increase in AlCl concentration of over one hundred thousandfold was noted, when aluminum was added to aluminum trichloride, over that observed by thermal dissociation of aluminum trichloride alone.

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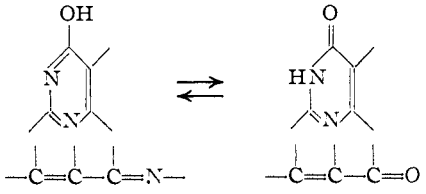
[CONTRIBUTION FROM THE LABORATORIES OF THE SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH]

The Ultraviolet Absorption Spectra of Pyrimidines and Purines[1]

BY LIEBE F. CAVALIERI AND AARON BENDICH

In a previous communication[2] evidence was presented which indicates that the ultraviolet absorption spectra of pyrimidines and purines is due mainly to the —C=C—C=N— or —C=C—C=O chromophore of the pyrimidine ring. We have



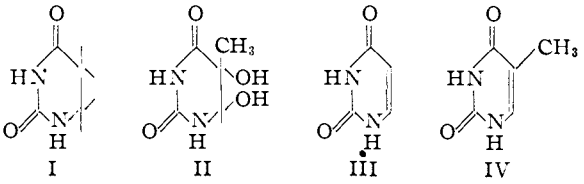
continued the investigation with the aim of gaining more knowledge concerning the effect of substituents on the spectra of these compounds.

Results

2,6- and 4,6-disubstituted and 2,4,6-trisubstituted pyrimidines exhibit a maximum in the region of 264 ± 6 mμ (Fig. 1); the 2,4,6-trisubstituted-5-formamidopyrimidines possess a band at 265 ± 6 mμ. In a homogeneous series, the molecular extinction coefficients decrease in the order: 2,4,6-trisubstituted > 2,4,6-trisubstituted-5-formamido > 4,6-disubstituted > 2,6-disubstituted. In both the 2,6- and 4,6-disubstituted pyrimidines an hydroxyl substituent results in a higher extinction than an amino substituent. In the trisubstituted series, 4,6-diamino-2-hydroxypyrimidine represents an exception since its molecular extinction is higher than that of 2,4,6-trihydroxypyrimidine. In all series an hydroxyl group in position 2 results in higher extinction values than an hydroxyl group in position 6.

Discussion

Additional corroborative evidence which supports the postulate that the —C=C—C=O system is a major chromophore is found in the spectra of 4,5-dihydrouracil (I) and thymine glycol (II). Whereas uracil (III) and thymine (IV) possess intense maxima at 260 mμ (ε = 9000) and 262



I II III IV

mμ (ε = 8600),[3] dihydrouracil (I)[4,5] and thymine glycol (II) do not absorb in this region. Since a —C=C—C=O grouping in I and II cannot exist by virtue of the fact that the —C=C— at the 4,5-position has been saturated, it is apparent that the —C=C—C=O system is a necessary feature for the absorption of light in this region. The —C=N— in the 2,3-position may be involved in the chromophoric system but previous[2] evidence indicates that an intense maximum in this region can occur when this double bond has been removed from the molecule. A clue as to the extent of contribution from the 2,3-double bond may be found by examining the chemical behavior of pyrimidines.

There is a considerable quantity of evidence which strongly suggests that the pyrimidine (and purine) nucleus possesses a rather low degree of aromaticity. Thus the action of nitrous acid on certain aminopyrimidines and aminopurines produces hydroxy derivatives rather than the diazonium salts commonly encountered with aromatic structures[6]; in some cases no reaction occurs. The reactions of halogens are atypical of aromatic compounds. Treatment of uracil with bromine leads to 5,5-dibromo-4-hydroxyhydrouracil. On heating, this compound is converted to 5-bromouracil and this bromine atom is easily hydrolyzed to an hydroxyl group.[6] In some instances nitration leads to 5-nitro derivatives, while in others addition of nitric acid across the 4,5-double bond occurs. There appears to be no record of sulfonation reactions. In general the pyrimidine ring is destroyed by the action of alkali; in some

(1) This work was supported by grants from the Office of Naval Research, United States Navy, the James Foundation of New York, Inc., the National Cancer Institute of the United States Public Health Service.

