved by utilizing the procedure of Ainsworth (21). 2-Amino-5-piperonyl-1,3,4-oxadiazole (XIXb) was prepared from XVIIIc and cyanogen bromide. Treatment of XIXb with hydrazine, utilizing the general procedure of Futaki and Tosa (22), yielded 3,4-diamino-5-piperonyl-1,2,4-triazole (XX).

Treatment of homopiperonylic acid hydrazide (XVIIIc) with cyanic acid, utilizing the reaction condition of Cheng and Lewis (23), gave near quantitative yield of 1-homopiperonoylsemicarbazide (XXIa). This compound readily cyclized in 10 percent potassium hydroxide to give 3-hydroxy-5-piperonyl-1,2,4-triazole (XXIIa). The corresponding 3-thio- (XXIIb) and 3-amino triazole (XXIIc) were similarly prepared from XXIb and XXIc, respectively. When homopiperonylic acid hydrazide (XVIIIc) was treated with a mixture of carbon disulfide and potassium hydroxide, the unstable potassium salt of piperonoyldithiocarbazoic acid (XXId) was formed. Without further purification, the product was cyclized with boron trifluoride etherate to give 2-piperonyl-5-thio-1,3,4-thiadiazole (XXIII).

Since the antimalarial activity of 3-piperonylsydnone (I) is not retained in 3-piperonylhydrazine (acid hydrolysis product of I) or *N*-nitroso-*N*-piperonylglycine (base hydrolysis of I) (2), it is postulated that compound I could undergo *in vivo* transformation and the resulting products may well be the "active forms" of I. Consequently, nonhydrolytic reactions of sydnones in general were searched. Huisgen and co-workers (24) reported that heating a variety of sydnones with the dimethyl ester of acetylenedicarboxylic acid resulted in the formation of the dimethyl ester of a substituted pyrazole; accordingly, dimethyl 1-piperonylpyrazole-3,4-dicarboxylate (XXIVa) was prepared from 3-piperonylsydnone (I) and dimethyl acetylenedicarboxylate. When XXIVa was refluxed with dilute potassium hydroxide, the corresponding dicarboxylic acid XXIVb was obtained in almost quantitative yield. At room temperature only one ester group of XXIVa was saponified and the structure of the resulting product was assigned as methyl 1-piperonyl-3-carboxypyrazole-4-carboxylate (XXIVc) for the following reason: decarboxylation of XXIVc gave methyl 1-piperonylpyrazole-4-carboxylate (XXVa), the structure of which was established by NMR spectroscopy.

When 3-piperonylsydnone (I) was refluxed with methyl propiolate in toluene (24), there was obtained a mixture of two isomeric monocarboxylic esters: 83 percent of methyl 1-piperonylpyrazole-3-carboxylate (XXVIa) and 17 percent of methyl 1-piperonylpyrazole-4-carboxylate (XXVa), as determined by the NMR spectrum of the mixture. Eight fractional recrystallizations yielded a pure specimen of the desired 3-carboxylate isomer XXVIa. Base hydrolysis of XXVIa readily yielded the free acid XXVIb. The other isomeric acid XXVb was similarly obtained from XXVa. The monoacid hydrazides (XXVc, XXVIc) were prepared from the corresponding methyl esters.

The aforementioned compounds have been tested against *P. berghei*. Since the mean survival time of infected control mice is 7.0 $\pm$ 0.5 days, and extension in survival time of chemically treated mice is interpreted as evidence of antimalarial activity, compounds which show survival time of 11 days or over are selected and reported in Table II. It is of interest to note that, with the exception

of the aforementioned 2,4-diamino-5-piperonylpyrimidine, all piperonyl derivatives reported in Table II possess a >N-N< linkage.

EXPERIMENTAL (25)

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

A solution of 5 g. (0.019 mole) of *N*-(3,4-dimethoxybenzyl)glycine hydrochloride (m.p. 218-219°, prepared from 3,4-dimethoxybenzylamine by essentially the same procedure described for the synthesis of *N*-piperonylglycine hydrochloride) (2) in 25 ml. of water was cooled to 10°. Sodium nitrite (1.4 g., 0.020 mole) in 10 ml. of water was added dropwise over a 5 minute period. The slurry was stirred at 0° for 75 minutes and filtered. The solid was washed with water and air dried to give 4.4 g. (90% yield) of *N*-(3,4-methoxybenzyl-*N*-nitrosoglycine as a white solid, m.p. 153-154°. The product was washed thoroughly with methanol to obtain a white solid, m.p. 168-170°. Recrystallization from 95% ethanol afforded an analytical specimen as white prisms, m.p. 172-173°.

Anal. Calcd. for $C_{11}H_{14}N_2O_5$: C, 52.0; H, 5.55; N, 11.0. Found: C, 52.2; H, 5.70; N, 11.0.

3-(3,4-Dimethoxybenzyl)sydnone.

A mixture of 4.3 g. (0.017 mole) of the nitrosoglycine described above and 8 ml. of acetic anhydride was heated on a steam bath for 2.5 hours. The mixture was allowed to stand overnight at room temperature. The reaction solvent was removed under reduced pressure to give a beige solid. Recrystallization from toluene afforded 2.2 g. (55% yield) of a beige solid, m.p. 97-98°. Three recrystallizations from ethyl acetate-petroleum ether (b.p. 60-68°) gave an analytical specimen of 3-(3,4-dimethoxybenzyl)sydnone as white prisms, m.p. 100-102°.

Anal. Calcd. for $C_{11}H_{12}N_2O_4$: C, 55.9; H, 5.12; N, 11.9. Found: C, 55.6; H, 5.00; N, 12.0.

1-*N*-Piperonylsemicarbazide (IIIa).

To a suspension of 15.0 g. (0.07 mole) of piperonal semicarbazone (6) in 100 ml. of glacial acetic acid was added, over a 30 minute period at room temperature, a solution of 20 ml. (17.6 g., 0.19 mole) of pyridine borane (Callery Chemical Company) in 100 ml. of glacial acetic acid. The mixture was stirred at room temperature for 4.5 hours, then poured onto ice and made basic with potassium hydroxide pellets. The white solid was removed by filtration and washed thoroughly with water, methanol and ether. This afforded 13.6 g. (90% yield) of IIIa, m.p. 178-181°. An analytical specimen was obtained by repeated recrystallizations from methanol, m.p. 181-183°. The infrared spectrum (potassium bromide) showed absorption at 2.81 μ (N-H) and 5.89 μ (C=O). The ultraviolet spectrum (ethanol) showed absorption maxima at 285 mμ (ϵ, 4,400) and 235 mμ (ϵ, 4,800).

Anal. Calcd. for $C_9H_{11}N_3O_3$: C, 51.7; H, 5.30; N, 20.1. Found: C, 51.6; H, 5.35; N, 20.1.

1-Piperonyl-3-hydroxy-1,2,4-triazole (IVa).

A suspension of 3.0 g. (0.014 mole) of the semicarbazide (IIIa) in 20 ml. of xylene containing 30 ml. of ethyl orthoformate and 2 mg. of *p*-toluenesulfonic acid was stirred under reflux for 24 hours. After 3 hours a heavy precipitate formed which differed in appearance from that of the starting material. The mixture was cooled in an ice bath, and was then filtered to afford 2.6 g. of a white solid. Recrystallization from ethylene glycol monomethyl ether afforded 2.16 g. (69% yield) of IVa as white prisms, m.p. 248-250°, which was found to be analytically pure. The infrared spectrum (KBr) showed absorption at 3.8 μ (strong hydrogen bonded O-H, broad). The ultraviolet spectrum (ethanol) showed absorption maxima at 285 mμ (ϵ, 4,400) and 237 mμ (ϵ, 6,100).

Anal. Calcd. for $C_{10}H_9N_3O_3$: C, 54.8; H, 4.14; N, 19.2. Found: C, 55.0; H, 4.50; N, 19.4.

1-Piperonylthiosemicarbazide (IIIb).

