Table I
Minimum Inhibiting Concentration (μg/ml)

Derivative	*Staphylococcus aureus*		*B. cereus*		*Streptococcus faecalis*		*E. coli*		*P. vulgaris*		*Saccharomyces cerevisiae*		*C. albicans*	
	24 hr	48 hr	24 hr	48 hr	24 hr	48 hr	24 hr	48 hr	24 hr	48 hr	24 hr	48 hr	24 hr	48 hr
8-Quinolinol	18.75	18.75	18.75	18.75	18.75	18.75	25.0	25.0	37.5	37.5	6.25	6.25	9.3	9.3
Tin 5,7-dichloroquinoline-8-thiolate	50.0	50.0	37.5	37.5	50.0	50.0	37.5	37.5	37.5	37.5	50.0	50.0	50.0	50.0
Sodium 5,7-dichloroquinoline-8-thiolate	>128	>128					>128	>128			>128	>128	>128	>128
Id	102.5	200					102.5	128			128	128	128	128
2	>200	>200					>200	>200			>200	>200	>200	>200

crystd from DMSO to give the Sn salt as prisms, mp 340–342°. *Anal.* ($C_{18}H_8Cl_4N_2S_2Sn$) Sn.

Sodium 5,7-Dichloroquinoline-8-thiolate.—The above Sn salt (1 g) was stirred in a solution of NaOH (1.5 g) in H_2O (25 ml) overnight. The Na salt was filtered, washed with H_2O, and dried. Recrystallization of the dried residue (0.55 g) from EtOH gave the sodium salt as yellow needles, mp 280° dec.

5,7-Dichloro-8-quinolyl Disulfide.—To a solution of NaOH (1.5 g) and I_2 (0.25 g) in H_2O (100 ml) was added finely ground tin 5,7-dichloroquinoline-8-thiolate (1.4 g). The mixture was stirred overnight and then filtered and the residue was thoroughly washed with H_2O. Recrystallization of the dried residue from dioxane gave product (0.30 g) as yellow prisms, mp 219–220°. *Anal.* ($C_{18}H_8Cl_4N_2S_2$) C, H, N.

5,7-Dichloroquinoline-8-thiol.—To a stirred suspension of the above disulfide (0.25 g) in oxygen-free MeOH (25 ml) were added successively, solutions of NaOH (0.65 g) in H_2O (5 ml) and glucose (0.65 g) in H_2O (5 ml). The mixture was stirred and heated under reflux for 3 hr, before evapn of the MeOH. The mixture was filtered and the residual Na salt was dissolved in H_2O (25 ml). CO_2 was passed through the solution for 10 min, and the white ppt was filtered and dried *in vacuo*. Recrystallization from MeOH gave the thiol (0.1 g) as needles, mp 102–103°; pmr spectrum as expected. *Anal.* ($C_9H_5Cl_2NS$) C, H, N.

Acknowledgment.—The authors thank Mr. L. S. Bark (University of Salford) for a Sn analysis on tin 5,7-dichloroquinoline-8-thiolate.

Structural Modification Studies of 3-Piperonylsydnone. 2. Synthesis of Piperonyl-Substituted Hydantoin, Thiohydantoin, Thiazolidinedione, Rhodanine, Imidazolinone, and Related Compounds[1]

William H. Burton, William L. Budde, and C. C. Cheng

Midwest Research Institute, Kansas City, Missouri 64110

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The antimalarial activity of a mesoionic compound, 3-piperonylsydnone (I), against *Plasmodium berghei* was reported.[2] Preliminary structure–activity relationship studies[2,3] revealed the importance of the piperonyl moiety for the antimalarial activity for compounds of this type. The mode of action of I is still unknown. One possible explanation for the many interesting biological activities exhibited

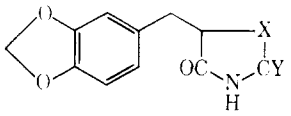
I

by the sydnones[4,5] is that these compounds may interfere with the biochemical role of amino acids. It is certainly not improbable for 3-piperonylsydnone to act as an amino acid antagonist since the compound itself was prepared from an N-substituted amino acid (*N*-piperonylglycine).[2] Consequently, syntheses of certain piperonyl derivatives containing a hydantoin (IIa),

(1) This investigation was supported by Contract DA-49-193-MD-2749 with the U. S. Army Medical Research and Development Command. This paper is Contribution No. 767 from the Army Research Program on malaria.

