sium carbonate, distillation gave 1.6 g. (23%) of recovered 1-methyl-3-propyl-4-piperidone, b.p. 50–60° (0.2 mm.), and 11.2 g. (65% based on unrecovered piperidone) of 1-methyl-3-propyl-4-phenyl-4-piperidinol, b.p. 140–160° (0.2 mm.), as a light yellow viscous liquid, which crystallized spontaneously. An analytical sample recrystallized from hexane melted at 105–106°.

Anal. Calcd. for $C_{15}H_{23}NO$: C, 77.20; H, 9.93. Found: C, 77.60; H, 10.31.

1-Methyl-3-propyl-4-phenyl-4-piperidyl Esters (X).—A mixture of 2.0 g. (0.0086 mole) of 1-methyl-3-propyl-4-phenyl-4-piperidinol, 20 ml. of the acid anhydride and 0.01 mole of the corresponding sodium salt were heated with protection from moisture on a water-bath for 3 hours. The remainder of the procedure was exactly the same as that described for the 3-benzyl-4-piperidyl esters. The acetate was recrystallized from hexane; the other esters, Xb and Xc, could not be induced to crystallize.

The hydrochloride salts of these esters were prepared by adding a saturated solution of dry hydrogen chloride in ether to an ether solution of the esters. These salts were recrystallized from ethyl acetate–ethyl alcohol and were extremely hygroscopic.

The properties and analyses of these esters and their salts are listed in Table I.

MADISON 6, WISCONSIN

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Studies on Condensed Pyrimidine Systems. XV. Some Pyrazolo[3,4-d]pyrimidines

BY ELVIRA A. FALCO AND GEORGE H. HITCHINGS

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A series of pyrazolo[3,4-d]pyrimidines has been synthesized. Treatment of pyrazole-3,4-dicarboxamide with sodium hypochlorite yielded 4,6-dihydroxypyrazolo[3,4-d]pyrimidine (III) from which 6-hydroxy-4-mercapto- (IV) and 4,6-dimercaptopyrazolo[3,4-d]pyrimidine (V) could be prepared. The mercapto derivatives reacted with ammonia and amines to furnish mercaptoamino, hydroxyamino and amino derivatives.

Antagonists of the natural purines have been prepared both by alterations in the functional groups and by changes in the nature or position of one or more ring atoms.[1] The present paper deals with derivatives of the pyrazolo[3,4-d]pyrimidine system. This ring structure may be regarded as being formed by an interchange of the 7-N and 8-C atoms of the purine skeleton. During the preparation of this paper there appeared a preliminary report dealing with the synthesis of some of the present compounds by another method.[2]

The approach adopted in the present, as in several previous problems,[3-5] was the preparation of a dihydroxy intermediate which could be converted by means of transformation reactions into derivatives with a variety of functional groups.

The 4,6-dihydroxypyrazolo(3,4-d)pyrimidine (III) was obtained by means of the Hofmann reaction[6] on pyrazole-3,4-dicarboxamide (II). The method of preparation, however, failed to provide a definitive proof of structure since either III or X might be formed in this reaction. The exclusion of 5,7-dihydroxypyrazolo(4,3-d)pyrimidine (X) as a possible product was based on the preparation of two derivatives of both ring systems, the bismethylmercapto derivatives XI and XII, and the two hydroxydimethylamino derivatives VII and XIII. Both XII and XIII had been synthesized by Rose[7] by unequivocal methods. The corresponding derivatives of the pyrazolo(3,4-d)pyrimidine system were readily prepared, XI by methylation of V and VII from IV as shown in the Reaction Scheme. Comparison of XI with XII and of XIII with VII established the non-identity of these representative derivatives of the two ring systems. Moreover, examination of the ultraviolet absorption spectra and paper chromatography of III failed to suggest the presence of a second isomer in detectable amounts.

A number of transformation reactions in the pyrazolo(3,4-d)pyrimidine series was studied as shown in the Reaction Scheme. The Hofmann reaction (II → III) ran smoothly with sodium hypochlorite in sodium hydroxide but did not go well with hypobromite under standard conditions. Treatment of the dihydroxy compound with phosphorus pentasulfide in pyridine gave chiefly the 6-hydroxy-4-mercapto derivative IV together with a small amount of the dimercapto derivative V. The preparation of the latter in two steps, as indicated, was generally more fruitful than when it was attempted, through alteration of the reaction conditions, to prepare the dimercapto compound directly from the dihydroxy derivative. In general the reactions of the pyrazolo(3,4-d)pyrimidine are typical of condensed pyrimidine systems and require no particucular comment. Similarly the physical properties, including the ultraviolet absorption spectra (Table I), closely resemble those of the corresponding purines.