To a suspension of 11.5 g. (0.051 mole) of piperonal thiosemicarbazone (26) (IIb) in 100 ml. of glacial acetic acid was added a solution of 20 ml. (17.6 g., 0.19 mole) of pyridine borane in 100 ml. of glacial acetic acid over a 1 hour period at 25°. The mixture was then stirred at 25° for 22 hours. The resulting clear solution was poured onto ice and the white solid was removed by filtration. The material was washed with water, then air dried, to give 10.5 g. (91% yield) of a white solid, m.p. 143-145°. Recrystallization twice from methanol afforded an analytical specimen of IIIb, m.p. 148-150°. The infrared spectrum (Nujol) showed absorption at 2.95 and 3.05 μ (N-N), and 6.5 and 8.0 μ (CS-NH). The ultraviolet spectrum (ethanol) showed absorption maxima at 285 mμ (ϵ, 4,700) and 243 mμ (ϵ, 20,700).

Anal. Calcd. for $C_9H_{11}N_3O_2S$: C, 48.0; H, 4.92; N, 18.7. Found: C, 48.1; H, 5.00; N, 18.7.

1-Formyl-1-piperonylthiosemicarbazide (Va).

A solution of 1.0 g. (0.004 mole) of 1-piperonylthiosemicarbazide (IIIb) in 25 ml. of the mixed anhydride of formic-acetic acid (previously cooled to 6°) was allowed to stand in the cold room (6°) for 1 hour. The clear solution was poured onto ice, then the solvent was removed under reduced pressure at 40°. The colorless glass was triturated with methanol to afford a white solid which was collected by filtration to give 0.80 g. (71% yield) of Va, m.p. 167-170°. One recrystallization from acetic acid afforded an analytical specimen, m.p. 170-172°. The infrared spectrum (Nujol) showed absorption at 2.92 and 3.09 μ (N-H) and 5.98 μ (-CONH). The ultraviolet spectrum showed absorption maxima at 285 mμ (ϵ, 5,000) and 245 mμ (ϵ, 20,700).

Anal. Calcd. for $C_{10}H_{11}N_3O_3S$: C, 47.4; H, 4.38; N, 16.6. Found: C, 47.4; H, 4.32; N, 16.4.

1-Piperonyl-3-thio-1,2,4-triazole (IVb).

A suspension of 1.19 g. of 1-formyl-1-piperonylthiosemicarbazide (Va), 20 ml. of methanol, and 10 ml. of a 1 *M* potassium carbonate solution was stirred at 25° for 15 minutes. The clear solution was added to ice, then was adjusted to *p*H 2 with a 10% hydrochloric acid solution. The precipitated solid was removed by filtration, washed thoroughly with water, methanol and ether, then air dried. This afforded 1.02 g. (92% yield) of IVb as white prisms, m.p. 233-236°. One recrystallization from ethylene glycol monomethyl ether yielded an analytical specimen, m.p. 237-238°. The infrared spectrum (Nujol) showed no N-H or carbonyl absorption. The ultraviolet spectrum (ethanol) showed an absorption maximum at 282 mμ (ϵ, 5,200) and strong end absorption at 235-220 mμ.

Anal. Calcd. for $C_{10}H_9N_3O_2S$: C, 51.1; H, 3.86; N, 17.9. Found: C, 50.8; H, 4.16; N, 17.8.

1,4-Diformylpiperonylthiosemicarbazide (VII).

A solution of 2.33 g. (0.01 mole) of 1-piperonylthiosemicarbazide (IIIb) in 20 ml. of the mixed anhydride of formic-acetic acid was stirred in an ice bath for 30 minutes, then at 25° for 15 hours. The mixture was cooled in an ice bath and the precipitated solid removed by filtration. The white solid was washed with ether, then air dried to afford 1.93 g. (66% yield) of VII as white prisms, m.p. 161-163°. Recrystallization from acetic acid afforded an analytical specimen, m.p. 161-163°. The infrared spectrum (Nujol) showed absorption at 3.01 and 3.16 μ (N-H) and 5.78 and 6.0 μ (broad) attributable to the imide portion. The ultraviolet spectrum (ethanol) showed absorption maxima at 284 mμ (ϵ, 5,800) and 243 mμ (ϵ, 14,200).

Anal. Calcd. for $C_{11}H_{11}N_3O_4S$: C, 47.0; H, 3.94; N, 14.9. Found: C, 47.0; H, 4.20; N, 14.8.

1-Piperonyl-4-methylsemicarbazide (IIIc).

To a solution of 10.5 g. (0.048 mole) of piperonal 4-*N*-methylsemicarbazone (6) (IIc) in 100 ml. of glacial acetic acid was added dropwise, over a 15 minute period at 25°, a solution of 15 ml. (11.2 g., 0.12 mole) pyridine borane in 70 ml. of glacial acetic acid. The mixture was stirred at 25° for 2 hours, then 40 ml. of a 10% hydrochloric acid solution was added over a 30 minute period. The mixture was stirred an additional 1.5 hours at 25°, then poured onto ice. The solution was made basic with a concentrated potassium hydroxide solution, then extracted with ethyl acetate. The organic phase was washed thoroughly with water, a saturated sodium chloride solution, then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to afford a white solid. The solid was dissolved in methanol and allowed to stand at 25° for 20 hours. This afforded, after filtration and drying, 6.19 g. (58% yield) of IIIc, m.p. 162-165°, as white rosettes. An analytical specimen, m.p. 162-165°, was prepared by two recrystallizations from methanol. The infrared spectrum (Nujol) showed absorption at 2.95 and 3.05 μ (N-H) and 6.15 μ (-CONH). The ultraviolet spectrum (ethanol) showed absorption maxima at 285 mμ (ϵ, 4,200) and 235 mμ (ϵ, 4,500).

Anal. Calcd. for $C_{10}H_{13}N_3O_3$: C, 53.8; H, 5.87; N, 18.8. Found: C, 53.7; H, 5.90; N, 18.7.

1-Formyl-1-piperonyl-4-methylsemicarbazide (Vb).

A suspension of 4.0 g. (0.018 mole) of 1-piperonyl-4-methylsemicarbazide (IIIc) and 100 ml. of the mixed anhydride of a formic acid-

acetic anhydride mixture was allowed to stand in the cold room (6°) for 24 hours. A white solid was removed by filtration, 1.61 g., m.p. 167-170°, mixed melting point with the starting material, 150-162°. The remaining solution was poured onto ice and the solvent removed under reduced pressure at 40°. This afforded a colorless oil which crystallized on standing. Concentration of the filtrate afforded an additional 1.69 g. of white prisms, m.p. 171-173°, for a total yield of 3.3 g. (73% yield). Recrystallization from methanol afforded an analytical specimen of Vb as white prisms, m.p. 171-173°. The infrared spectrum (Nujol) showed absorption maxima at 2.92 and 2.98 μ (N-H) and 6.0 μ (-CONH). The ultraviolet spectrum (ethanol) showed absorption maxima at 285 mμ (ε, 3,800) and 237 mμ (ε, 4,300).

Anal. Calcd. for $C_{11}H_{13}N_3O_4$: C, 52.6; H, 5.22; N, 16.7. Found: C, 52.3; H, 5.15; N, 16.5.

ψ-1-Piperonyl-3-oxo-4-methyl-1,3-dihydro-1,2,4-triazole (Anhydro-1-piperonyl-3-hydroxy-4-methyl-1,2,4-triazolium hydroxide) (VIa).

To a suspension of 4.2 g. (0.017 mole) of 1-formyl-1-piperonyl-4-methylsemicarbazide (Vb) in 60 ml. of methanol was added 30 ml. of a 1 *M* potassium carbonate solution. The solid slowly disappeared, and after 2 hours at 25°, a clear solution resulted. The solution was adjusted to *p*H 7 with acetic acid, then the total volume reduced to 30 ml. (water aspirator). The precipitated solid was removed by filtration, washed with water, then air dried. This afforded 2.56 g. of VIa, m.p. 198-202°. An additional 0.27 g. was obtained by further concentration of the residual liquor to give a total of 2.83 g. (72% yield) of white needles. Two recrystallizations from ethanol afforded an analytical specimen, m.p. 202-204°. The infrared spectrum (Nujol) showed no N-H absorption, and showed broad absorption of a carbonyl band at 6.08 μ. The ultraviolet spectrum (ethanol) showed absorption maxima at 285 mμ (ε, 4,700) and 247 mμ (ε, 7,500).