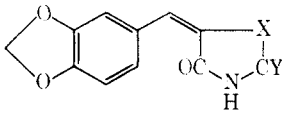
(2) W. H. Nyberg and C. C. Cheng, *J. Med. Chem.*, **8**, 531 (1965).
(3) S. G. Boots and C. C. Cheng, *J. Heterocycl. Chem.*, **4**, 272 (1967).
(4) L. B. Kier and E. B. Roche, *J. Pharm. Sci.*, **56**, 149 (1967).
(5) E. Ackermann, *Pharmazie*, **22**, 537 (1967).

thiohydantoin (IIb), thiazolidinedione (IIc), rhodanine (IId), and an imidazolinone (IIe) moiety, as well as other related compounds, were studied. These compounds, on *in vitro* or *in vivo* hydrolysis, may yield either a β-substituted alanine or other analogous derivatives.



IIa, X = NH; Y = O
b, X = NH; Y = S
c, X = S; Y = O
d, X, Y = S
e, X, Y = NH

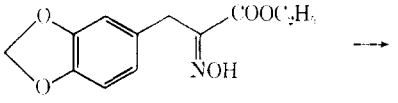
Condensation of piperonal with 2-thiohydantoin and with rhodanine in AcOH, according to the general procedure of Gränacher, *et al.*,[6] readily yielded the piperonylidene derivatives, IIIb and IId, respectively. Similar preparations of the corresponding hydantoin and thiazolidinedione compounds (IIIa and IIIc) required the presence of a large amount of NaOAc. The yield of IIIa by the direct condensation method was generally low. This intermediate can be obtained in bettter yield through the desulfurization of 5-piperonyl idene-2-thiohydantoin (IIIb).



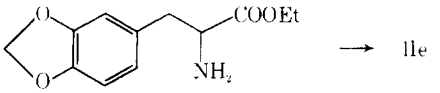
IIIa, X = NH; Y = O
b, X = NH; Y = S
c, X = S; Y = O
d, X, Y = S

The desired 5-piperonylhydantoin (IIa) was readily obtained by either catalytic or chemical reduction[7] of IIIa. Other analogs (IIb–d), owing to the presence of sulfur in the molecules, cannot be prepared by ordinary catalytic reduction of the corresponding unsaturated compounds (IIIb–d). Na-Hg treatment of IIIb and IIIc gave 5-piperonyl-2-thiohydantoin (IIb) and 5-piperonyl-2,4-thiazolidinedione (IIc), respectively, in good yields. A much lower yield of IIb was obtained on reduction of IIIb with either Sn and ethanolic HCl[8,9] or HI.[8] Application of the aforementioned methods to the piperonylidene derivative of rhodanine (IIId), however, resulted either in failure or in substantial hydrolysis of the rhodanine portion of the molecule.

Synthesis of 2-amino-5-piperonyl-4-imidazolinone (IIe, as the imino form) was accomplished as follows: ethyl 2-oximino-3-(3,4-methylenedioxyphenyl)propionate (IV), prepared by the treatment of diethyl piperonyl-malonate with ethyl nitrite, according to the general procedure of Shivers and Hauser,[10] was reduced catalytically. The resulting 2-amino ester V was condensed with guanidine to give IIe in 86% yield.

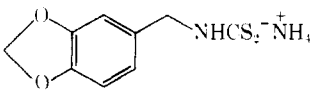


IV

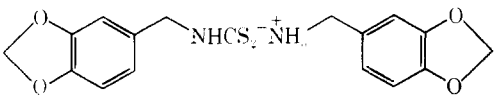


V

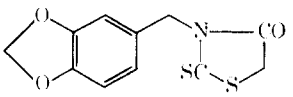
Treatment of piperonyldithiocarbamate salt (VI) with $ClCH_2CO_2H$[11,12] should theoretically yield 3-piperonylrhodanine (VIII), an isomer of 5-piperonylrhodanine. However, preparation of VI according to the general method of Dains, *et al.*,[13] gave instead piperonylammonium *N*-piperonyldithiocarbamate (VII). Nevertheless, when VII was treated with $ClCH_2CO_2H$, the desired 3-piperonylrhodanine VIII was obtained.



