TABLE IV

ACTION ON ISOLATED RAT DUODENUM AND GUINEA PIG ILEUM

No.[a,b]	Acetylcholine	No.[b,c]	$BaCl_2$	No.[b,d]	Histamine
Atr.[e]	8.9	Pap.[f]	8.4	Prom.[g]	8.2
VI	5	V	4	XIII	5.8
V	4.5	XX	4	VI	5.7
IX	4.2	XIX	3.5	VII	5.5
X	4	IX	3	V	4
XX	4	XVIII	3	X	3.8
II	3.75	VII	3	XI	3.7
VII	3.75	VI	2.75	II	3.7
IV	3.5	X	2.75	VIII	3.7
XIX	3	II	2.70	IV	3.5
VIII	2.8	IV	2.5	XVII	3.5
XI	2.7	XI	2	XX	3.5
III	2.6	XVII	1.8	XIX	3
XVII	2	III	1.7	XVIII	2.5

[a] Compounds I and XII–XVI are inactive. [b] Activities of other numbers are not yet available. [c] Compounds I, VIII, and XII–XVI are inactive. [d] Compounds I, III, IX, XII, and XIV–XVI are inactive. [e] Atropine. [f] Papaverine. [g] Promethazine.

show only half that toxicity or even less (VI, 70 mg., and VIII, 150 mg.; XIX, 40 mg., and XX, 150 mg.). Concerning the effects on blood pressure, Table III shows that, here also, there are two peaks, this time in the doses required for hypotensive activity, encountered for both an ester and a hydrazide with the same radical, *i.e.*, isobutyl. From Table IV, which lists the antispasmodic activities in their order of potency, a minimum of 3 carbons is required in the radical substituting the amino group for the musculotropic, neurotropic, and, in part, antihistaminic activities to appear; branching at the α-carbon atoms of the amine substituent causes a decrease in or loss of activity, while branching at the β-carbon does not. Results in the hydrazide series are as yet insufficient for similar comparisons to be made, but already they appear to follow the same lines though the degree of activities is lower; it may also be noted that the hydrazides, contrary to expectation,[7] are not convulsant (XIV is a weak depressant). This suggests that the influence of the dialkylamino group is by no means negligible.

TABLE V

ACTION ON ISOLATED FROG HEART

No.	Concn.	Inotropic act.[a]	Toxic concn.	No.	Concn.	Inotropic act.[a]	Toxic concn.
I	10^{-7}	+	0	IX	10^{-4}	−	10^{-3}
II	10^{-7}	+	10^{-2}	X	10^{-8}	+	10^{-3}
II	10^{-3}	−		X	10^{-4}	−	
III	10^{-4}	−	0	XI	10^{-9}	+	10^{-3}
IV	10^{-8}	+	10^{-2}	XI	10^{-6}	−	
V	10^{-8}	+	10^{-3}	XII	10^{-14}	+	10^{-2}
V	10^{-4}	−		XVI	10^{-9}	+	10^{-7}
VI	10^{-12}	−	10^{-9}	XVII	10^{-5}	+	10^{-3}
VII	10^{-9}	+	10^{-3}	XVIII	10^{-9}	+	10^{-3}
VIII	10^{-14}	+	0				

[a] No chronotropic action noticed.

Experimental[15]

Preparation of Esters (Table I). General Procedure.—One mole of ethyl chloroacetate was added all at once, at room temperature, to 2 moles of a secondary amine, with stirring; the mixture may be warmed to start the reaction, but cooling was required when the hydrochloride of the secondary amine began to deposit. When the mixture had cooled completely and set solid, which required at least 4 hr., it was filtered through sintered glass, washed four times with isopropyl ether, the solvent was evaporated, and the residue was distilled on a spinning-band fractionating column under vacuum. For the less stable amines, in particular the dialkoxyethylamine, it is preferable to add a saturated solution of sodium carbonate instead of filtering and extracting and to flash-distil in a rotary evaporator under vacuum. The liquid obtained by this means is then distilled without any special precautions: infrared absorption, 3.4–3.5, 5.75, 6.85, 8.35–8.55 μ.