Anal. Calcd. for $C_{11}H_{11}N_3O_3$: C, 56.7; H, 4.76; N, 18.0. Found: C, 56.9; H, 5.06; N, 18.0.

4-*N*-Methylpiperonal Thiosemicarbazone (IId).

To a solution of 15 g. (0.1 mole) of piperonal in 250 ml. of 95% ethanol was added a solution of 10.5 g. (0.1 mole) of 4-*N*-methylthiosemicarbazide (Aldrich) in 300 ml. of water containing 20 ml. of acetic acid. The mixture was heated on the steam bath for 1 hour, then cooled at 0° for 3 hours. The white needles were removed by filtration. This afforded, after air drying, 24.0 g. (97% yield) of IId, m.p. 210-214°. Two recrystallizations from methanol afforded an analytical specimen, m.p. 213-215°. The infrared spectrum (potassium bromide) showed absorption at 2.98 μ (N-H) and 7.98 μ (C=S). The ultraviolet spectrum (ethanol) showed absorption maxima at 318 mμ (ε, 44,600) and 301 mμ (ε, 21,800).

Anal. Calcd. for $C_{10}H_{11}N_3O_2S$: C, 50.6; H, 4.67; N, 17.7. Found: C, 50.9; H, 4.90; N, 17.5.

1-Piperonyl-4-(methyl)thiosemicarbazide (IIId).

To a suspension of 15.0 g. (0.063 mole) of 4-*N*-methylpiperonal thiosemicarbazone (IId) in 100 ml. of glacial acetic acid was added a solution of 20 ml. (17.6 g., 0.19 mole) of pyridine borane in 100 ml. of glacial acetic acid, over a 1 hour period at 25°. The mixture was stirred at 25° for 15 hours, then poured onto ice. The precipitated solid was removed by filtration, washed with water, methanol and ether, then air dried. This afforded 14.0 g. (93% yield) of IIId as white prisms. Two recrystallizations from methanol afforded an analytical specimen, m.p. 162-164°. The infrared spectrum (Nujol) showed absorption at 3.00 and 3.10 μ (N-H) and 6.41 and 8.02 μ (CSNH). The ultraviolet spectrum (ethanol) showed absorption maxima at 285 mμ (ε, 4,900) and 240 mμ (ε, 21,700).

Anal. Calcd. for $C_{10}H_{13}N_3O_2S$: C, 50.2; H, 5.48; N, 17.6. Found: C, 50.5; H, 5.50; N, 17.3.

1-Formyl-1-piperonyl-4-(methyl)thiosemicarbazide (Vc).

A suspension of 2.20 g. (0.0092 mole) of 1-piperonyl-4-(methyl)-thiosemicarbazide (III) in 50 ml. of the mixed anhydride of formic-acetic acid (cooled to 6°) was allowed to stand in the cold room (6°) for 1 hour. The clear solution was poured onto ice, then the solvent was removed under reduced pressure at 40°. The colorless glass afforded white crystals when triturated with acetic acid, 1.84 g. (75% yield) of Vc, m.p. 153-156°, which resolidified and remelted at 234-236°. Recrystallization once from acetic acid-methanol afforded an analytical specimen as white prisms, m.p. 160-162°, resolidified and remelted at 234-236°. The infrared spectrum (Nujol) showed absorption at 3.00 and 3.18 μ (N-H) and 5.95 μ (-CO-). The ultraviolet spectrum (ethanol) showed absorption maxima at 285 mμ (ε, 3,300) and 243 mμ (ε, 20,300).

Anal. Calcd. for $C_{11}H_{13}N_3O_3S$: C, 49.4; H, 4.90; N, 15.7. Found: C, 49.5; H, 4.94; N, 16.0.

1-Piperonyl-4-formyl-4-(methyl)thiosemicarbazide (VIII).

A suspension of 2.0 g. (0.0083 mole) of 1-piperonyl-4-methylthiosemicarbazide (IIId) and 50 ml. of the mixed anhydride of formic-acetic acid was allowed to stand at 25° for 20 hours. The resulting clear solution was poured onto ice, then the solvent was removed under reduced pressure at 40° to afford a white solid. This was slurried with acetic acid, then filtered to afford 1.2 g. (54% yield) of VIII as white prisms. One recrystallization from acetic acid afforded an analytical specimen, m.p. 157-159°. The infrared spectrum (Nujol) showed absorption at 2.97 μ (N-H) and 5.82 and 5.91 μ (C=O doublet characteristic of imides). The ultraviolet spectrum (ethanol) showed an absorption maximum at 276 mμ (ε, 8,800).

Anal. Calcd. for $C_{11}H_{13}N_3O_3S$: C, 49.4; H, 4.90; N, 15.7. Found: C, 49.4; H, 4.60; N, 15.7.

ψ-1-Piperonyl-3-thioxo-4-methyl-1,3-dihydro-1,2,4-triazole (Anhydro-1-piperonyl-3-thio-4-methyl-1,2,4-triazolium hydroxide, VIb).

Method 1.

To a suspension of 1.0 g. of 1-formyl-1-piperonyl-4-methylthiosemicarbazide (Vc) in 20 ml. of methanol was added 10 ml. of a 1 *M* potassium carbonate solution. Immediately a heavy precipitate formed. The mixture was allowed to stand at 25° for 5 minutes then was filtered. The solid was washed thoroughly with water, then air dried to give 0.9 g. (97% yield) of VIb, m.p. 244-247°. Recrystallization once from ethylene glycol monomethyl ether afforded an analytical specimen as white needles, m.p. 246-248°. The infrared spectrum (Nujol) showed no N-H absorption and no carbonyl absorption.

The ultraviolet spectrum (ethanol) showed absorption maxima at 284 mμ (ε, 5,700) and 240 mμ (ε, 21,900).

Anal. Calcd. for $C_{11}H_{11}N_3O_2S$: C, 53.0; H, 4.45; N, 16.9. Found: C, 53.2; H, 4.28; N, 16.8.

Method 2.

A 0.32 g. sample of the 1-piperonyl-4-formyl-4-methylthiosemicarbazide (VIII) was recrystallized from 5 ml. of acetic acid and 5 ml. of methanol. This afforded 0.20 g. of a white chalk-like solid, m.p. 219-222°. An additional recrystallization from methanol-acetic acid afforded 0.1 g. of VIb, m.p. 242-243°. A mixed melting point with the product obtained by method 1 melted at 242-243°. The infrared spectrum (Nujol) and the ultraviolet spectrum (ethanol) were superimposable with the product described above.

Ethyl Piperonylcyanoacetate (Xa).

A mixture of 14.0 g. of ethyl piperonylidenecyanoacetate (27) (IXa) was dissolved in 200 ml. of ethyl acetate. Palladium-on-charcoal catalyst (10%), 1.4 g. was added and the mixture was hydrogenated at 25° and 37 psig. The theoretical amount of hydrogen was absorbed after 2.5 hours. The mixture was filtered and the solvent was removed under reduced pressure. This afforded a yellow viscous oil which slowly crystallized on standing to afford 14.0 g. (99% yield) of ethyl piperonylcyanoacetate as a pale yellow solid, m.p. 48-50°. Two recrystallizations from ether-petroleum ether afforded an analytical specimen as fine white needles, m.p. 53-54°. The infrared spectrum (Nujol) showed absorption at 4.52 (C≡N) and 5.85 μ (CO_2Et). The ultraviolet spectrum (ethanol) showed absorption maxima at 284 mμ (ε, 4,700) and 235 mμ (ε, 4,700).

Anal. Calcd. for $C_{13}H_{13}NO_4$: C, 63.2; H, 5.30; N, 5.67. Found: C, 63.1; H, 5.14; N, 5.93.

Piperonylcyanoacetic Acid Hydrazide (XI).