VI

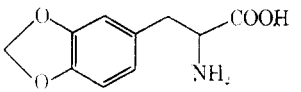


VII

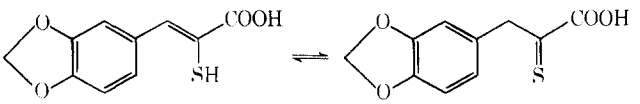


VIII

Alkaline hydrolysis of 5-piperonylhydantoin (IIa) in $Ba(OH)_2$[14] yielded the amino acid 3-(3,4-methylenedioxyphenyl)alanine (IX). The general acid hydrolysis procedure[9] could not be applied for the preparation of IX from the corresponding thiohydantoin IIb, due to the insolublity of the latter in acid medium. Hydrolysis of 5-piperonylidenerhodanine (IIId) in NaOH gave



IX



Xa Xb

(6) C. Gränacher, M. Gerö, A. Ofner, A. Klopfenstein, and E. Schlattec, *Helv. Chim. Acta*, **6**, 458 (1923).

(7) Analysis of ir spectra is useful in characterizing the condensation products IIIa and IIIb as well as the reduced derivatives IIa and IIb. The imide function in heterocyclic rings gives two absorptions in the C=O region. In the case of 5-piperonylidenehydantoin (IIIa), the absorption at 1700 cm^{-1} is assigned to C=O at the 2 position and the other at 1740 cm^{-1} to C=O at the 4 position (*cf.* L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, Wiley, New York, N. Y., 1958, p 221). Reduction of IIIa to IIa caused these absorptions to shift to 1730 and 1775 cm^{-1}, respectively. This shift is consistent with a higher CO band order (a shift of 30 cm^{-1} to higher energies) as conjugation with the C=C bond (1640–1650 cm^{-1}) is eliminated.

(8) H. L. Wheeler, C. Hoffman, and T. B. Johnson, *J. Biol. Chem.*, **10**, 117 (1911).

(9) T. B. Johnson and W. B. O'Brien, *ibid.*, **12**, 205 (1912).

(10) J. C. Shivers and C. R. Hauser, *J. Amer. Chem. Soc.*, **69**, 1264 (1947).

(11) F. C. Brown, C. K. Bradsher, E. C. Morgan, M. Tetenbaum, and P. Wilder, Jr., *ibid.*, **78**, 384 (1956).

(12) R. Andreasch, *Monatsh. Chem.*, **29**, 399 (1908).

(13) F. B. Dains, R. Q. Brewster, and C. P. Olander, "Organic Syntheses," Collected Vol. I, 1941, p 447.

(14) V. Deulofeu and J. Meadive, *Z. Physiol. Chem.*, **211**, 1 (1932).

3,4-methylenedioxy-α-thiolcinnamic acid (Xa). Examination of its ir spectrum revealed that the product is in equilibrium with its tautomeric form, 3-(3,4-methylenedioxyphenyl)-2-thiopyruvic acid (Xb).

Antimalarial screening results in rodents[15] indicated that none of the compounds synthesized were active against *P. berghei*. In mosquito screening tests using a standard strain of *Aedes aegypti* infected with *P. gallinaceum*,[15] it was found that 5-piperonyl-2-thiohydantoin (IIb) resulted in complete suppression of sporozoite development at 0.1% concentration and 5-piperonylidenehydantoin (IIIb) gave a 75% sporozoite suppression at the same concentration. In antifolic acid assay,[15] 2-amino-5-piperonyl-4-imidazolinone (IIe) was found to be active against the growth of *Streptococcus faecalis*. The effect can be reversed by the addition of 0.2 μg of folic acid. 3-(3,4-Methylenedioxyphenyl)-2-thiopyruvic acid (X) was active against the growth of *Lactobacillus casei*, and the activity was not reversed by 0.1 μg of folic acid.