Preparation of Hydrazides (Table II). General Procedure.—The hydrazides were prepared by refluxing for 24 hr. a mixture of 1 mole of ester and 1.5 moles of hydrazine hydrate to which an adequate quantity of ethanol was added to homogenize. The alcohol and excess hydrazine hydrate were then evaporated in a rotary evaporator under vacuum and the residue was distilled: infrared absorption, 3, 3.4, 5.9–6.2, 6.6–6.8, 9.15, 9.9 μ.

(15) Melting points are uncorrected and were determined on a Reichert microscope with heating stage. Boiling points were taken during separation on a spinning-band fractionating column. Infrared spectra were recorded on an Infracord 137 Perkin-Elmer. Analyses were carried out by the Department of Microanalyses of the Centre National de la Recherche Scientifique.

Notes

3-Piperonylsydnone. A New Type of Antimalarial Agent[1]

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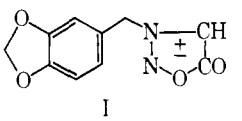
In connection with our continuing investigation on the structural variation of 3-(*p*-methoxybenzyl)sydnone,[2] an analog, 3-piperonylsydnone (I), has been synthesized in our laboratory. Compound I has now been shown to be an active agent in preliminary antimalarial evaluation. At a dose of 10 mg./kg., I was



I

found to be active against *Plasmodium berghei* in mice. The compound, which is comparable to chloroquine, is active when administered either orally or subcutaneously. No toxicity was observed at a dose of 500 mg./kg.[3]

(1) This investigation was supported by the Cancer Chemotherapy National Service Center, National Cancer Institute of the National Institutes of Health, Public Health Service, Contract SA-43-ph-3025.

(2) The confirmed antitumor activity of 3-(*p*-methoxybenzyl)sydnone in preliminary screening has been reported in our previous paper: see C. V. Greco, W. H. Nyberg, and C. C. Cheng, *J. Med. Pharm. Chem.*, **5**, 861 (1962).

(3) Information kindly provided by an antimalarial screening contractor of Walter Reed Army Institute of Research. We thank Dr. David P. Jacobus of the Walter Reed Army Medical Center for his permission to release this information. All compounds tested in the malaria program were furnished to WRAIR under the auspices of the CCNSC.

TABLE I
N-NITROSO-N-SUBSTITUTED GLYCINES AND GLYCONITRILES

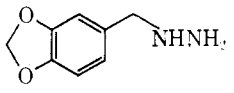
R—N(X)—CH(Y)—Z

R	X	Y	Z	Recrystn. solvents	Yield, %	M.p., °C.	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
3,4-$CH_2O_2C_6H_3$	H	H	COOH	*a*	57.0	147–150 dec.	55.3	4.62	7.17	55.0	4.77	7.07
3,4-$CH_2O_2C_6H_3CH_2$	H	H	COOH	*b*	88.3	229[c]	48.8[d]	4.88	5.71	48.4	4.65	5.60
3,4-$CH_2O_2C_6H_3CH_2$	H	CH_3	COOH	*e, f*	67.5	272	59.2	5.83	6.28	59.0	5.94	5.95
3,4-$CH_2O_2C_6H_3C_2H_4$	H	H	COOH	*g, h*	55.0	239–240[i]	50.9[j]	5.40	5.40	51.3	5.36	5.30
3-CH_3O-4-$C_2H_5OC_6H_3CH_2$	H	H	COOH	*j, k*	90.0	228–229	52.2[d]	6.54	5.10	51.6	6.60	5.40
3,4-$CH_2O_2C_6H_3CH_2$	H	H	CN	*g*	85.0	193–194 dec.[l]	53.0[d]	4.85	12.4	52.7	5.10	12.2
3,4-$CH_2O_2C_6H_3CH_2$	H	CH_3	CN	*m*	66.7	223–226	54.9[d]	5.42	11.7	54.5	5.43	11.5
3,4-$CH_2O_2C_6H_3CH_2$	NO	H	COOH	*j, k*	71.3	114–116	50.5	4.20	11.8	50.6	4.40	12.0
3-CH_3O-4-$C_2H_5OC_6H_3CH_2$	NO	H	COOH	*j, k*	40.4	114–116	53.7	5.97	10.4	53.9	6.06	10.5
3,4-$CH_2O_2C_6H_3CH_2$	NO	H	CN	*m*	73.2	56–58	55.8	4.11	19.2	55.8	4.41	19.3
3,4-$CH_2O_2C_6H_3CH_2$	NO	CH_3	CN	*f*	73.0	50–52	56.6	4.72	18.0	56.9	4.70	17.8

