phanthoside, a trioside, by the comparison of the median systolic doses in frogs, and the mean (geometric) lethal doses in cats based on either body weight or heart weight. The differences are highly significant statistically. On the other hand, periplocin, a bioside, shows a tendency of having a stronger action than periplocymarin, a monoside. The difference in frogs approaches significance at the 5% point, and in cats the difference is definitely significant. The median emetic doses in pigeons by intravenous injection of periplocin and periplocymarin showed a similar relationship as disclosed in a previous note.[11]

The above data clearly indicate that the cardiac action of a glycoside does not necessarily decrease as the number of sugar molecules increases. The position of linkage, perhaps, partly determines the potency of the product. It will require an investigation of many other compounds of the same type before any generalization can be safely made.

Summary. K-Strophanthin-β is more potent than K-strophanthoside in frogs and cats, while periplocymarin is less potent than periplocin. The decrease in the number of sugar molecules of a cardiac glycoside, therefore, may or may not be accompanied by an increase in activity.

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Substituted Sulfanilamidopyrimidines.*

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Experimental[1, 2] and clinical[3, 4, 5] bacterial chemotherapeutic activity has been reported for 2-sulfanilamidopyrimidine (sulfadiazine). Modification of the pyrimidine portion of this compound, without concurrent loss of chemotherapeutic effectiveness, appears possible

* This investigation was supported in part by the D. J. McCarthy Foundation.

1 Roblin, R. O., Williams, J. H., Winnek, P. S., and English, J. P., *J. Am. Chem. Soc.*, 1940, **62**, 2002.

2 Feinstone, W. H., Williams, R. D., Wolff, R. T., Huntington, E., and Crossley, M. L., *Bull. Johns Hopkins Hosp.*, 1940, **67**, 427.

3 Flippin, H. F., Rose, S. B., Schwartz, L., and Domm, A. H., *Am. J. Med. Sci.*, 1941, **201**, 585.

4 Finland, M., Strauss, E., and Peterson, O. L., *J. A. M. A.*, 1941, **116**, 2641.

5 Dingle, J. H., Thomas, L., Morton, A. R., *J. A. M. A.*, 1941, **116**, 2666.

from the report[1] that the protective power of the 4-methyl derivative was comparable with that of its parent, sulfadiazine. A number of substituted sulfanilamidopyrimidines (Table I) prepared by Caldwell, Kornfeld and Donnell[6] were tested for protective action in the present studies† in mice infected with a 10^{-6} dilution of an 18-hour serum broth culture‡ of β-hemolytic streptococcus. This infective dose of 100-1000 MLD's always was injected intraperitoneally in 0.5 cc of serum broth. Therapy consisted of administration of a 10 mg dose of a given compound in 0.5 cc of 10% acacia solution by stomach tube 30 minutes after infection and once daily for 2 days thereafter. All of 90 control mice died within 48 hours after infection (Table I). Compounds III, IV and V were inactive and I exhibited only a slight protective action, whereas a definite prolongation of survival time was observed after sulfadiazine,§ VI and II (Table I). While sulfadiazine and VI gave almost complete protection, 50% of the mice receiving II died during the period of therapy (Table I). The 10-day survival rate after sulfadiazine, compounds VI and II was 22.5, 10.0 and 2.5% respectively (Table I).

Derivative VI by mouth killed 10/10 mice in doses of 5.0 g/kg, 9/10 in 2.5 g/kg and 5/10 in 1.5 g/kg doses. No deaths were observed after sulfadiazine in doses up to 5.0 g/kg in the present studies and survival of all mice receiving doses up to 10.0 g/kg of this compound previously has been reported.[2] It would appear, therefore, that VI, the most effective antistreptococcic agent in the present group of substituted sulfanilamidopyrimidines is unworthy of extended study because of its relatively high oral toxicity in mice.

Summary. 2-sulfanilamido-5,6,7,8-tetrahydroquinazoline (I), 2-sulfanilamido-4,5-dimethyl pyrimidine (II), 2-sulfanilamido-bornylene pyrimidine (III), 2-sulfanilamido-4-n-hexylpyrimidine (IV), 2-sulfanilamido-5,6,7,8-tetrahydro-8-isopropyl-5-methyl quinazoline (V) and 2-sulfanilamido-4,6-dimethyl pyrimidine (VI) were tested for chemotherapeutic activity in mice infected with strain C-203 of β-hemolytic streptococcus. Compounds III, IV and V were inactive and I exhibited only a slight protective action. A