A mixture of 2.46 g. of the ester Xa and 0.8 ml. of hydrazine hydrate in 13 ml. of 95% ethanol was allowed to stand at 25° for 18 hours. The precipitated solid was removed by filtration, washed thoroughly with water and dried. This afforded 2.10 g. (91% yield) of piperonylcyanoacetic acid hydrazide as white prisms, m.p. 138-139°. Two recrystallizations from a mixture of methanol and 95% ethanol afforded an analytical specimen of XI as white prisms, m.p. 140-141°. The infrared spectrum (Nujol) showed absorption at 3.0 (N-H), 4.47 (C≡N), and 6.08 μ ($CONHNH_2$). The ultraviolet spectrum (ethanol) showed absorption maxima at 284 mμ (ε, 3,700) and 235 mμ (ε, 4,700).

Anal. Calcd. for $C_{11}H_{11}N_3O_3$: C, 56.7; H, 4.72; N, 18.0. Found: C, 56.9; H, 4.71; N, 18.0.

3-Amino-4-piperonyl-5-hydroxypyrazole (XII).

A mixture of 7.1 g. of the acid hydrazide XI and 70 ml. of triethylene glycol was heated at 165° for 2 hours. The solution was then

cooled and poured over ice. The precipitated solid was removed by filtration, washed with water and dried. This afforded 6.8 g. (96% yield) of XII as a beige solid, m.p. 230-231°. Two recrystallizations from 95% ethanol afforded an analytical specimen, beige prisms, m.p. 235-237°. The infrared spectrum (Nujol) showed absorption at 3.0 and 6.3 μ. The ultraviolet spectrum (ethanol) showed the following absorption maxima: *p*H 1, 7, 11 at 284 mμ (ε, 4,200); *p*H 1 at 233 mμ (ε, 13,700); *p*H 7 at 239 mμ (ε, 12,800) and *p*H 11 at 232 mμ (ε, 11,700).

Anal. Calcd. for $C_{11}H_{11}N_3O_3$: C, 56.7; H, 4.72; N, 18.0. Found: C, 56.9; H, 4.71; N, 18.2.

Ethyl Piperonylideneacetate (IXb).

The methods of Phillips and Chatterjee (28) and Elsner and Parker (29) were adapted for this preparation. To a stirred and heated suspension of 7.8 g. (0.12 g.-atom) of zinc (20 mesh) and 0.5 g. of mercuric bromide in 20 ml. of anhydrous ether was added dropwise, over a 30 minute period, a solution prepared from 15 g. (0.1 mole) of piperonal, 18 g. (0.11 mole) of ethyl bromoacetate and 25 ml. of anhydrous benzene. The mixture was stirred at reflux for 3 hours then cooled. A saturated solution of ammonium chloride (aq.) adjusted to *p*H 7 by the addition of ammonium hydroxide was added dropwise. Ether was added, and the mixture was filtered. The solvent was removed under reduced pressure to give a viscous oil which was heated on the steam bath with 50 ml. of 98-100% formic acid for 1 hour. The solvent was removed under reduced pressure and the residue was added to ether. The organic phase was washed thoroughly with a potassium hydroxide solution, water, a saturated sodium chloride solution, then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to give 17 g. (0.08 mole, 74% yield) of a yellow waxy solid. An analytical specimen of IXb was prepared by two recrystallizations from ether-petroleum ether (b.p. 60-68°). This afforded colorless cubes, m.p. 66-69° (reported (30) m.p. 67-68°). The infrared spectrum (chloroform) showed absorption at 5.85 μ (CO_2Et). The ultraviolet spectrum (ethanol) showed absorption maxima at 325 mμ (ε, 22,000); 290 mμ (ε, 14,700); and 237 mμ (ε, 14,000).

Anal. Calcd. for $C_{12}H_{12}O_4$: C, 65.5; H, 5.49. Found: C, 65.4; H, 5.63.

Ethyl Piperonylacetate (Xb).

A mixture of 17 g. of the ester IXb, 2 g. of a 5% palladium-on-charcoal catalyst and 150 ml. of ethyl acetate was hydrogenated on a Paar apparatus at 25° and 26 psig for 5 minutes. The mixture was filtered and the solvent was removed under reduced pressure to a yellow oil. Distillation of the oil afforded 17 g. (99% yield) of Xb as a colorless liquid, b.p. 180° (14 mm.) [reported (31) b.p. 184-185° (14 mm.)]. The infrared spectrum (film) showed absorption at 5.78 μ ($CO_2C_2H_5$). The ultraviolet spectrum (ethanol) showed absorption maxima at 285 mμ (ε, 3,800) and 233 mμ (ε, 4,400).

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.9; H, 6.35. Found: C, 64.6; H, 6.30.

Formylation of Ethyl Piperonylacetate.

The procedure of Horning and Schock (32) was used. To a cooled suspension of 18 g. (0.33 mole) of sodium methoxide in 30 ml. of ether was added a mixture of 11.1 g. (0.05 mole) of ethyl piperonylacetate (Xb), 8 g. (0.11 mole) of ethyl formate and 15 ml. of ether. The suspension was stirred at 25° for 1.5 hours, then an additional 8 g. (0.11 mole) of ethyl formate was added. The mixture was allowed to stand at 25° for 15 hours, poured onto ice, then extracted with ether. The cold, basic aqueous phase was acidified with glacial acetic acid, then extracted with ether. The organic phase was washed with water, a saturated sodium chloride solution, and then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to give 11 g. of a red oil (XIII), which was not purified but used immediately. The infrared spectrum (film) showed absorption bands at 3.0 μ (broad), 5.90 and 6.10 μ.

3-Hydroxy-4-piperonylpyrazole (XIVa).

A mixture of 10.0 g. (0.04 mole) of the crude hydroxymethylene ester XIII, 50 ml. of 95% ethanol and 3 ml. (0.06 mole) of 65% hydrazine hydrate was allowed to stand at 25° for 18 hours. The solution was cooled, and the precipitated solid removed by filtration. The yellow solid was washed thoroughly with water, then air dried to give 1 g. of XIVa. Two recrystallizations from 95% ethanol afforded an analytical specimen as white prisms, m.p. 181-183°. The infrared spectrum (Nujol) showed absorption at 2.92 μ (N-H). The ultraviolet spectrum (ethanol) showed the following absorption maxima: *p*H 1, 7, 11, at 285 mμ (ε, 3,900): *p*H 1, 232 mμ (ε, 9,800): *p*H 7, at 239 mμ (ε, 8,300): and *p*H 11, at 237 mμ (ε, 9,800).

Anal. Calcd. for $C_{11}H_{10}N_2O_3$: C, 60.6; H, 4.62; N, 12.8. Found: C, 60.4; H, 4.65; N, 13.1.

3-Hydroxy-4-piperonyl-5-methylpyrazole (XIVb).

A mixture of 5.0 g. (0.02 mole) of ethyl piperonylacetoacetate (15) (Xc), 25 ml. of 95% ethanol and 1.5 ml. (0.03 mole) of 65% hydrazine hydrate was allowed to stir at room temperature for 3 hours. The precipitated solid was removed by filtration, washed thoroughly with water, then dried. This afforded 2.2 g. (50% yield) of XIVb as white plates, m.p. 225-226°. Two recrystallizations from ethanol afforded an analytical specimen as colorless plates, m.p. 226-227°. The infrared spectrum (Nujol) showed no carbonyl absorption; however, it showed strongly hydrogen bonded OH at 3.7 μ. The ultraviolet spectrum (ethanol) showed the following absorption maxima: *p*H 1, 7 and 11 at 285 mμ (ε, 3,700); *p*H 1 at 230 mμ (ε, 9,300); *p*H 7 at 240 mμ (ε, 9,300); and *p*H 11 at 236 mμ (ε, 9,300).

Anal. Calcd. for $C_{12}H_{12}N_2O_3$: C, 62.1; H, 5.21; N, 12.1. Found: C, 61.8; H, 5.02; N, 11.7.

Ethyl α-piperonylidene-β-ketovalerate (IXd).

A mixture of 79 g. (0.55 mole) of ethyl propionylacetate, 67 g. (0.46 mole) of piperonal, 40 ml. of benzene, 2 ml. of piperidine and 6 ml. of acetic acid was stirred at reflux for 18 hours. A Dean-Stark apparatus was used to separate the water formed. The yellow solution was extracted with ether. The ether extract was washed thoroughly and successively with water, a 5% sodium hydroxide solution, acetic acid, water, and a saturated sodium chloride solution, and then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and distilled to give 130 g. (97% yield) of IXd as a yellow viscous liquid, b.p. 171° (0.5 mm.). The infrared spectrum (film) showed absorption at 6.0, 6.3 and 6.39 μ.