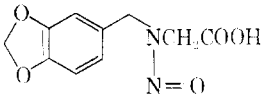
[a] Butanol. [b] Methanol. [c] Lit.[10] m.p. 224°. [d] Isolated as monohydrochloride. [e] Acetone. [f] Diethyl ether. [g] Ethanol. [h] Methyl acetate. [i] Lit.[11] m.p. 241°. [j] Ethyl acetate. [k] Heptane. [l] Lit.[9] m.p. 185. [m] Not recrystallized.

Up to the present time, known major antimalarial agents can be assembled into the following categories[4]: (1) cinchona alkaloids (4-quinolylcarbinols, *e.g.*, quinine and cinchonine), (2) 4-aminoquinolines (*e.g.*, chloroquine and amodiaquine), (3) 8-aminoquinolines (*e.g.*, pamaquine and primaquine), (4) 4-quinazolones (*e.g.*, alkaloids from Chang-shan), (5) 9-aminoacridines (*e.g.*, quinacrine), (6) diaminopyrimidines (*e.g.*, pyrimethamine), (7) biguanides (*e.g.*, proguanil), and (8) 4,4′-diaminodiphenyl sulfones. Since 3-piperonylsydnone is a cyclic mesoionic compound, it cannot be categorized in any of the aforementioned series. Consequently, this new type of compound may be less susceptible to cross resistance against strains of malarial parasites which developed resistance to the known antimalarial agents.[4b,5]

The site or mode of action of I as an antimalarial agent is not yet known. Sydnones, in general, yield hydrazines or N-nitrosoglycines on hydrolysis with acid or base, respectively.[6] Piperonylhydrazine[7] (II) and N-nitroso-N-piperonylglycine (III) were accordingly prepared. However, no antimalarial activity was detected with these compounds.[3]



II



III

The following related compounds have also been synthesized in our laboratory and tested: 3-phenylsydnone,[6] 3-[(3,4-methylenedioxy)phenyl]sydnone, 4-chloro-3-piperonylsydnone, 4-methyl-3-piperonylsydnone, 3-piperonylsydnone imine, 4-methyl-3-piperonylsydnone imine, 3-(4-ethoxy-3-methoxybenzyl)sydnone, 3[(3,4-methylenedioxy)phenethyl]sydnone, 3,4-methylenedioxy-β-nitrostyrene,[8] N-piperonylglyconitrile,[9] N-piperonylglycine,[10] N-nitroso-N-piperonylglyconitrile, N-piperonyl-α-methylglycine, N-homopiperonylglycine,[11] N,N′-dipiperonalazine,[12,13] N-piperonal-N-piperonyl hydrazone,[12] N,N′-dipiperonylhydrazine,[12] and 3-(N-*exo*-*p*-acetylaminobenzenesulfonyl)piperonylsydnone imine. Among these, only 3-phenylsydnone has demonstrated some activity against *P. berghei*. This compound is *ca.* 25% as active, but much more toxic than 3-piperonylsydnone.[3]

N-Substituted glycines and glyconitriles were prepared according to previously described procedures.[2] Although many sydnone imines have been prepared by cyclization of the corresponding N-nitrosoglycines in ether, acetone, or alcohols with dry HCl,[14] in our laboratory it was found that many undesirable side reactions[15] could be eliminated or suppressed by the use of nonpolar, nonoxygen-containing solvents, such as methylene chloride. We have also noted that the yield of sydnone imines could be further increased by the isolation and purification of the intermediate nitrosoglyconitriles prior to cyclization.