Experimental Section

All melting points (corrected) were taken on a Thomas-Hoover melting point apparatus. Absorption bands of uv and ir spectra have been taken and were as expected. Microanalyses were performed at Midwest Research Institute. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

5-Piperonylidene-2-thiohydantoin (IIIb).—A mixture of 75 g (0.5 mole) of piperonal, 58 g (0.5 mole) of 2-thiohydantoin, 2 ml of piperidine, and 400 ml of AcOH was refluxed for 5 hr, during which time yellow crystals gradually deposited from the reaction solution. The cooled mixture was filtered to give 100 g of crystalline solid, which decomposed at 215–218°. Recrystallization from THF gave 87 g (70% yield) of analytically pure IIIb, dec at 282–284°. *Anal.* ($C_{11}H_8N_2O_3S$) C, H, N.

5-Piperonylidenerhodanine (IIId).—A mixture of 30 g (0.2 mole) of piperonal, 26.6 g (0.2 mole) of rhodanine, and 200 ml of AcOH was refluxed for 5 hr and the product isolated by filtration of the cooled reaction mixture to give 33.9 g (64% yield) of crystalline solid, mp 293–294°. Recrystallization from DMF gave analytically pure IIId, mp 298–300° (lit. 256–258° dec,[16a] 255° dec[16b]) *Anal.* ($C_{11}H_7NO_3S_2$) C, H, N.

A higher yield (80%) of IIId was obtained when 53 g (0.65 mole) of anhydrous NaOAc was added to the reaction mixture prior to reflux.

5-Piperonylidenehydantoin (IIIa). Method A.—A mixture of 42.5 g (0.28 mole) of piperonal, 25 g (0.25 mole) of hydantoin, 50 g (0.61 mole) of NaOAc, and 200 ml of AcOH was refluxed for 4 hr. The resulting solution was cooled, diluted with 300 ml of saturated aqueous NaCl solution, and extracted with four 300-ml portions of CH_2Cl_2. The AcOH–CH_2Cl_2 extract was added to 500 ml of H_2O to give 9.1 g (15% yield) of product (which did not contain the unchanged hydantoin), mp 248–250°. Recrystallization from 95% EtOH gave analytically pure IIIa, mp 251.5–253° (lit. mp 245°[17]). *Anal.* ($C_{11}H_8N_2O_4$) C, H, N.

Method B.—A mixture of 18 g (0.073 mole) of IIIb, 45 g (0.48 mole) of chloroacetic acid, 150 ml of DMF, and 150 ml of H_2O was refluxed for 2 hr. On cooling, 15 g (89% yield) of crystalline solid was isolated by filtration. The product was found to be identical with that prepared by method A.

5-Piperonylidene-2,4-thiazolidinedione (IIIc) was prepared in a similar manner from 15 g (0.1 mole) of piperonal, 11.7 g (0.1 mole) of 2,4-thiazolidinedione, 41 g (0.5 mole) of anhydrous NaOAc, and 100 ml of AcOH to give 10 g (40%) of solid, mp 247–249°. Recrystallization from THF gave analytical sample, mp 249–250°. *Anal.* ($C_{11}H_7NO_4S$) C, H, N.

5-Piperonylhydantoin (IIa). Method A.—A mixture of 19 g (0.082 mole) of IIIa and 2 g of 5% Pd–C in 250 ml of EtOH was hydrogenated at 3.5 kg/cm² for 24 hr. The reaction mixture was heated to boiling and filtered. On cooling, 8 g (42% yield) of analytically pure IIa, mp 184–185° (lit.[14] mp 182–183°), was collected.

Method B.—A mixture of 4 g (0.017 mole) of IIIa, 31 g of 3% Na–Hg (1 g of Na), and 30 ml of H_2O was stirred for 4 hr at room temperature. The clear, dark solution was decanted from Hg and filtered, and the pH of the filtrate was adjusted to 3 with dil HCl. The resulting white precipitate was collected by filtration and recrystallized from toluene and EtOAc to give 3.8 g (94%) of product, mp 185–186°. It was found to be identical with that prepared by method A.

