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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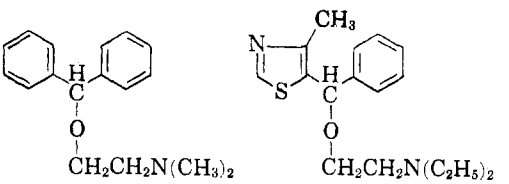
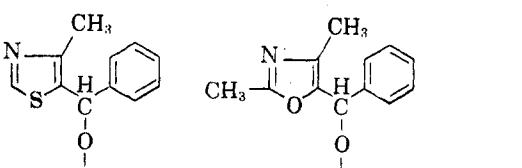
A series of seven aminoethers structurally related to the antihistaminic drug diphenhydramine (I) was synthesized in order to study the pharmacological effects produced by (1) substitution of a heterocyclic ring system for one of the phenyl groups, and (2) changing the nature of the side chain. The heterocyclic 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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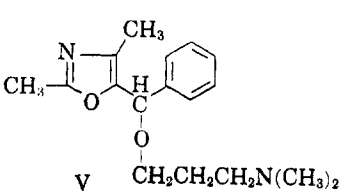

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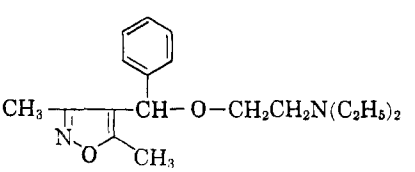

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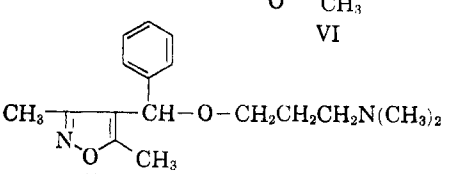
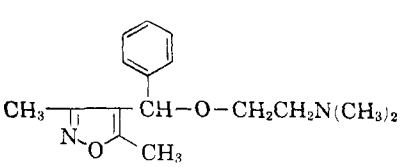


VII



VIII

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

TABLE I

Structure	B.P.	M.P. and Recryst. Solvent	Analysis Calcd. C	Calcd. H	Found C	Found H
4-Methyl-5-benzoylthiazole	176–178°/10 mm.	79.5–80.5° C_6H_6, pet. ether	65.00	4.46	65.20	4.53
2,4-Dimethyl-5-benzoyloxazole	113–114°/0.7 mm.	.....	71.62	5.51	71.53	5.77
3,5-Dimethyl-4-benzoylisoxazole	105°/0.2 mm.	62–63° cyclohexane	71.62	5.51	71.54	5.61

TABLE II

Structure	B.P.	M.P. and Recryst. Solvent	Analysis Calcd. C	Calcd. H	Found C	Found H
4-Methyl-5-thiazolylphenylcarbinol	152–157°/0.7 mm.	106–107° C_6H_6-pet. ether	64.36	5.40	64.36	5.38
2,4-Dimethyl-5-oxazolylphenylcarbinol	132–136°/0.7 mm.	91.5–92° EtOH-H_2O	70.91	6.45	70.76	6.62
3,5-Dimethyl-4-isoxazolylphenylcarbinol	140°/0.3 mm.	53–54° C_6H_6-pet. ether	70.91	6.45	70.90	6.55