The sydnones prepared in this report were cyclized from the corresponding N-nitrosoglycines in benzene by means of N,N′-dicyclohexylcarbodiimide.[16] Yields from the carbodiimide cyclization were generally very good and the sydnones of high purity were readily isolated. It is of interest to note that previous investigators[17] had used N,N′-diisopropylcarbodiimide in water for the preparation of 3-substituted sydnones. However, under these conditions the reaction product was composed of an equimolar mixture of N,N′-diisopropylurea

(4) For excellent reviews and discussion of known antimalarial drugs, see (a) R. C. Elderfield in "Heterocyclic Compounds," Vol. 4, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1952, pp. 1–343; A. Albert, *ibid.*, pp. 491–563; (b) "Chemotherapy of Malaria," G. Covell, G. R. Coatney, J. W. Field, and J. Singh, Ed., World Health Organization Monograph Series No. 27, Geneva, 1955; (c) P. B. Russell in "Medicinal Chemistry," A. Burger, Ed., Interscience Publishers, Inc., New York, N. Y., 1960, p. 814.

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(14) F. H. C. Stewart, *Chem. Rev.*, **64**, 129 (1964), and references cited therein.

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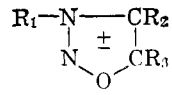
(16) E. Schmidt, F. Hitzler, and E. Lahde, *Ber.*, **71**, 1933 (1938). Available from Mann Research Laboratories, Inc., New York, N. Y.

(17) W. Püttner and G. Wolfrom, British Patent 823,001 (Nov. 4, 1959); German Patent 1,069,633 (Nov. 26, 1959).

TABLE II

3-SUBSTITUTED SYDNONES AND SYDNONE IMINES



R_1	R_2	R_3	Recrystn. solvents	Yield, %	M.p., °C.	λ_{max}^{EtOH}, mμ	ϵ_{max}	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
3,4-$CH_2O_2C_6H_3$	H	O	*a*	41.5[b]	165–166	308	9,500	52.5	2.92	13.6	52.3	3.21	13.3
3,4-$CH_2O_2C_6H_3CH_2$	H	O	*c*	72.4	158–159	288	11,450	54.5	3.63	12.7	54.7	3.98	12.6
3,4-$CH_2O_2C_6H_3CH_2$	CH_3	O	*c*	58.8[b]	138–141	291	12,650	56.4	4.28	12.0	56.6	4.53	11.8
3-CH_3O-4-$C_2H_5OC_6H_3CH_2$	H	O	*d, e*	98.0	115–119	285	10,000	57.6	5.60	11.2	57.3	5.46	11.2
3,4-$CH_2O_2C_6H_3C_2H_4$	H	O	*d, f*	36.0[b]	122–125	287	12,200	56.4	4.28	12.0	56.1	4.20	11.7
3,4-$CH_2OC_6H_3CH_2$	Cl	O	*d*	13.2	110–111 dec.	292	10,700	47.2	2.75	11.0	47.2	3.00	11.0
3,4-$CH_2O_2C_6H_3CH_2$	H	NH·HCl	*f, g*	42.6	97 dec.	291	9,500	46.9	3.91	16.4	46.7	4.13	16.1
3,4-$CH_2O_2C_6H_3CH_2$	CH_3	NH·HCl	*f, g*	71.1	111 dec.	294	11,600	49.0	4.45	15.6	49.1	4.71	15.4
3,4-$CH_2O_2C_6H_3CH_2$	H	*p*-$(NSO_2C_6H_4)NHCOCH_3$	*f*	36.9	111 dec.	262 317	23,500 11,700	49.8[h,i]	4.15	12.9	49.6	4.20	12.9

[a] Butanol. [b] Yield calculated from the corresponding glycine. [c] Toluene. [d] Heptane. [e] Ethyl acetate. [f] Ethanol. [g] Petroleum ether (b.p. 35–60°). [h] Monohydrate. [i] Karl–Fischer determination of water: calcd., 4.15; found, 4.11.

and sydnone, and the latter could only be isolated after repeated recrystallizations.

