of the ether and recrystallization of the resulting solid from hot water gave 8.7 g. (79%) yield of 2,4-hexadiyne-1,6-diol (II).

*Propargyl hydrogen phthalate* (III). Phthalic anhydride (148 g., 1.00 mole) and 84 g. propargyl alcohol (1.50 moles) were stirred together and heated gradually to 110° over a period of 4 hr. After allowing it to cool overnight, the mixture was filtered and the solid portion recrystallized from benzene to give 186 g. (91.2%) propargyl hydrogen phthalate (III), m.p. 106–107°.

*Anal.* Calcd. for $C_{11}H_8O_4$: C, 64.71; H, 3.95. Found: C, 64.71; H, 4.26.

*2,4-Hexadiyne-1,6-diol di-(hydrogen phthalate)* (IV). Propargyl hydrogen phthalate (20.4 g., 0.10 mole) was added to a stirred mixture of 12.5 g. copper(I) chloride (0.065 mole), 34.4 g. *t*-butylamine (0.47 mole), 63 mole of 6*N* hydrochloric acid (0.38 mole) and 100 ml. water. The mixture was stirred under a slight positive pressure of oxygen for 20 hr., the solid removed by filtration and triturated with 250 ml. sulfuric acid (3*N*). The acid mixture was filtered and the solid recrystallized from aqueous acetone to give 16.7 g. (82%) yield of 2,4-hexadiyne-1,6-diol di-(hydrogen phthalate), m.p. 145.5–147°.

*Anal.* Calcd. for $C_{22}H_{14}O_8$: C, 65.17; H, 3.48. Found: C, 65.07; H, 3.67.

A run with propargyl hydrogen phthalate (0.10 mole), cuprous chloride (0.065 mole), ammonia (0.09 mole), ammonium chloride (0.038 mole) under the same reaction and work-up conditions gave a 10.7 g. (53%) yield of 2,4-hexadiyne-1,6-diol (IV), m.p. 145.5–147°.

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## Mercaptotriazolopyrimidines[1,2]

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Synthesis of triazolopyrimidines containing sulfur at the 5- or 7- position[3–5] has been continued in order that the action of these compounds on tumors might be compared with the effects of 6-mercaptopurine and 8-azaguanine.

Kidder, Dewey, Parks, and Woodside[6] reported that 5-mercapto-7-amino-1-v-triazolo[d]pyrimidine (I) was not an inhibitor of the growth of Adenocarcinoma 755, but they did not give data on the preparation or other properties of the compound. A later paper[7] has described the preparation of a material which gave a volumetric chloride analysis corresponding to the dihydrochloride salt of I and was a strong inhibitor of the growth of *Streptococcus faecalis R*. The free compound I has now been prepared in this laboratory and its ultraviolet absorption has been determined. Boiling dilute hydrochloric acid converted it into a yellow solid that gave a Volhard analysis very close to that reported for the supposed dihydrochloride of I, but was found to have the ultraviolet absorption maxima characteristic of 5-mercapto-7-hydroxy-1-v-triazolo[d]pyrimidine (II), not I. An explanation of the apparently inconsistent observations was found when it was discovered that under the conditions of the Volhard analysis, II reacted with silver nitrate in a 1:1 molar ratio to form a precipitate, probably through forming the silver salt of the —SH group, whereas I did not. Since the equivalent weights of II·2$H_2O$·HCl, molecular weight 240.6, and I·2HCl, molecular weight 241.1, thus happen to be almost identical, the Volhard analysis was in agreement with either formula. (Both 5-mercapto-1-v-triazolo[d]pyrimidine and 7-mercapto-1-v-triazolo[d]pyrimidine behaved like II in this respect.) In view of these facts it appears likely that the material previously referred to as I dihydrochloride was actually a hydrated monohydrochloride of II. Probably the inhibition of *Streptococcus faecalis R* was due to II, formed from I during the heating.