5-Piperonyl-2-thiohydantoin (IIb). Method A.—A mixture of 24.8 g (0.1 mole) of IIIb, 183 g of 3% Na–Hg, and 150 ml of H_2O was stirred for 1.5 hr at room temperature. The orange–red solution was decanted from Hg, filtered, and acidified to pH 3 with dil HCl. The bright yellow precipitate was filtered off, yield 17.9 g (72%), mp 184–187°. Recrystallization from 50% aq EtOH gave analytically pure, sample, mp 187–189°. *Anal.* ($C_{11}H_{10}N_2O_3S$) C, H, N.

Method B.—A mixture of 12.4 g (0.05 mole) of IIIb, 20 ml of 57% HI, and 200 ml of AcOH was warmed at 100° for 3 hr with stirring. The cooled solution was treated with excess $Na_2S_2O_3$, the inorganic salt was separated by filtration, and the filtrate chilled to give 3.3 g (26%) of solid. The product was found to be identical with that prepared by method A.

5-Piperonyl-2,4-thiazolidinedione (IIc) was prepared by the Na–Hg method from 10 g (0.04 mole) of IIIc, 75 g of 3% Na–Hg, 600 ml of THF, and 75 ml of H_2O. After recrystallization from 50% aq EtOH, 2 g (20% yield) of analytically pure IIc was obtained, mp 116–117°. *Anal.* ($C_{11}H_9NO_4S$) C, H, N.

Ethyl 2-Oximino-3-(3,4-methylenedioxyphenyl)propionate (IV).—To 88 g (0.3 mole) of diethyl piperonylmalonate was added at 0°, with stirring, 34 g (0.45 mole) of EtONO[18] in 5 min. The reaction flask was cooled to −10° and a solution of 6.9 g (0.3 g-atom) of Na in 150 ml of EtOH was added over a period of 1 hr. The flask was sealed and stored overnight at −20°. The brown solid obtained on evaporation of the solvents was dissolved in 100 ml of ice–water, and the solution was extracted with Et_2O. The aq layer was acidified at 10° with cold, concentrated HCl to pH 3. The yellow precipitate was filtered and washed with H_2O. The solid was again dissolved in 300 ml of Et_2O and extracted twice (H_2O). The dried Et_2O solution was concd to 50 ml and, on addition of heptane, there was obtained 60 g (80%) of IV, mp 92–95°. Recrystallization of a small portion of the product from C_6H_6–heptane gave analytically pure sample, mp 96–97°. *Anal.* ($C_{12}H_{13}NO_5$) C, H, N.

Ethyl 2-Amino-3-(3,4-methylenedioxyphenyl)propionate (V) Hydrochloride.—A mixture of 25.1 g (0.1 mole) of IV, 5.5 ml of concd HCl, and 2 g of 5% Pd–C in 280 ml of EtOH was hydrogenated for 6 hr at 3.5 kg/cm². The catalyst was removed by filtration and the solution saturated with HCl. Evaporation to one-half of its original volume gave 34 g (70%) of crude product, mp 140–150°. Recrystallization from EtOH gave 28 g of analytically pure product, mp 160–161°. *Anal.* ($C_{12}H_{15}NO_4 \cdot HCl$) C, H, N.

2-Amino-5-piperonyl-4-imidazolinone (IIe).—To a stirred slurry of 3 g (0.033 mole) of guanidine carbonate in 10 ml of EtOH was added a solution of 0.7 g (0.03 g-atom) of Na in 20 ml of EtOH. After 5 min the mixture was filtered directly into a stirred Et_2O solution containing 7.1 g (0.03 mole) of V (prepared from the preceding product by neutrallzation and Et_2O extraction of the aq solution). A precipitate formed rapidly and NH_3 was evolved. After the mixture was stirred for 48 hr, the solid was collected by filtration, washed (H_2O, EtOH), and dried to give 6 g (86%) of product, mp 258–260° dec. It was purified by dissolving it in dil AcOH and reprecipitating with dil NaOH followed by drying at 140°. The melting point remained the same. *Anal.* ($C_{11}H_{11}N_3O_3$) C, H, N.