Anal. Calcd. for $C_{15}H_{16}O_5$: C, 65.2; H, 5.84. Found: C, 64.9; H, 5.68.

Ethyl α-piperonyl-β-ketovalerate (Xd).

Sixty grams (0.22 mole) of the ketoester IXd in 200 ml. of ethyl acetate was hydrogenated at room temperature in the presence of 2 g. of a 10% palladium-on-charcoal catalyst. After 2 hours, 90% of the theoretical amount of hydrogen was absorbed. The mixture was filtered and the solvent removed under reduced pressure to afford 61 g. of a pale yellow colored oil. Distillation of this solution afforded 50 g. (83% yield) of Xd as a colorless liquid, b.p. 214-216° (14 mm.). The infrared spectrum (film) showed absorption at 5.72, 5.82 and 6.2 μ.

Anal. Calcd. for $C_{15}H_{18}O_5$: C, 64.7; H, 6.52. Found: C, 64.4; H, 6.50.

3-Hydroxy-4-piperonyl-5-ethylpyrazole (XIVc).

A mixture of 10.3 g. (0.04 mole) of the ketoester Xd, 50 ml. of ethanol and 3 ml. of 65% hydrazine hydrate was allowed to stand at 25° for 18 hours. It was then cooled and filtered to afford 2.7 g. (30% yield) of XIVc as white prisms, m.p. 193-195°. Two recrystallizations from 95% ethanol afforded an analytical specimen as white needles, m.p. 195-197°. The infrared spectrum (Nujol) showed broad absorption at 3.62 μ. The ultraviolet spectrum (ethanol) showed the following absorption maxima: *p*H 1 at 232 mμ (ε, 11,300); *p*H 7 at 241 mμ (ε, 10,800); and *p*H 11 at 235 mμ (ε, 11,600).

Anal. Calcd. for $C_{13}H_{14}N_2O_3$: C, 63.4; H, 5.73; N, 11.4. Found: C, 63.2; H, 5.77; N, 11.5.

3-Methyl-4-piperonyl-5-isoxazolone (XVI).

A solution of 10.0 g. (0.04 mole) of ethyl piperonylacetoacetate (15) (Xc) in 50 ml. of absolute ethanol containing 3.4 g. (0.05 mole) of hydroxylamine hydrochloride was heated at reflux for 2 hours. The mixture was cooled and the solid removed by filtration. This afforded 5 g. (57% yield) of XVI, m.p. 114-115°, as a bright yellow solid. Four recrystallizations from ethyl acetate-hexane afforded an analytical specimen as beige needles, m.p. 115-117°. Various color changes were noted when the material was recrystallized and the compound seemed to be easily oxidized. The infrared spectrum (Nujol) showed absorption at 5.90 and 5.95 μ (C=O and >C=N-). The ultraviolet spectrum (ethanol) showed the following absorption maxima: *p*H 1, 7, and 11 at 285 mμ (ε, 4,000); *p*H 7 and 11 at 257 mμ (ε, 10,000); and *p*H 1 at 260 mμ (ε, 14,700).

Anal. Calcd. for $C_{12}H_{11}NO_4$: C, 61.8; H, 4.75; N, 6.01. Found: C, 62.1; H, 4.48; N, 5.74.

3-Amino-4-piperonyl-5-isoxazolone (XVa).

To a cooled mixture of 1.18 g. (0.017 mole) of hydroxylamine hydrochloride in 18 ml. of methanol and 1.4 g. (0.025 mole) of po-

tassium hydroxide in 4 ml. of methanol was added, with shaking 2.0 g. (0.008 mole) of ethyl piperonylcyanoacetate (Xa). The reaction mixture was filtered immediately with suction and the colorless filtrate allowed to stand at 25° for 18 hours. The solution was then neutralized with glacial acetic acid and the solvent was removed under reduced pressure to afford 1.1 g. (58% yield) of XVa as a white powder, m.p. 161-162°. Two recrystallizations from a mixture of methanol and water afforded an analytical specimen as beige prisms, m.p. 163-164°. The infrared spectrum (Nujol) showed absorption at 2.93 and 2.98 (NH_2), 3.10 (NH), 5.68 (C=O), 6.1 and 6.31 μ. The ultraviolet spectrum (ethanol) showed the following absorption maxima: *p*H 1 at 247 mμ (ϵ, 17,000) and 285 mμ (ϵ, 3,500); *p*H 7 at 238 mμ (ϵ, 13,000) and 285 mμ (ϵ, 3,700); *p*H 11 at 237 mμ (ϵ, 12,300) and 285 mμ (ϵ, 3,700).

Anal. Calcd. for $C_{11}H_{10}N_2O_4$: C, 56.4; H, 4.30; N, 12.0. Found: C, 56.1; H, 4.29; N, 12.0.

4-Piperonyl-5-amino-3-isoxazolone (XVb).

To a solution of 2.56 g. (0.032 mole) of hydroxylamine hydrochloride in 70 ml. of methanol was added 27.8 ml. (0.06 mole) of 2.5 *M* sodium methylate solution in methanol. The mixture was cooled in an ice bath for 10 minutes. After introduction of 8.24 g. (0.033 mole) of ethyl piperonylcyanoacetate (Xa) the reaction mixture was allowed to stir at 25° for 18 hours. The precipitated sodium chloride was removed by filtration and the filtrate neutralized with glacial acetic acid. The solid product was filtered, washed with water and dried to afford 7.33 g. (94% yield) of XVb as a beige solid, m.p. 200-202°. Two recrystallizations from ethyl acetate afforded an analytical specimen as white prisms, m.p. 204-205°. The infrared spectrum (Nujol) showed absorption at 2.98 (NH_2), 3.25 (NH) and 6.17 μ (C=O). The ultraviolet spectrum (ethanol) showed the following absorption maxima: *p*H 1, 7, 11 at 285 mμ (ϵ, 4,000), *p*H 1 at 244 mμ (ϵ, 20,800), *p*H 7 at 241 mμ (ϵ, 15,700), and *p*H 11 at 230 mμ (ϵ, 13,000).

Anal. Calcd. for $C_{11}H_{10}N_2O_4$: C, 56.4; H, 4.30; N, 12.0. Found: C, 56.6; H, 4.29; N, 12.0.

Homopiperonylic Acid Hydrazide (XVIIIc).

A mixture of 31 g. of methyl homopiperonylate (20) (XVIIIb), 300 ml. of methanol, and 70 ml. of 65% hydrazine hydrate was allowed to stir at 25° for 20 hours. The white solid was removed by filtration and washed thoroughly with water. This afforded, after drying, 26.0 g. (84% yield) of XVIIIc as white needles, m.p. 153-155°. Two recrystallizations from methanol afforded an analytical specimen as long white needles, m.p. 154-156°. The infrared spectrum (Nujol) showed absorption at 3.03 μ (N-H) and 6.13 μ (-CONH-), while the ultraviolet spectrum showed absorption maxima at 286 mμ (ϵ, 4,200) and 235 mμ (ϵ, 4,750) in ethanol.

Anal. Calcd. for $C_9H_{10}N_2O_3$: C, 55.7; H, 5.19; N, 14.4. Found: C, 55.6; H, 5.13; N, 14.6.

2-Piperonyl-1,3,4-oxadiazole-5-thione (XIXa).

To a solution of 3.88 g. (0.02 mole) of homopiperonylic acid hydrazide (XVIIIc) in 100 ml. of absolute ethanol were added 1 g. (0.02 mole) of 85% potassium hydroxide pellets and 4 ml. (5 g., 0.06 mole) of carbon disulfide. The mixture was heated at reflux for 31 hours, then allowed to stand at room temperature overnight. White plates (4 g.) had precipitated and were removed by filtration. The solid was then dissolved in a minimum amount of water, acidified with glacial acetic acid, and the white solid was removed by filtration. This afforded 2.9 g. (61% yield) of XIXa as white prisms, m.p. 117.5-120°. Two recrystallizations from ethanol afforded an analytical specimen as long white needles, m.p. 117.5-119°. The infrared spectrum (Nujol) showed absorption at 6.14 μ (C=N) and 8.0 μ ($C\overset{\nearrow S}{\underset{\searrow N}{}}$), while the ultraviolet spectrum (ethanol) showed the following absorption maxima: *p*H 1 at 265 mμ (ϵ, 21,000) and *p*H 11 at 248 mμ (ϵ, 19,000).