(2) Cavalieri, Bendich, Tinker and Brown, THIS JOURNAL, **70**, 3875 (1948).

(3) Heyroth and Loofbourow, *ibid.*, **56**, 1728 (1934); Baudisch and Davidson, *J. Biol. Chem.*, **64**, 233 (1925).

(4) A weak band (λ = 258 mμ, ε = 700) for I has been reported, Austin, THIS JOURNAL, **56**, 2141 (1934). In our hands a carefully purified sample showed no maximum.

(5) Fischer and Roeder, *Ber.*, **34**, 3751 (1901).

(6) Levene and Bass, "Nucleic Acids," Reinhold Publ. Corp., New York, N. Y., 1931,

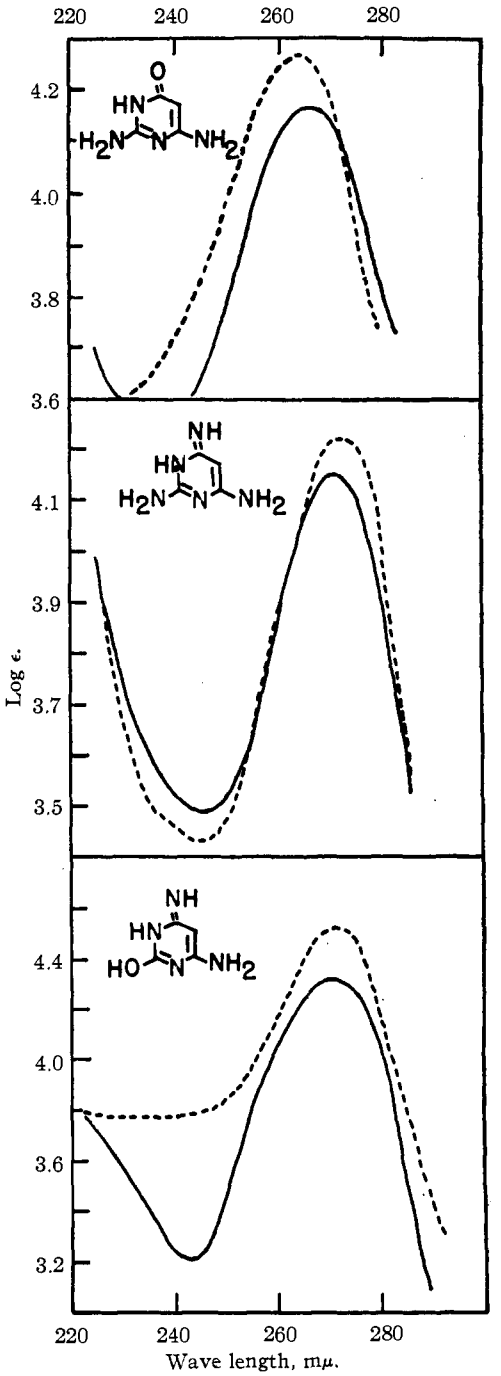
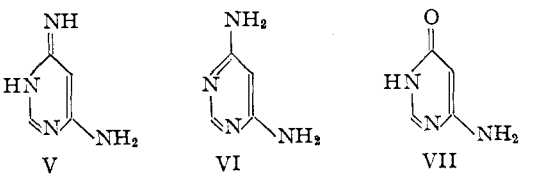


Fig. 1.—*p*H 2, – – – –; *p*H 6 ——.

cases considerable destruction occurs in neutral solutions. Stability toward alkaline[7] or acidic oxidizing agents[8] is rather low.