Acknowledgments.—The authors are indebted to Samuel W. Blackman, P. R. W. Baker and Mrs. Veronica Purdy for microanalyses.

Experimental

Pyrazole-3,4-dicarboxamide.—To 7.5 g. of pyrazole-3,4-dicarboxylic acid[8] was added 150 ml. of thionyl chloride, and the mixture was heated under reflux conditions for 10 hours. The thionyl chloride was removed *in vacuo* and the powdery residue was added in portions to a vigorously stirred, self-cooled flask of liquid ammonia (250 ml.) over the course of one hour. The reaction mixture was stirred until the ammonia had all evaporated. The residue was taken up in boiling water and, on cooling, colorless plates, melting at 327° dec., precipitated.

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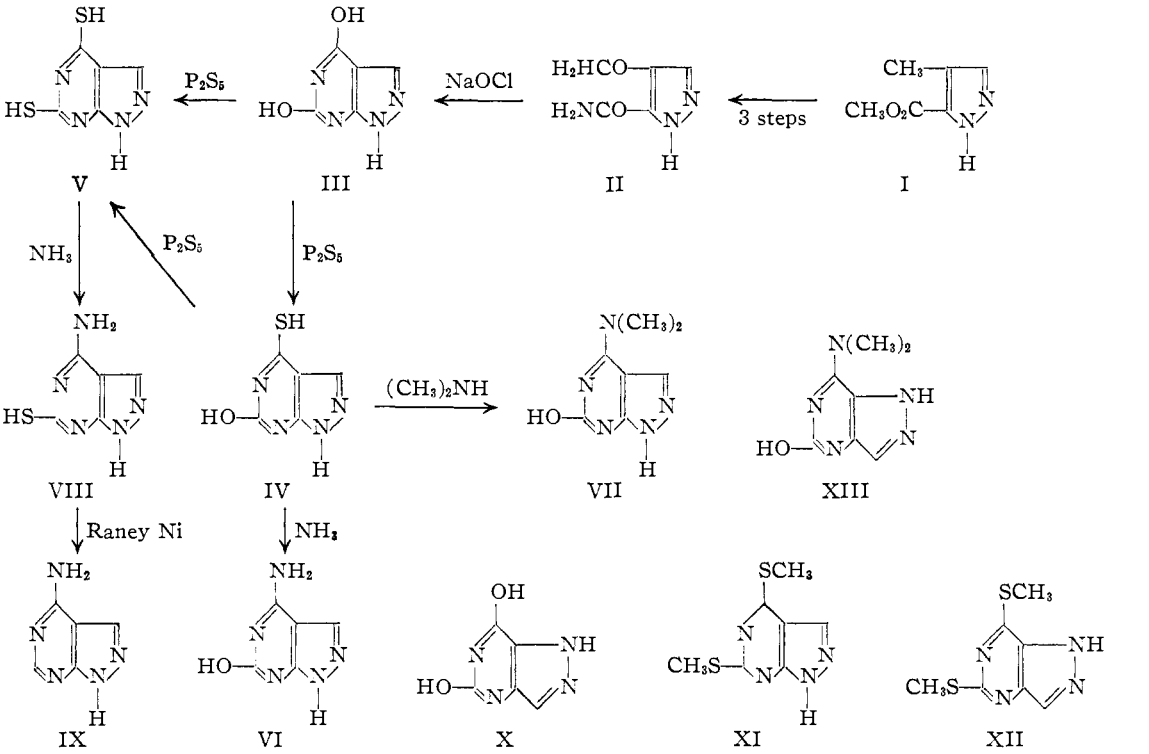
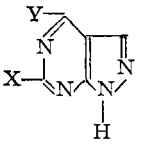
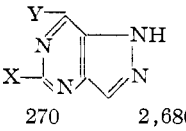


TABLE I

ULTRAVIOLET ABSORPTION SPECTRA OF PYRAZOLOPYRIMIDINES

Substituents Y	Substituents X	pH 1 λmax. mμ	pH 1 Emax.	pH 1 λmin. mμ	pH 1 Emax.	pH 10.5 λmax. mμ	pH 10.5 Emax.	pH 10.5 λmin. mμ	pH 10.5 Emax.
									