Anal. Calcd. for $C_{10}H_8N_2O_3S$: C, 50.9; H, 3.41; N, 11.9. Found: C, 51.1; H, 3.66; N, 11.7.

2-Amino-5-piperonyl-1,3,4-oxadiazole (XIXb).

A suspension of 6.0 g. (0.03 mole) of the acid hydrazide XVIIIc, 3.6 g. (0.036 mole) of potassium bicarbonate and 3.0 g. (0.03 mole) of cyanogen bromide in 150 ml. of water was stirred at room temperature for 20 hours. The mixture was filtered and the white solid washed thoroughly with water, then air dried. This afforded 6.5 g. (96% yield) of XIXb as white plates, m.p. 167-170°. Two recrystallizations from water afforded an analytical specimen as white plates, m.p. 171-172°. The infrared spectrum (Nujol) showed absorption at 2.99, 3.19 and 6.02 μ. The ultraviolet spectrum (ethanol) showed the following absorption maxima: *p*H 1, 7, and 11 at 284 mμ (ϵ, 4,400); and *p*H 11 at 230 mμ (ϵ, 8,800).

Anal. Calcd. for $C_{10}H_9N_3O_3$: C, 54.8; H, 4.14; N, 19.2. Found: C, 54.5; H, 4.18; N, 19.1.

3,4-Diamino-5-piperonyl-1,2,4-triazole (XX).

A mixture of 3.0 g. of 2-amino-5-piperonyl-1,3,4-oxadiazole (XIXb) and 5 ml. of 85% hydrazine hydrate was heated at reflux for 24 hours. The beige solution was cooled and the precipitated solid was removed by filtration, washed with water, then dried. This afforded 0.93 g. (29% yield) of XX as a beige solid, m.p. 195-197°. Two recrystallizations from water afforded an analytical specimen as white prisms, m.p. 197-199°. The infrared spectrum (Nujol) showed absorption at 2.90, 2.98, 6.1 and 8.0 μ. The ultraviolet spectrum (ethanol) showed the following absorption maxima: *p*H 1, 7, 11 at 285 mμ (ϵ, 4,700); *p*H 1 at 235 mμ (ϵ, 5,300); and *p*H 11 at 233 mμ (ϵ, 6,500).

Anal. Calcd. for $C_{10}H_{11}N_5O_2$: C, 51.5; H, 4.75; N, 30.0. Found: C, 51.8; H, 4.72; N, 30.0.

1-Homopiperonoylsemicarbazide (XXIa).

To a solution of 3.0 g. (0.015 mole) of homopiperonylic acid hydrazide (XVIIIc), in 25 ml. of water containing 9 ml. of 10% hydrochloric acid was added a solution of 1.7 g. (0.022 mole) of potassium cyanate in 10 ml. of water. Immediately, a white precipitate began to form. The mixture was allowed to stand at 25° for 2 hours, then was cooled, and the solid removed by filtration. This afforded 3.7 g. (99% yield) of XXIa as white prisms, m.p. 202-206°. Two recrystallizations from ethylene glycol monomethyl ether afforded an analytical specimen, m.p. 210-212°. The infrared spectrum (Nujol) showed absorption at 2.91 and 3.05 μ (N-H) and 5.90 and 6.10 μ (-CONH-). The ultraviolet spectrum (ethanol) showed absorption maxima at 285 mμ (ϵ, 4,700) and 237 mμ (ϵ, 4,800).

Anal. Calcd. for $C_{10}H_{11}N_3O_4$: C, 50.7; H, 4.67; N, 17.7. Found: C, 50.8; H, 4.88; N, 17.7.

3-Hydroxy-5-piperonyl-1,2,4-triazole (XXIIa).

A solution of 5.2 g. of 1-homopiperonoylsemicarbazide (XXIa) in 100 ml. of a 10% potassium hydroxide solution was heated on the steam bath for 2.5 hours. The mixture was acidified with glacial acetic acid, cooled, then filtered to give 3.7 g. of a white solid, m.p. 245-250°. Recrystallization from ethylene glycol monomethyl ether afforded 2.24 g. (47% yield) of XXIIa as white prisms, m.p. 262-264°. An additional recrystallization afforded an analytical specimen, m.p. 265-266°. The infrared spectrum (Nujol) showed absorption at 3.05 μ (N-H), 5.84 μ (C=O), and 5.96 μ (C=N-). The ultraviolet spectrum (ethanol) showed absorption maxima at 285 mμ (ϵ, 3,700) and 233 mμ (ϵ, 4,400).

Anal. Calcd. for $C_{10}H_9N_3O_3$: C, 54.8; H, 4.14; N, 19.2. Found: C, 55.0; H, 3.92; N, 19.1.

1-Homopiperonoylthiosemicarbazide (XXIb).

A suspension of 5.0 g. (0.026 mole) of homopiperonylic acid hydrazide (XVIIIc), 3.5 g. (0.036 mole) of potassium thiocyanate, 3 ml. of concentrated hydrochloric acid, and 50 ml. of methanol was gently evaporated to dryness on the steam bath, then heated for an additional hour. The resulting white solid was heated with three 125-ml. portions of water. From the cooled aqueous phase was deposited 2.2 g. (31% yield) of XXIb as white needles, m.p. 195-197°. Two recrystallizations from water afforded an analytical specimen, m.p. 197-197.5°. The infrared spectrum (Nujol) showed absorption at 2.85, 3.12, 5.96 and 6.02 μ. The ultraviolet spectrum (ethanol) showed the following absorption maxima: *p*H 1 at 284 mμ (ϵ, 4,000) and 240 mμ (ϵ, 18,500); *p*H 7 at 282 mμ (ϵ, 5,300) and 250 mμ (ϵ, 20,000); and *p*H 11 at 273 mμ (ϵ, 17,500).

Anal. Calcd. for $C_{10}H_{11}N_3O_3S$: C, 47.4; H, 4.38; N, 16.6. Found: C, 47.3; H, 4.07; N, 16.6.

3-Thio-5-piperonyl-1,2,4-triazole (XXIIb).

A solution of 2.2 g. of the thiosemicarbazide XXIb in 20 ml. of 10% aqueous potassium hydroxide was allowed to stand at room temperature for 15 hours. The pale yellow colored solution was acidified with glacial acetic acid and the white solid removed by filtration. This afforded 2.1 g. of white prisms, m.p. 242-247°. Recrystallization from ethanol afforded 1.6 g. (78% yield) of XXIIb as white prisms, m.p. 254-256°. An analytical specimen was prepared by a second recrystallization from ethanol, m.p. 255-256°. The infrared spectrum (Nujol) showed absorption at 3.20 and 6.24 μ. The ultraviolet spectrum (ethanol) showed the following absorption maxima: *p*H 1 and 7 at 284 mμ (ϵ, 4,700) and 245 mμ (ϵ, 20,700) and *p*H 11 at 284 mμ (ϵ, 4,200) and 237 mμ (ϵ, 20,000).

Anal. Calcd. for $C_{10}H_9N_3O_2S$: C, 51.1; H, 3.86; N, 17.9. Found:

C, 50.8; H, 3.84; N, 17.6.

1-Homopiperonoylaminoguanidine Hydrochloride (XXIc).