Experimental[18]

N-Nitroso-N-piperonylglycine (III).—To a solution of 24.4 g. of N-piperonylglycine hydrochloride[9] in 250 ml. of water cooled to 0° was added dropwise, with stirring, during a period of 30 min., a concentrated aqueous solution of 7.5 g. of $NaNO_2$. After the addition was complete the reaction mixture was stirred at 0° for an additional 3 hr. and extracted with six 200-ml. portions of ether. The ether extract was treated with decolorizing charcoal, dried (Na_2SO_4), filtered, and evaporated to a sirup under reduced pressure. The sirup was triturated with a small amount of petroleum ether (b.p. 35–60°) and the resulting solid was recrystallized from a mixture of ethyl acetate and heptane to give 17 g. of analytically pure product, m.p. 114–116° (see Table I).

α-Methyl-N-nitroso-N-piperonylglycine, N-nitroso-N-piperonylglyconitrile, and other related compounds (see Table I) were prepared by essentially the same procedure.

3-Piperonylsydnone (I).—To a warm (70°) solution of 4 g. of III in 150 ml. of dry benzene was added a warm (70°) solution of N,N′-dicyclohexylcarbodiimide[16] in 50 ml. of dry benzene. N,N′-Dicyclohexylurea precipitated immediately. The mixture was stirred at 50–60° for 2 hr. and filtered while hot. The filtrate was evaporated to dryness *in vacuo*, and the residue was recrystallized from 75 ml. of toluene to give 2.7 g. of I as shiny needles, m.p. 158–159° (see Table II).

In a parallel run, a comparable yield of the same purity was obtained when acetic anhydride was used as the cyclizing agent.[2] Products prepared by both methods had identical antimalarial activity. Other 3-substituted sydnones were prepared by the carbodiimide procedure.

3-Piperonylsydnone Imine Hydrochloride.—Dry HCl was bubbled at a moderate rate into a solution of 6.6 g. of N-nitroso-N-piperonylglyconitrile in 150 ml. of dry methylene chloride cooled at −50°. After 10 min. the gas inlet was disconnected and the reaction mixture was evaporated below 0° under high vacuum. To the resulting residue there was added a small amount of petroleum ether (b.p. 35–60°), and the solid product which separated was filtered. It was recrystallized from a mixture of ethanol and petroleum ether to give 3.3 g. of analytically pure product (see Table II). **4-Methyl-3-piperonylsydnone imine hydrochloride** was prepared by essentially the same procedure.

3-Piperonyl-4-chlorosydnone was prepared by chlorination of I, according to the method of Baker, Ollis, and Poole[19] (see Table II).

3-(N-Exo-*p*-acetylaminobenzenesulfonyl)piperonylsydnone imine was prepared by treating 3-piperonylsydnone imine hydrochloride with *p*-acetylaminobenzenesulfonyl chloride in pyridine, according to the procedures of Yashunskii and Ermolaeva[20] and Daeniker and Druey[21] (see Table II).

Acknowledgment.—The authors wish to express their appreciation to Mr. Hal P. Van Fossen, Mr. John R. Gravatt, and Mrs. Margaret Rounds for the analytical and instrumental measurements.

(18) All melting points (corrected) were taken on a Thomas–Hoover melting point apparatus. The ultraviolet absorption spectra were determined with a Beckman DK-2 spectrometer.

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Thyroxine Analogs. XV.[1] Synthesis and Antigoitrogenic Activity of the 3′-*t*-Butyl Analog of 3,5,3′-Triiodo-L-thyronine and Its O-Methyl Ether

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Analog studies carried out to define structural features necessary for thyroid hormonal activity have led to active compounds in which the iodine atoms of thyroxine (Ia) and 3,5,3′-triiodothyronine (Ib) have been replaced by other halogen atoms[2] and by alkyl groups.[3–6] Iodine has proved to be the most effective

(1) (a) Paper XIV: E. C. Jorgensen and J. A. W. Reid, *Endocrinology*, **76**, 312 (1965). This investigation was supported by Research Grant AM-04223 from the National Institute of Arthritis and Metabolic Diseases, U. S. Public Health Service. (b) The synthesis and biological evaluation in the tadpole of 3-[4-(3-*t*-butyl-4-hydroxyphenoxy)-3,5-diiodophenyl]-L-alanine hydrochloride (compound Va hydrochloride) is reported independently by C. M. Buess, T. Giudici, N. Kharasch, W. King, D. D. Lawson, and N. N. Saha, *J. Med. Chem.*, **8**, 469 (1965).

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