TABLE III

Compound	Empirical Formula	B.P. of Base	M.P. of Citrate Salt	Analysis Calcd. C	Calcd. H	Found C	Found H	Pharmacological Data[a]
II	$C_{17}H_{24}N_2OS$	137°/0.2 mm.	103–105°	55.63	6.50	55.48	6.72	No protection at 25 mg./kg., protects 3/3 at 50 mg./kg.
III	$C_{16}H_{22}N_2OS$	145–150°/0.6 mm.	100–103°	54.76	6.27	54.75	6.05	Protects 1/3 at 25 mg./kg., protects 3/3 at 50 mg./kg.
IV	$C_{18}H_{26}N_2O_2$	168–171°/0.1 mm.	82–86°[b]	57.24	7.01	57.45	7.13	No protection at 50 mg./kg.
V	$C_{17}H_{24}N_2O_2$	130–140°/0.7 mm.	118–119.5°[b]	56.43	6.92	56.43	6.64	No protection at 25 mg./kg., protects 1/3 at 50 and 100 mg./kg.
VI	$C_{18}H_{26}N_2O_2$	135–136°/0.2 mm.	70–72°	58.29	6.93	58.07	7.18	No protection at 25 mg./kg., protects 2/3 at 50 mg./kg.
VII	$C_{17}H_{24}N_2O_2$	145–150°/0.7 mm.	121–123°	57.49	6.71	57.21	6.45	No protection at 25 mg./kg., protects 2/3 at 50 mg./kg.
VIII	$C_{16}H_{22}O_2N_2$	143–148°/0.3 mm.	130–132°	56.64	6.48	56.38	6.78	No protection at 10 mg./kg., protects 1/3 at 25 mg./kg.

[a] Antihistaminic activity in guinea pigs after intraperitoneal injection; aerosolized histamine test. Diphenhydramine (also known as "Benadryl") affords complete protection at 10 mg./kg. [b] Hemihydrate.

were β-dimethylaminoethyl, β-diethylaminoethyl, and γ-dimethylaminopropyl. The following compounds were synthesized:

The ethers were prepared by the Williamson ether synthesis in 70–85% yields, using heterocyclic phenylcarbinols and chloroalkylamines. The racemic aminoethers were converted to citrate salts by reacting the ether with one mole of citric acid in acetone and recrystallization from alcohol.

The following reaction sequence was employed, starting with a heterocyclic ester:

$$\text{Het—COOC}_2\text{H}_5 \xrightarrow{\text{NaOH}} \text{Het—COOH} \xrightarrow{\text{SOCl}_2} \text{Het—COCl} \xrightarrow[\text{C}_6\text{H}_6]{\text{AlCl}_3}$$

$$\text{Het—C(=O)—C}_6\text{H}_5 \xrightarrow{\text{LiAlH}_4} \text{Het—CH(OH)—C}_6\text{H}_5 \xrightarrow[\text{R—Cl}]{\text{NaH}} \text{Het—CH(OR)—C}_6\text{H}_5$$

4-Methyl-5-thiazolylcarboxylic acid chloride was prepared by the method of Karrer and Graf.[2] 2,4-Dimethyl-5-oxazolylcarboxylic acid was prepared by the method of Cornforth and Cornforth[3] and was converted to the acid chloride, which was not isolated, but was used immediately in the

(2) P. Karrer and W. Graf, *Helv. Chim. Acta*, **28**, 824 (1945).

(3) J. W. Cornforth and R. H. Cornforth, *J. Chem. Soc.*, 93 (1953).

Friedel-Crafts reaction. 3,5-Dimethyl-4-isoxazolylcarboxylic acid was prepared by the method of Claisen[4] and converted to the acid chloride, b.p. 85°/10 mm., in 90% yield.

The acid chlorides were converted to the following ketones in over 90% yield, using typical Friedel-Crafts procedures (Table I).

The ketones were converted to the following carbinols in 80–85% yield, using lithium aluminum hydride in ether (Table II).

Table III summarizes the physical and biological data for the aminoethers described.

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Improved Procedure for Preparation of Aromatic Thiols[1]

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The preparation of aromatic thiols from the corresponding aryl ethyl xanthates by alkaline hydrolysis has not been satisfactory in many instances. Yields are relatively low due to loss by oxidation, and to incomplete hydrolysis in the case of hindered xanthates. Although Tarbell and Fukushima[2] report yields of 63–75% in the case of *m*-tolyl ethyl xanthate, we have been unable to duplicate these yields with more hindered compounds. In our hands the conventional method gave at best a yield of only 49% in the case of 2,6-dimethylthiophenol, and even poorer yields in the case of *o*-thiocresol (39%) and *o*-phenylthiophenol (21%). In the latter case, even prolonged hydrolysis (24 hr.), followed by isolation as the disulfide to avoid apparent loss observed in isolation of the less stable thiol, gave at best a 58% yield.