Piperonylammonium *N*-Piperonyldithiocarbamate (VII).—To a stirred solution of 14.1 g (0.1 mole) of piperonylamine in 200 ml of Et_2O was added 3.8 g (0.05 mole) of CS_2 during 20 min at below 30°. The mixture was stirred for an additional 30 min and the resulting white precipitate was collected by filtration. It was washed with Et_2O and dried *in vacuo* to give 16 g (85%) of VII,

(15) For detailed explanation of test procedures and interpretation of results, see protocols issued by Division of Medicinal Chemistry, Walter Reed Institute of Research, Walter Reed Army Medical Center, Washington, D. C.

(16) (a) R. Andreasch and A. Zipser, *Monatsch. Chem.*, **24**, 499 (1903); (b) A. Mackie and A. Misra, *J. Chem. Soc.*, 3919 (1954).

(17) H. L. Wheeler and C. Hoffman, *Amer. Chem. J.*, **45**, 368 (1911).

(18) W. L. Semon and V. R. Damerell, "Organic Syntheses," Coll. Vol. II, Wiley, New York, N. Y., 1943, p 204.

mp 140–142° dec. Recrystallization from EtOH gave an analytical sample, mp 142–144° dec. *Anal.* ($C_{17}H_{18}N_2O_4S_2$) C, H, N.

3-Piperonylrhodanine (VIII).—A solution of 4.7 g (0.05 mole) of $ClCH_2CO_2H$ in 5 ml of H_2O was treated with 1 g (0.025 mole) of NaOH and sufficient Na_2CO_3 to bring the pH to 7.5. To this stirred solution was added, during 30 min, 12.2 g (0.05 mole) of VII. During the addition, 15 ml of H_2O and 40 ml of DMF were added to facilitate the solution of the carbamate salt. The mixture was stirred for 36 hr and the resulting solid, mp 144–145° dec, was collected by filtration and washed (H_2O, EtOH). It was slurried in 50 ml of H_2O and acidified with 6 *N* HCl to pH 2. The mixture was heated at 80° for 15 min and cooled. The yellow solid was collected by filtration, washed (H_2O), and dried *in vacuo* to give 6.5 g (52% yield) of product, mp 117–118°. Recrystallization from aq EtOH gave analytically pure VIII, mp 117–118°. *Anal.* ($C_{11}H_9NO_3S_2$) C, H, N.

3-(3,4-Methylenedioxyphenyl)alanine (IX).—A mixture of 7 g (0.03 mole) of IIa and 66 g (0.21 mole) of $Ba(OH)_2 \cdot 8H_2O$ in 350 ml of H_2O was refluxed with stirring for 3 days until evolution of NH_3 had ceased. The reaction mixture was cooled to 20° and acidified with conc H_2SO_4 to *p*H 1. The pptd $BaSO_4$ was filtered and washed with 200 ml of H_2O. The filtrate and washings were combined and evaporated to one-third of the original volume. It was then neutralized with NH_4OH. The resulting precipitate was collected by filtration and recrystallized from H_2O to give 1.4 g (22%) of IX, mp 253–254° dec (lit.[6] mp 250–255°). *Anal.* ($C_{10}H_{11}NO_4$) C, H, N.

3-(3,4-Methylenedioxyphenyl)-2-thiopyruvic Acid (X).—A mixture of 12 g (0.045 mole) of IIId and 100 ml of 4 *N* NaOH was refluxed with stirring for 30 min. The clear solution was cooled rapidly to 10° and acidified with 100 ml of cold 4 *N* HCl. After 15 min the pale yellow precipitate was collected by filtration, washed with H_2O, and dried, mp 198–200° dec. Two recrystallizations from MeOH gave 4 g (40%) of X, mp 201–203° (lit.[19] mp 208–210° dec.). *Anal.* ($C_{10}H_8O_4S$) C, H, S.

Acknowledgment.—The authors wish to thank Dr. Howard W. Bond and Dr. Leo Rane for their interest, and Mrs. Margaret L. Rounds and Mr. John R. Gravatt for the analytical and instrumental measurements.

(19) R. Andreasch, *Monatsh. Chem.*, **39**, 419 (1918).