On the basis of these reactions, it is reasonable to postulate that interaction of the 2,3-double bond (in these compounds) with the remainder of the molecule which would result in stabilization (aromaticity) of the ring occurs to a small extent.[8a]

The relative intensities of the various pyrimidine derivatives present an interesting situation. There appears to be a relationship between the intensity of absorption and the symmetry of the molecule. Thus pyrimidine, which may be considered to be symmetrical, exhibits a band at 240 mμ of relatively low intensity (ϵ = 2850).[9] The introduction of an amino or hydroxyl group in position 6[10] destroys the symmetry of the pyrimidine nucleus. The asymmetry is accompanied by an increase in intensity of absorption. 6-Amino- and 6-hydroxypyrimidines each possess two bands: namely, 232 mμ (ϵ = 11,300), 265 mμ (ϵ = 3780) and 225 mμ (ϵ = 7300), 261 mμ (ϵ = 3340), respectively.[9] The bands at 265 mμ and 261 mμ probably correspond to the maximum at 240 mμ exhibited by pyrimidine. The maxima of 4,6-diamino- and 4-amino-6-hydroxypyrimidines are more intense than those of either 6-amino or 6-hydroxypyrimidine. It would appear at first that 4,6-diaminopyrimidine is a symmetrical molecule; however, there is evidence[11] indicating that this compound possesses the asymmetrical structure V rather than the symmetrical structure VI.



In the case of 4-amino-6-hydroxypyrimidine, VII is the more likely structure.

It is seen from Table I that the bands of the 2,6-disubstituted pyrimidines are lower than those of the corresponding 4,6-disubstituted compounds but higher than those (261 mμ, 265 mμ) of the monosubstituted pyrimidines. The trisubstituted

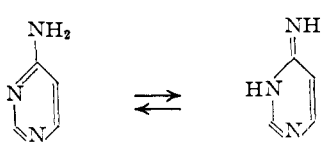
(7) Gilman, "Organic Chemistry," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1938, p. 980.

(8) Cavalieri, Tinker and Brown, THIS JOURNAL, **71**, 3973 (1949).

(8a) The alternative of interpreting the spectra of these compounds in terms of an essentially aromatic chromophore involving the entire ring has been considered by us and advocated by a referee. However, the chemical behavior of the amino- and hydroxypyrimidines can be better correlated with a cyclic ureide-type structure. The authors feel that in such a structure the 2,3-double bond would contribute but to a small extent to the aromaticity of the ring.

(9) These values are in agreement with those obtained by Williams, Ruehle and Finkelstein, THIS JOURNAL, **59**, 526 (1937).

(10) These compounds would be designated as 4-amino and 4-hydroxypyrimidine, according to *Chem. Abs.* However, in order to better correlate the pyrimidines and purines and to avoid confusion with previous literature, the older system is used throughout this paper.



(11) The action of nitrous acid on 2,6-diaminopyrimidine produces 2-hydroxy-6-aminopyrimidine (cytosine), indicating the predominance of the imino form in position 6 and the amino form in position 2. Further, compounds of type V form Schiff-bases with only one of the amino groups, Todd, *J. Chem. Soc.*, 649 (1946).