OH	OH	240	4,750			242	9,200	258	5500
		255	5,600			268	6,050		
SH	OH					260	6,850	285	5100
						335	17,400		
NH_2	OH	250	6,500						
		265[a]	6,200			270	8,900	240	5000
$N(CH_3)_2$	OH	250	6,350	260	6,250	235[a]	7,350		
		275	6,950			255	9,850		
HS	SH	265	20,600	285	8,460	275	22,400	240	8800
		318	21,400			295[a]	18,600	317	8800
						335	9,560		
CH_3S	CH_3S	245	14,800	275	10,400	250	18,900	283	7610
		265[a]	11,200	290	10,300	303	10,000		
		283	10,510						
		305	11,700						
NH_2	SH	248	6,680	250	6,250	255	15,300	265	8350
		260	6,680	285	3,310	275	8,600	285	8350
		295	3,750			290	8,750		
NH_2	H	261	8,100	240	5,050	265	7,400	240	4050
									
$N(CH_3)_2$	OH	305	5,810	270	2,680	255	12,400	235	8750
						300	7,500	280	6280
CH_3S	CH_3S	253	16,700	235	8,400	250	23,100	315	2760
		310	17,000	275	8,000	345	4,230		
		340[a]	9,750						

[a] Inflection.

Anal. Calcd. for $C_5H_6N_4O_2$: C, 39.0; H, 3.9; N, 36.3. Found: C, 39.4; H, 3.8; N, 36.3.

4,6-Dihydroxy-1-pyrazolo(3,4-d)pyrimidine.—To a cold solution of 0.4 *M* sodium hypochlorite solution (16.6 ml.) there was added (all at once) 500 mg. of pyrazole-3,4-dicarboxamide. The reaction mixture turned bright pink and then faded to pale yellow in a short time. After standing at room temperature for 1 hour the reaction mixture was acidified with 2 *N* hydrochloric acid to *p*H 3. A flocculent precipitate formed. Recrystallization of the precipitate from boiling water gave colorless needles in rosettes which did not melt at 320°.

Anal. Calcd. for $C_5H_4N_4O_2$: C, 39.5; H, 2.63; N, 36.8. Found: C, 39.11; H, 2.68; N, 36.5.

6-Hydroxy-4-mercapto-1-pyrazolo(3,4-d)pyrimidine.—To 4 g. of the 4,6-dihydroxy compound described above, there was added 12 g. of phosphorus pentasulfide and 60 ml. of dry pyridine. This mixture was heated for three hours at reflux temperature. The pyridine was removed *in vacuo* and the residue taken up in cold dilute sodium hydroxide solution to *p*H 10. On acidification there was obtained 3.5 g. of pale yellow compound. On recrystallization from boiling water it formed pale yellow plates which did not melt at 360°.

Anal. Calcd. for $C_5H_4N_4OS$: C, 35.7; H, 2.38; N, 33.3; S, 19.0. Found: C, 35.3; H, 2.1; N, 32.8; S, 19.4.

4,6-Dimercapto-1-pyrazolo(3,4-d)pyrimidine.—To the monomercapto compound described above (8 g.) were added 21 g. of phosphorus pentasulfide and 500 ml. of tetrahydronaphthalene. The mixture was heated (185–190°) with stirring for three hours. The temperature was then allowed to rise to 205° and this temperature was maintained for an additional 16 hours without stirring. The reaction mixture was cooled, the precipitate filtered and washed with petroleum ether. Sodium hydroxide (2 *N*) was added to the residue until the solution became permanently alkaline (*p*H 10). After treatment with decolorizing carbon the mixture was filtered, and the filtrate was acidified (*p*H 3) by the addition of 2 *N* hydrochloric acid. The yellow precipitate which formed was redissolved in dilute ammonium hydroxide solution and reprecipitated at *p*H 3 by means of 2 *N* hydrochloric acid. Recrystallization of the product from a large volume of water gave a bright yellow powder which did not melt at 360°.

Anal. Calcd. for $C_4H_4N_4S_2$: C, 32.6; H, 2.18; S, 34.8. Found: C, 33.0; H, 2.36; S, 34.22.