Studies on the *in Vivo* Antiviral Effects of Benzothiazole Derivatives against Various Influenza A2 Strains

STIG ÅKERFELDT

Virology Department, Research Department of the KABI Group, S-104 25 Stockholm 30, Sweden

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During an investigation of the effect of various heterocyclic ring systems on mice infected with various influenza virus strains, it was found that 2-aminobenzothiazole, when administered intraperitoneally to mice, gave a protection to the animals quite comparable to that of aminoadamantane. A structure–activity study was then undertaken to investigate whether certain structural changes could improve the antiviral effect of the compound. A remarkable sensitivity to variations in structure was found. Indeed, out of 17 benzothiazoles only the 2-amino- and 2-amino-4-chloro derivatives showed significant protective effect at the dose levels tested.

All 17 compounds were also tested in *in vitro* systems using human amnionic cells infected with rhino virus 33342, adeno virus 3, and herpes simplex virus. No protective effects could be demonstrated with any compound in the concentration range of 1–50 μg/ml.

Hungarian workers[1,2] have reported the effectiveness of some 2-(pyridyl)benzothiazole compounds against certain strains of influenza virus when tested in chick embryo chorioallantoic membrane cultures. However, the investigated substances were completely ineffective *in vivo* in mice.[2] Recently Paget, *et al.*,[3] have demonstrated the *in vivo* effect of certain benzothiazoleureas against Coxsackie A 21 virus in mice.

Table I describes the results of the *in vivo* tests.

TABLE I

EFFECT OF BENZOTHIAZOLE DERIVATIVES IN MICE INFECTED WITH INFLUENZA A2/STOCKHOLM/63

Substituents	Dose, mg/animal	% survivors treated group	% survivors control group
None	0.5 ip	10	33
	1.0 ip	10	20
2-NH_2	0.4 intranasal	10	7
	0.5 po	20	20
	0.1–1.5 ip	See Table II	
2-NH_2-4-Cl·HBr	0.1–0.5	See Table II	
2-NH_2-6-Cl	0.5 ip	0	27
	0.5 ip	25	20
2-NH_2-4,6-Cl_2	0.5 ip	Toxic dose	
	0.1 ip	Toxic dose	
2-NH_2-5,6-Cl_2	0.5 ip	Toxic dose	
	0.1 ip	0	20
2-NH_2-6-Br	0.5 ip	30	46
2-NH_2-6-Me	0.5 ip	0	27
2-NH_2-5,6-Me_2	0.5 ip	10	20
2-NH_2-6-EtO	0.5 ip	30	20
2-NH_2-6-Me	0.5 ip	40	24
2-NH_2-6-SO_3H	0.5 ip	0	0
2-NH_2-5-Me-7-SO_3H	0.5 ip	10	0
5-NH_2-2-Me	1.0 ip	0	20
2-(4-$H_2NC_6H_4$)-6-Me	0.5 ip	40	33
6-OH-2-SO_2NH_2	4.0 ip	10	7
6-EtO-2-SO_2NH_2	4.0 ip	0	7

The substances were administered either intraperitoneally (ip) or intranasally to male mice (10–12 g, 2–3 weeks old, NMRI-strain) 15 min before intranasal infection with virus of the Et_2O-anesthetized animals. For each experiment 10 mice were used. The number of surviving animals was recorded daily for 15 days.

Benzothiazole derivatives are often rather toxic compounds, producing tremors in the animals at near-toxic dose levels. The acute LD_{50} values for 2-aminobenzothiazole and for 2-amino-4-chlorobenzothiazole were estimated at 180 mg/kg in the mouse strain used. The toxic properties of the compounds studied may explain the lower number of surviving animals in certain treated groups as compared to the corresponding control groups.

Table II shows experiments where 2-aminobenzothiazole, 2-amino-4-chlorobenzothizaole, and aminoadamantane·HCl were tested against various mouse-adapted influenza strains. A single dose of substance was administered ip 15 min before intranasal infection of Et_2O-anesthetized animals. From the results with

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(3) C. J. Paget, K. K. Kisner, R. L. Stone, and D. C. de Long, *J. Med. Chem.*, **12**, 1016 (1969).