A mixture of 5.0 g. (0.026 mole) of the acid hydrazide XVIIIc, 50 ml. of methanol, 9 ml. of a 10% hydrochloric acid solution and 2 g. (0.05 mole) of cyanamide was heated and evaporated to dryness on the steam bath. The white solid was leached with hot absolute ethanol, filtered, and the ethanol removed. The remaining white solid was slurried with cold ethanol, filtered and dried. This afforded 5.0 g. of a white solid, m.p. 203-205°. The solid was dissolved in hot water, filtered, then the water was removed under reduced pressure. The remaining solid was recrystallized from methanol to give 2.6 g. (37% yield) of XXIc, m.p. 225-226°, as white prisms. Two additional recrystallizations from methanol afforded an analytical specimen as white prisms, m.p. 224-226°. The infrared spectrum (Nujol) showed absorption at 5.90 and 6.00 μ (C=O and C=$\overset{+}{N}H_2Cl^-$). The ultraviolet spectrum (ethanol) showed the following absorption maxima: *p*H 1, 7 and 11 at 284 mμ (ϵ, 4,900); *p*H 1 and 7 at 234 mμ (ϵ, 4,900); *p*H 1 and 7 at 234 mμ (ϵ, 5,450); and *p*H 11 at 234 mμ (ϵ, 6,800).

Anal. Calcd. for $C_{10}H_{13}ClN_4O_3$: C, 44.0; H, 4.80; N, 20.6. Found: C, 44.0; H, 4.64; N, 20.7.

3-Amino-5-piperonyl-1,2,4-triazole (XXIIc).

A mixture of 185 mg. of the aminoguanidine hydrochloride XXIc, 5 ml. of methanol and 5 ml. of a 1 *M* potassium carbonate solution was allowed to stand at room temperature for 18 hours. The solvent was removed under reduced pressure and the residue slurried with water. The solid was collected by filtration, then dried, to give 79 mg. (53% yield) of XXIIc as white needles, m.p. 209-210°. Two recrystallizations from water afforded an analytical specimen as pale yellow rosettes, m.p. 212-213°. The infrared spectrum (Nujol) showed absorption at 2.80, 2.92, 6.13, 6.32 and 8.0 μ. The ultraviolet spectrum (ethanol) showed the following absorption maxima: *p*H 1, 7 and 11 at 284 mμ (ϵ, 3,700); *p*H 1 and 7 at 234 mμ (ϵ, 4,360); and *p*H 11 at 235 mμ (ϵ, 6,300).

Anal. Calcd. for $C_{10}H_{10}N_4O_2$: C, 55.0; H, 4.62; N, 25.6. Found: C, 54.8; H, 4.85; N, 25.5.

2-Piperonyl-5-thio-1,3,4-thiadiazole (XXIII).

A mixture of 8.0 g. of homopiperonylic acid hydrazide (XVIIIc), 80 ml. of methanol, 2.0 g. of 85% potassium hydroxide pellets and 4 ml. of carbon disulfide was stirred at room temperature for 4 hours. Ether (200 ml.) was added and the mixture was cooled in an ice bath. The precipitated solid was removed by filtration and washed thoroughly with ether. This afforded 10 g. of potassium piperonoyldithiocarbazate (XXId), m.p. 240-250°. These salts are usually not stable, hence the product was used without further purification. A mixture of 9.5 g. of XXId, 250 ml. of methylene chloride and 30 ml. of boron trifluoride etherate was allowed to stand at room temperature under nitrogen for 17 hours. The orange solution was poured onto ice, then extracted with ether. The organic phase was washed thoroughly with 10% potassium hydroxide and the basic aqueous phase was acidified to *p*H 2 with ice cold 10% hydrochloric acid. The white solid was removed by filtration, washed thoroughly with water and dried. This afforded 2.0 g. (25% yield) of XXIII as a beige solid, m.p. 122-124°. Three recrystallizations from aqueous ethanol afforded an analytical specimen as long white needles, m.p. 125-127°. The infrared spectrum (Nujol) showed absorption at 6.48, 7.88 and 8.0 μ. The ultraviolet spectrum (ethanol) showed the following absorption maxima: *p*H 1 at 307 mμ (ϵ, 16,100) and 231 mμ (ϵ, 6,000); and *p*H 11 at 290 mμ (ϵ, 15,600) and 232 mμ (ϵ, 7,600).

Anal. Calcd. for $C_{10}H_8N_2O_2S_2$: C, 47.6; H, 3.20; N, 11.1; S, 25.4. Found: C, 47.8; H, 2.95; N, 10.8; S, 25.2.

Dimethyl 1-Piperonylpyrazole-3,4-dicarboxylate (XXIVa).

A mixture of 20 g. (0.091 mole) of 3-piperonylsydnone (I), 14.2 g. (0.10 mole) dimethyl acetylenedicarboxylate and 100 ml. of xylene was refluxed for 4 hours and was then allowed to cool to room temperature. The mixture was cooled in ice and the crystals were collected by filtration to give 26 g. (90% yield) of XXIVa, m.p. 110-112.5°. Recrystallization from a mixture of benzene and petroleum ether afforded an analytical specimen, m.p. 117-118°. The infrared spectrum (potassium bromide) showed absorption at 5.75 and 5.85 μ (CO_2CH_3). The ultraviolet spectrum (ethanol) showed an absorption maximum at 283 mμ (ϵ, 7,000). The NMR spectrum ($CDCl_3$) showed absorption for three protons (s) at 3.84 ppm (CO_2CH_3), three protons (s) at 3.98 ppm (CO_2CH_3), two protons (s) at 5.28 ppm (Ar-CH_2-), two protons (s) at 6.03 ppm (-O-CH_2-O-), three protons at 6.87 ppm (three aromatic protons) and one proton at 7.90 ppm (proton at C-3 on the pyrazole ring).

Anal. Calcd. for $C_{15}H_{14}N_2O_6$: C, 56.6; H, 4.43; N, 8.80. Found: C, 56.8; H, 4.58; N, 8.88.

1-Piperonylpyrazole-3,4-dicarboxylic Acid (XXIVb).

A solution of 4 g. (0.013 mole) of dimethyl 1-piperonylpyrazole-3,4-dicarboxylate (XXIVa) in 40 ml. of water and 80 ml. of methanol containing 6 g. (0.12 mole) of potassium hydroxide pellets (85%) was heated at reflux for 5 hours. The mixture was cooled, acidified to *p*H 2 with a 10% hydrochloric acid solution and the precipitated solid removed by filtration. This afforded 3.6 g. (99% yield) of XXIVb as white needles, m.p. 214-216°. One recrystallization from water afforded an analytical specimen as white needles, m.p. 216-218°. The infrared spectrum (Nujol) showed absorption at 5.80 and 6.15 μ. The ultraviolet spectrum (ethanol) showed an absorption maximum at 285 μ (ϵ, 11,000).

Anal. Calcd. for $C_{13}H_{10}N_2O_6$: C, 53.8; H, 3.47; N, 9.65. Found: C, 54.0; H, 3.56; N, 9.73.

Methyl 1-Piperonyl-3-carboxypyrazole-4-carboxylate (XXIVc).

A suspension of 10.0 g. (0.031 mole) of dimethyl 1-piperonylpyrazole-3,4-dicarboxylate (XXIVa) in 100 ml. of water and 200 ml. of methanol containing 5.5 g. (0.083 mole) of 85% potassium hydroxide pellets was stirred at 35° for 30 minutes. (No heating or cooling was used.) The mixture was extracted with ether, then the basic aqueous phase was acidified to *p*H 2 with concentrated hydrochloric acid at 0°. The precipitated solid was removed by filtration, then recrystallized from ethylene glycol monomethyl ether. This afforded 4.1 g. (43% yield) of XXIVc as white prisms, m.p. 178-180°. Recrystallization from ethylene glycol monomethyl ether afforded an analytical specimen, m.p. 176-177°. The infrared spectrum (Nujol) showed absorption at 3.14 and 3.76 μ (OH), 5.70 μ (CO_2CH_3) and 6.06 μ (CO_2H). The ultraviolet spectrum (ethanol) showed absorption maxima at 285 mμ (ϵ, 4,000) and 235 mμ (ϵ, 16,100).

Anal. Calcd. for $C_{14}H_{12}N_2O_6$: C, 55.3; H, 3.98; N, 9.21. Found: C, 55.4; H, 4.15; N, 9.50.

Methyl 1-Piperonylpyrazole-4-carboxylate (XXVa).