The replacement of the amino group in I by a hydroxyl group suggested that 5-hydroxy-7-mercapto-1-v-triazolo[d]pyrimidine (III) might be formed as a by-product under the acid conditions encountered in the preparation of 5-amino-7-mercapto-1-v-triazolo[d]pyrimidine and 5,7-dimercapto-1-v-triazolo[d]pyrimidine. A solid which appeared to be the oxidation product of III was found among the reaction products.

### EXPERIMENTAL

*5-Mercapto-7-amino-1-v-triazolo[d]pyrimidine*, I. A solution of 3.5 g. of $KNO_2$ in 110 ml. of $H_2O$ was added to 10 g. of 4,5,6-triamino-2-mercaptopyrimidine hydrosulfate in 3.5 l. of $H_2O$. The crystals of I were filtered off after stirring 20 min. and were washed with methanol and acetone.[8] The analysis values for C, H, and N were a fraction of a per cent low. Accordingly the product was purified by dissolving in 0.05*N* potassium hydrosulfide, neutralizing the solution with acetic acid, filtering, washing the precipitate with 3% acetic acid, and drying. Ultraviolet absorption: at *p*H 6.5 log $\epsilon_{256}$ 4.18, log $\epsilon_{310}$ 3.98; at *p*H 10 log $\epsilon_{255}$ 4.26, log $\epsilon_{307}$ 3.95.

*Anal.* Calcd. for $C_4H_4N_6S$: C, 28.56; H, 2.31. Found: C, 28.46, 28.69; H, 2.31, 2.19.

When a sample of I was tested by the Volhard method

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(2) Part of this paper was presented before the Tennessee Academy of Science at Cookeville, Tenn., December 3, 1955.

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(6) G. W. Kidder, V. C. Dewey, R. E. Parks, Jr., and G. L. Woodside, *Cancer Research*, **11**, 204 (1951).

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(8) On standing in air, I formed what appeared to be an oxidation product having a strong absorption peak at 236 mμ at *p*H 6.5, from which I was obtained again by reduction with NaSH.

only a trace of silver nitrate was consumed, but an authentic sample of II·$H_2O$ was analyzed by the Volhard method.

*Anal.* Calcd. for $C_4H_3N_5OS.H_2O$: formula wt., 187. Found: equiv. wt., 184 ($AgNO_3$ titration, Volhard technique).

A solution of 1.0 g. of I in 75 ml. of 6*N* HCl was refluxed for 35 min. Upon cooling, filtering, and air drying, 0.85 g. of crystals were obtained which decomposed at 265°. The absorption maxima and minima for this compound were practically identical with those for an authentic sample of II monohydrate[3] and for a sample of the substance previously referred to as the dihydrochloride salt of I.[7] (It is recognized that changes might have occurred in the latter sample during the three years since it was prepared.)

*Anal.* Calcd. for $C_4H_3N_5SO·2H_2O·HCl$: equiv. wt. 121. Found: equiv. wt. 121 ($AgNO_3$ titration, Volhard technique).

*5-Hydroxy-7-mercapto-1-v-triazolo[d]pyrimidine.* The mother liquor from which the yellow 5,7-dimercapto-1-v-triazolo[d]pyrimidine had been obtained[4] deposited on standing 2.2 g. of tan crystals which seemed to be an oxidation product of 5-hydroxy-7-mercapto-1-v-triazolo[d]pyrimidine. This solid was insoluble in acetone and in ethanol, but dissolving it in aqueous sodium hydrosulfide and precipitating by addition of acetic acid produced a solid which was recrystallized from methanol to give yellow crystals, m.p. 300°. Ultraviolet absorption: at *p*H 6.5 log $E_{299}$ 4.09, at *p*H 10 log $E_{309}$ 4.03. A qualitative test for sulfur was obtained by the sodium fusion method.

*Anal.* Calcd. for $C_4H_3N_5OS$: C, 28.39; H, 1.79; N, 41.39. Found: C, 28.59, 28.50; H, 2.28, 2.50; N, 41.40; 41.34.