Djerassi, *et al.*,[3] obtained excellent yields of aliphatic mercaptans by reduction of xanthates with lithium aluminum hydride. They also demonstrated that this method was applicable to aryl xanthates by the conversion of *o*-aminophenol *via* the ethyl xanthate to *o*-mercaptophenol in 64% over-all yield, which compares favorably with the variable yields of 30–70% for this compound reported by Greenwood and Stevenson,[4] using alkaline hydrolysis of the xanthate.

Reduction of the xanthates by lithium aluminum hydride proved to be a much more effective method for preparing hindered aromatic thiols. Yields of 84–89% were consistently obtained. For example, reduction of *o*-biphenyl ethyl xanthate with lithium aluminum hydride gave an 84% yield of pure *o*-phenylthiophenol, while even better yields were obtained in the preparation of 2,6-dimethylthiophenol (86%) and *o*-thiocresol (89%) by the reduction of their respective xanthates. With lithium aluminum hydride, the thiol was obtained directly, since loss through oxidation was avoided. Moreover, the method of isolation was both faster and simpler than by alkaline hydrolysis. The by-products of this reductive cleavage were not isolated, but methyl mercaptan was obviously present.

Pure *o*-phenylthiophenol and 2,6-dimethylthiophenol have not previously been reported. These were characterized and converted to their respective disulfides and to their 2,4-dinitrophenyl sulfides.

EXPERIMENTAL

o-Thiocresol (*lithium aluminum hydride method*). *o*-Tolyl ethyl xanthate was prepared by the method of Bourgeois.[5] Fifty-three and five-tenths grams (0.5 mole) of *o*-toluidine was diazotized and added dropwise to 60 g. (0.375 mole) of technical potassium ethyl xanthate. The crude *o*-tolyl ethyl xanthate was extracted with ether and the ethereal solution, after washing with sodium carbonate solution and then with water, was carefully dried over anhydrous sodium sulfate to be used directly without further purification.

The lithium aluminum hydride reduction required a good hood. To 1 l. of anhydrous ether contained in a 3-liter, three necked flask, 19 g. (0.5 mole) of lithium aluminum hydride was added. The resulting slurry was stirred rapidly while the ethereal solution of *o*-tolyl ethyl xanthate was added dropwise at such a rate that the ether refluxed gently without external cooling. Stirring was continued at room temperature for 1 hr. after the addition was complete. One hundred fifty ml. of water was then added dropwise (very carefully!) at such a rate that only a small amount of ether escaped from the reflux condenser. The mixture became thick during this addition and efficient stirring was necessary. Five hundred ml. of 10% sulfuric acid was then added carefully from the separatory funnel to dissolve the precipitated alumina. The ether layer was separated and the aqueous phase extracted twice with ether. The combined ether solutions were washed thoroughly with water and dried over anhydrous calcium chloride. The ether was removed under reduced pressure and the residual thiol was distilled through a short fractionating column. The yields of colorless *o*-thiocresol was 55.2 g. (89% based on *o*-toluidine), b.p 104° (48 mm.).

Alkaline hydrolysis of o-tolyl ethyl xanthate. For comparison purposes the crude xanthate, obtained by evaporation of the ethereal solution described above was hydrolyzed in alcoholic potassium hydroxide, by the conventional method.[2] Although Bourgeois reports adequate yields in the hydrol-

(1) Contribution No. 755 from the Chemical Laboratories of Indiana University. Taken from a thesis to be submitted by S. W. Osborn for the degree of Doctor of Philosophy. This work was supported by a research grant [C-1948(C)] from the National Cancer Institute of the National Institutes of Health, Public Health Service.

(2) D. S. Tarbell and D. K. Fukushima, *Org. Syntheses*, Coll. Vol. III, 809 (1955).

(3) C. Djerassi, M. Gorman, F. X. Markley, and E. B. Oldenburg, *J. Am. Chem. Soc.*, **77**, 568 (1955).

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