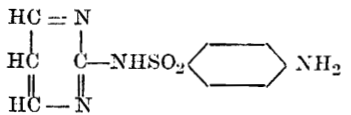
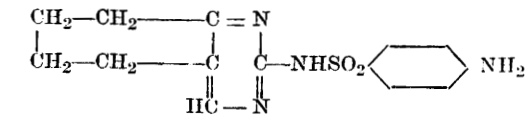
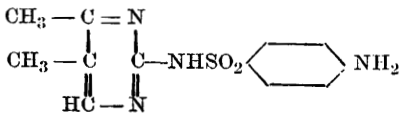
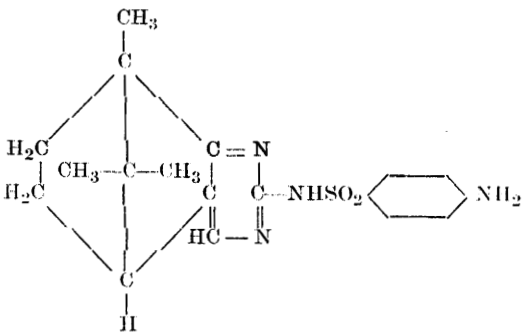
[6] Caldwell, W. T., Kornfeld, E., and Donnell, C. K., *J. Am. Chem. Soc.*, **1941**, **63**, 2188.

† Samples of the substituted sulfanilamidopyrimidines used in the present experiments were made available by Dr. William T. Caldwell of the Department of Organic Chemistry, Temple University.

‡ Culture C-203 was made available through the courtesy of Dr. E. K. Marshall, Jr.

§ The sulfadiazine used in the present studies was supplied through the courtesy of Dr. David A. Bryce of the Calco Chemical Company.

TABLE I.
Chemotherapeutic Effectiveness in Hemolytic Streptococcal Infection of Mice.

Compound	No. of mice	No. of deaths (Days after infection) 1	2	3	4	5	6	7	8	9	10	Survival %
None (Controls)	90	87	3									0
 2-sulfanilamidopyrimidine (Sulfadiazine)	40	0	0	0	5	13	4	4	4	1	0	22.5
(I)  2-sulfanilamido-5,6,7,8-tetrahydroquinazoline	35	16	15	1	1	1	1					0
(II)  2-sulfanilamido-4,5-dimethyl pyrimidine	40	3	13	4	7	5	4	3	0	0	0	2.5
(III)  2-sulfanilamidobornylene pyrimidine	35	35										0

(IV)

2-sulfanilamido-4-n-hexylpyrimidine

(V)

2-sulfanilamido-5,6,7,8-tetrahydro-8-isopropyl-5-methyl quinazoline

(VI)

2-sulfanilamido-4,6-dimethyl pyrimidine

IV	35	35	0										
V	35	35	0										
VI	40	0	2	0	5	11	6	6	6	0	0	0	10.0

definite prolongation of survival time was caused by II and VI, however, neither of these appeared worthy of extended study because II failed to afford complete protection during therapy and VI exhibited a relatively high acute oral toxicity in mice.

I wish to express my thanks and appreciation to Dr. A. E. Livingston for encouragement and helpful suggestions.

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Graying of Hair Produced by Ingestion of Phenylthiocarbamide.

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The results of previous experiments demonstrated the high degree of toxicity of the bitter tasting phenylthiocarbamide for rats (Richter and Clisby[1]), 1 to 2 mg usually being lethal. With these and slightly larger doses the rats died within 3 to 18 hours with one outstanding symptom, pleural edema and effusion. In some rats from 10 to 14 cc of a clear serous fluid accumulated in the thoracic cavity within only a few hours' time. By administering the drug in sublethal doses for a few days and then gradually increasing the doses over a period of several months, we succeeded in increasing the tolerance to 18 mg per day in some animals. At autopsy rats treated for several months did not show any thoracic changes, but all of them demonstrated marked hyperplasia and hyperactivity of the thyroid gland. Histologically such a gland had all the characteristics of an exophthalmic goiter. Two of these rats which originally had been solid black became gray over a saddle blanket area on the back. The observations on this effect of the drug were limited to these 2 rats since the other rats used for the experiments were either white or tan hooded.

Further observations have now been undertaken to determine (1) the consistency with which feeding phenylthiocarbamide causes the hair to turn gray, (2) the constancy of the gray hair patterns which it produces, and (3) whether after the phenylthiocarbamide is no longer given the hair returns to normal.

Including the 2 rats from the previous experiments we have a group of 23 black rats which received phenylthiocarbamide for

[1] Richter, C. P., and Clisby, K. H., *Arch. Pathol.*, in press.