*5-Mercapto-1-v-triazolo[d]pyrimidine.*[9] Sodium nitrite (2.6 g. in 30 ml. of water) was added to 5.4 g. of 2-mercapto-4,5-diaminopyrimidine in 200 ml. of 1*N* sulfuric acid at 60°. After 20 min. at 60° the solution was cooled and filtered. The 3.8 g. of crystals were recrystallized twice from water, dried, and found to darken about 233° and decompose suddenly at 249°.

*Anal.* Calcd. for $C_4H_3N_5S$: C, 31.37; H, 1.97. Found: C, 31.72, 31.50; H, 1.56, 1.41.

Samples of the compounds were screened against Adenocarcinoma 755 at the Southern Research Institute. None of the seven compounds produced nearly so great a retardation of the growth of the tumor as did 8-azaguanine or 6-mercaptopurine. The compounds were not proved to be totally inactive, however, for the average tumor weights of the treated animals, taking into account all runs with each particular compound, ranged from 53% to 86% of the tumor weights of the untreated animals. The apparent mild inhibition was decidedly erratic, possibly because of variations in the rate of absorption of the difficultly soluble compounds.

*Acknowledgment.* Carbon, hydrogen, and oxygen analyses were carried out by Galbraith Microanalytical Laboratories. Sodium hydrosulfite used in the preparation of 4,5,6-triamino-2-mercaptopyrimidine was donated by the Virginia Smelting Company. Tumor inhibition tests were carried out by the courtesy of Dr. Howard Skipper, Dr. Lee Bennett, and their associates at Southern Research Institute. The initiation of the series of syntheses was inspired by the request of Dr. Alfred Gellhorn of Columbia University for analogs of 8-azaguanine.

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## Synthesis of Heterocyclic Aminoethers Related to Diphenhydramine[1]

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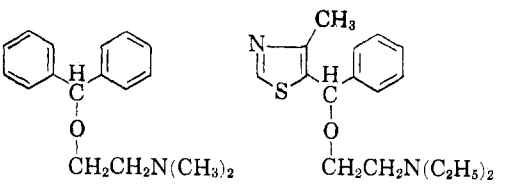
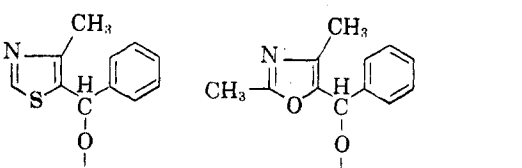
A series of seven aminoethers structurally related to the antihistaminic drug diphenhydramine (I) was synthesized in order to study the pharmacological effects produced by (1) substitution of a heterocyclic ring system for one of the phenyl groups, and (2) changing the nature of the side chain. The heterocyclic systems used were 4-methyl-5-thiazolyl; 2,4-dimethyl-5-oxazolyl; and 3,5-dimethyl-4-isoxazolyl. The side chains used




I




II

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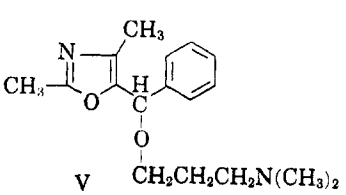


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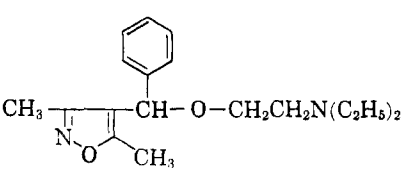


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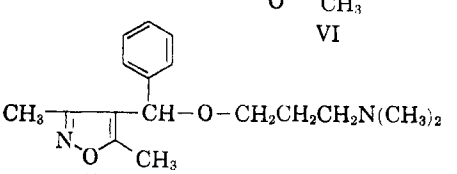


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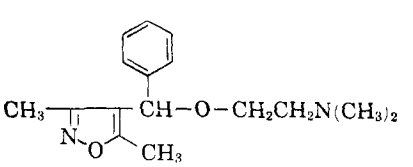


VIII

(1) Presented at the First Delaware Valley Regional Meeting, AMERICAN CHEMICAL SOCIETY, February 16, 1956, Philadelphia, Pa.