A suspension of 3.0 g. (0.01 mole) of methyl 1-piperonyl-3-carboxypyrazole-4-carboxylate (XXIVc) in 50 ml. of triethylene glycol was immersed in an oil bath preheated to 200°. The external temperature was maintained at 200 ± 10° for 1 hour. The colorless solution was allowed to cool to room temperature, poured onto ice, and the solid removed by filtration. The white material was washed thoroughly with water, then air dried to afford, after combination with five other identical runs, 11.0 g. of XXVa, m.p. 90-93°, a yield of 72%. Two recrystallizations from methanol afforded an analytical specimen as white needles, m.p. 99-100°. The infrared spectrum (chloroform) showed absorption at 5.74 μ (CO_2CH_3). The ultraviolet spectrum (ethanol) showed an absorption maximum at 285 mμ (ϵ, 4,700) and end absorption at 230 mμ (ϵ, 15,600). The NMR spectrum (deuterochloroform) showed absorption for three protons (s) at 3.82 ppm (CO_2CH_3), two protons (s) at 5.22 ppm (Ar-CH_2-), two protons (s) at 5.96 ppm (-OCH_2O-), three protons (s) at 6.78 ppm (three aromatic protons) and two protons (two singlets at 7.92 and 7.98 ppm, protons at C-3 and C-5 on the pyrazole ring).

Anal. Calcd. for $C_{13}H_{12}N_2O_4$: C, 60.0; H, 4.65; N, 10.8. Found: C, 60.2; H, 4.74; N, 10.8.

Methyl 1-Piperonylpyrazole-3-carboxylate (XXVIa) and -4-carboxylate (XXVa).

A mixture of 12.0 g. (0.055 mole) of 3-piperonylsydnone, 10.2 g. (0.12 mole) of methyl propiolate and 90 ml. of toluene was heated at reflux for 17 hours. The brown solution was allowed to cool to room temperature, and the solvent was removed under reduced pressure. The residue was then added to ethyl acetate. The organic phase was washed with water, 10% potassium bicarbonate, water, a saturated sodium chloride solution, then was dried over anhydrous sodium sulfate. The organic phase was decolorized with charcoal and the solvent was removed under reduced pressure. This afforded 12.8 g. of a pale yellow colored solid. The NMR spectrum (deuterochloroform) showed this material to be a mixture of methyl 1-piperonylpyrazole-3-carboxylate (83%) and methyl 1-piperonylpyrazole-4-carboxylate (17%). Six recrystallizations from methanol afforded a mixture consisting of 96% of the 3-carboxylate and 4% of the 4-carboxylate. Two additional recrystallizations from ethyl acetate-petroleum ether (b.p. 60-68°) afforded an analytical specimen of methyl 1-piperonylpyrazole-3-carboxylate (XXVIa) as white rosettes, m.p. 92-94.5°. The infrared spectrum (chloroform) showed absorption at 5.76 μ (CO_2CH_3). The ultraviolet spectrum (ethanol)

showed an absorption maximum at 285 mμ (ε, 4,400) and end absorption at 230 mμ (ε, 14,000). The NMR spectrum (deuterochloroform) showed absorption for three protons (s) at 3.90 ppm (CO_2CH_3), two protons (s) at 5.92 ppm ($-OCH_2O-$), three protons (m) at 6.78 ppm (three aromatic protons and two protons as a multiplet-symmetrical AB pattern--centered at 6.80 and 7.41 ppm, protons as C-4 and C-5 on the pyrazole ring).

Anal. Calcd. for $C_{13}H_{12}N_2O_4$: C, 60.0; H, 4.65; N, 10.8. Found: C, 59.9; H, 4.52; N, 10.7.

1-Piperonylpyrazole-4-carboxylic Acid (XXVb).

A solution of 1.87 g. of methyl 1-piperonylpyrazole-4-carboxylate (XXVa), 30 ml. of methanol, 15 ml. of water and 1.2 g. of 85% potassium hydroxide pellets was heated at reflux for 5 hours. The solvent was removed under reduced pressure to a volume of 10 ml. and the slurry was acidified at 0° to *p*H 2 with 10% hydrochloric acid, then dried to give 1.64 g. (93% yield) of XXVb as white needles, m.p. 148-149°. Two recrystallizations from methanol-water afforded an analytical specimen as long white needles, m.p. 148-149°. The infrared spectrum (Nujol) showed absorption at 5.84 μ (CO_2H). The ultraviolet spectrum (ethanol) showed the following absorption maxima: *p*H 1, 7, 11 at 284 mμ (ε, 4,000); *p*H 1 and 7, strong end absorption 220-240 mμ; and *p*H 11 at 233 mμ (ε, 9,800).

Anal. Calcd. for $C_{12}H_{10}N_2O_4$: C, 58.5; H, 4.09; N, 11.4. Found: C, 58.5; H, 4.36; N, 11.2.

1-Piperonylpyrazole-3-carboxylic Acid (XXVIb).

A solution of 3.2 g. of the 4-carboxylate ester (XXVIa) in 30 ml. of water and 60 ml. of methanol containing 2.4 g. of 85% potassium hydroxide was stirred at reflux for 2.5 hours. The mixture was cooled, then acidified to *p*H 2 with a 10% hydrochloric acid solution. The precipitated solid was removed by filtration, washed thoroughly with water, then air dried. This afforded 2.5 g. (83% yield) of XXVIb as pale yellow prisms. Thorough drying at 100°/0.1 mm. for 8 hours was required to remove all the water; the melting point of the dried material was 122-126°. Two recrystallizations from methanol water afforded an analytical specimen as long white needles, m.p. 126.5-128°. The infrared spectrum (chloroform) showed absorption at 5.85 μ (CO_2H). The ultraviolet spectrum (ethanol) showed an absorption maximum at 285 mμ (ε, 4,200) and broad end absorption at 233 mμ (ε, 13,500).

Anal. Calcd. for $C_{12}H_{10}N_2O_4$: C, 58.5; H, 4.09; N, 11.4. Found: C, 58.7; H, 4.38; N, 11.2.

1-Piperonylpyrazole-4-carboxylic Acid Hydrazide (XXVc).

A solution of 2.3 g. of methyl 1-piperonylpyrazole-4-carboxylate (XXVa) in 40 ml. of methanol containing 10 ml. of 64% hydrazine hydrate was heated under reflux for 3 hours. The solution was cooled, adjusted to *p*H 7 with glacial acetic acid and the precipitated solid removed by filtration. This afforded 2.2 g. (96% yield) of XXVc as white prisms, m.p. 130-132°. Two recrystallizations from methanol afforded an analytical specimen as white needles, m.p. 158-160°. The infrared spectrum (Nujol) showed absorption at 3.07 and 6.13 μ. The ultraviolet spectrum (ethanol) showed the following absorption maxima at 284 mμ (ε, 4,400); *p*H 1 at 230 mμ (ε, 17,000); *p*H 7 at 231 mμ (ε, 15,900); *p*H 11 at 234 mμ (ε, 15,000).

Anal. Calcd. for $C_{12}H_{12}N_4O_3$: C, 55.4; H, 4.65; N, 21.5. Found: C, 55.3; H, 4.36; N, 21.6.

1-Piperonylpyrazole-3-carboxylic Acid Hydrazide (XXVIc).

A mixture of 3.5 g. of methyl 1-piperonylpyrazole-3-carboxylate (XXVIa), 10 ml. of 64% hydrazine hydrate and 40 ml. of methanol was heated at reflux for 3 hours. The solution was cooled, poured onto ice, then adjusted to *p*H 7 with glacial acetic acid. The precipitated solid was removed by filtration, washed with water, then dried, to give 2.4 g. (69% yield) of XXVIc, m.p. 134-136°. Two recrystallizations from methanol afforded an analytical specimen as white rods, m.p. 135-137°. The infrared spectrum (Nujol) showed absorption at 3.10 μ (N-H) and 6.02 μ (-CONH). The ultraviolet spectrum (ethanol) showed absorption maxima at 284 mμ (ε, 4,400), *p*H 1 at 231 mμ (ε, 14,800); *p*H 7 at 234 mμ (ε, 14,000) and *p*H 11 at 237 mμ (ε, 13,000).

Anal. Calcd. for $C_{12}H_{12}N_4O_3$: C, 55.4; H, 4.65; N, 21.5. Found: C, 55.5; H, 4.42; N, 21.7.

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