4-Amino-6-mercapto-1-pyrazolo(3,4-d)pyrimidine.—To 50 ml. of alcohol (saturated at 0° with ammonia) there was added 650 mg. of the dimercapto compound described above. This mixture was heated in a sealed tube for 18 hours at 150° and cooled. The tube contents were allowed to evaporate on the steam-bath and the residue was taken up in cold 0.5 *N* hydrochloric acid, and precipitated at *p*H 7 by the addition of 2 *N* sodium hydroxide. The precipitate was recrystallized from boiling water to give 400 mg. of a compound which did not melt at 325°.

Anal. Calcd. for $C_5H_5N_5S$: C, 36.0; H, 3.0; N, 41.99; S, 19.2. Found: C, 36.41; H, 2.99; N, 41.47; S, 18.9.

4-Amino-1-pyrazolo(3,4-d)pyrimidine.—To 900 mg. of the above aminomercapto compound there was added 200 ml. of water, 15 ml. of ammonium hydroxide (concd.) and 2.8 g. of W-5 Raney nickel catalyst. This mixture was heated under reflux conditions for 3 hours and then was filtered hot. The residual nickel was washed three times with 50-ml. portions of boiling water. The washings and the reaction mixture filtrate were combined and evaporated to dryness *in vacuo*. The residue was taken up in 75 ml. of boiling water and allowed to stand. There was formed 250 mg. of a pale yellow micro-crystalline material which did not melt at 300°.

Anal. Calcd. for $C_5H_5N_5$: C, 43.83; H, 4.06; N, 52.0. Found: C, 44.44; H, 3.71; N, 51.8.

4-Dimethylamino-6-hydroxy-1-pyrazolo(3,4-d)pyrimidine.—To 500 mg. of 6-hydroxy-4-mercapto-1-pyrazolo(3,4-d)-pyrimidine was added 100 ml. of 30% dimethylamine. This mixture was heated in a sealed tube at 130° for 16 hours. The tube contents were allowed to evaporate to dryness on the steam-bath, and the residue taken up in 0.5 *N* hydrochloric acid. Adjusting the mixture to *p*H 7 by the addition of 2 *N* sodium hydroxide afforded 175 mg. of colorless needles which did not melt at 360°. The compound was dried for 2 hours at 120° and still contained one molecule of water of crystallization.

Anal. Calcd. for $C_7H_9N_5O \cdot H_2O$: C, 44.3; H, 5.42; H_2O, 4.8. Found: C, 44.3; H, 5.42; H_2O (Karl Fischer), 5.5.

4-Amino-6-hydroxy-1-pyrazolo(3,4-d)pyrimidine.—To 1.5 g. of the 4-mercapto-6-hydroxy compound described above there was added 200 ml. of alcohol saturated with ammonia at 0°. This mixture was heated in a closed vessel for 72 hours at 143°. The bomb contents were evaporated on the steam-bath and the residue dissolved in cold 0.5 *N* hydrochloric acid. On the addition of ammonium hydroxide to approximately *p*H 7, there was obtained about 650 mg. of a colorless powder which did not melt at 360°.

Anal. Calcd. for $C_5H_5N_5O$: C, 39.8; H, 3.31; N, 46.4. Found: C, 39.2; H, 3.5; N, 46.3.

4,6-Bismethylmercapto-1-pyrazolo(3,4-d)pyrimidine.—To 500 mg. of 4,6-dimercaptopyrazolo(3,4-d)pyrimidine were added 100 ml. of water, 2.7 ml. of 2 *N* sodium hydroxide and 766 mg. of methyl iodide. The reaction mixture was shaken for one hour and allowed to stand an additional hour. The solution was found to be neutral and the precipitate which had been formed was removed, recrystallized from 400 ml. of water and dried at 125°. The compound melted at 188–189° after sintering at 186°.

Anal. Calcd. for $C_7H_8N_4S_2$: C, 39.62; H, 3.78; N, 26.4. Found: C, 40.09; H, 4.00; N, 26.67.

Ultraviolet absorption spectra were determined using the Beckman model DU spectrophotometer in aqueous solutions at a concentration of 10 mg./l. in 0.1 *N* hydrochloric acid and in a Sørensen glycine–sodium hydroxide buffer at *p*H 10.5. The absorption values are presented in terms of molecular extinction coefficients.

TUCKAHOE 7, N. Y.