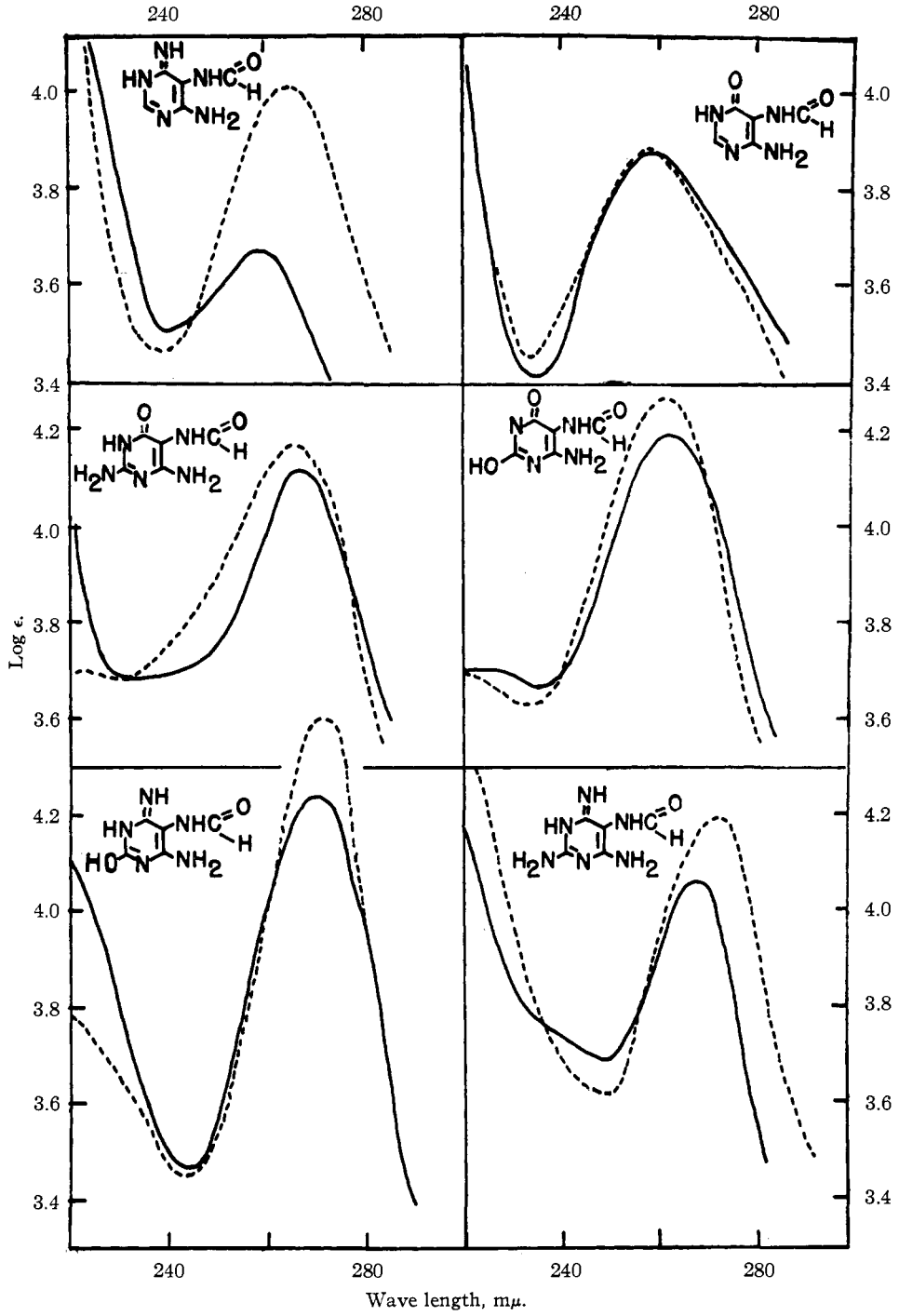


Fig. 2.—*p*H 2, -------; *p*H 6, ———; *p*H 9, — — — —.

pyrimidines exhibit molecular extinction values higher than those of either the mono- or disubstituted derivatives. It is of interest to note (though it may be fortuitous) that the sum of the extinction values of 2,6- and 4,6-diaminopyrimidines is 11,800, as compared to 14,500 observed for 2,4,6-triaminopyrimidine (VIII), and that the sum of the values of 2-amino-6-hydroxypyrimidine and 4-amino-6-hydroxypyrimidine is 12,500 as compared to the observed value of 14,800 for 2,4-diamino-6-hydroxypyrimidine (IX). The 2-amino group serves to increase the basicity of the 1-nitrogen atom which in turn favors the carbonyl and imino forms. Thus compounds VIII

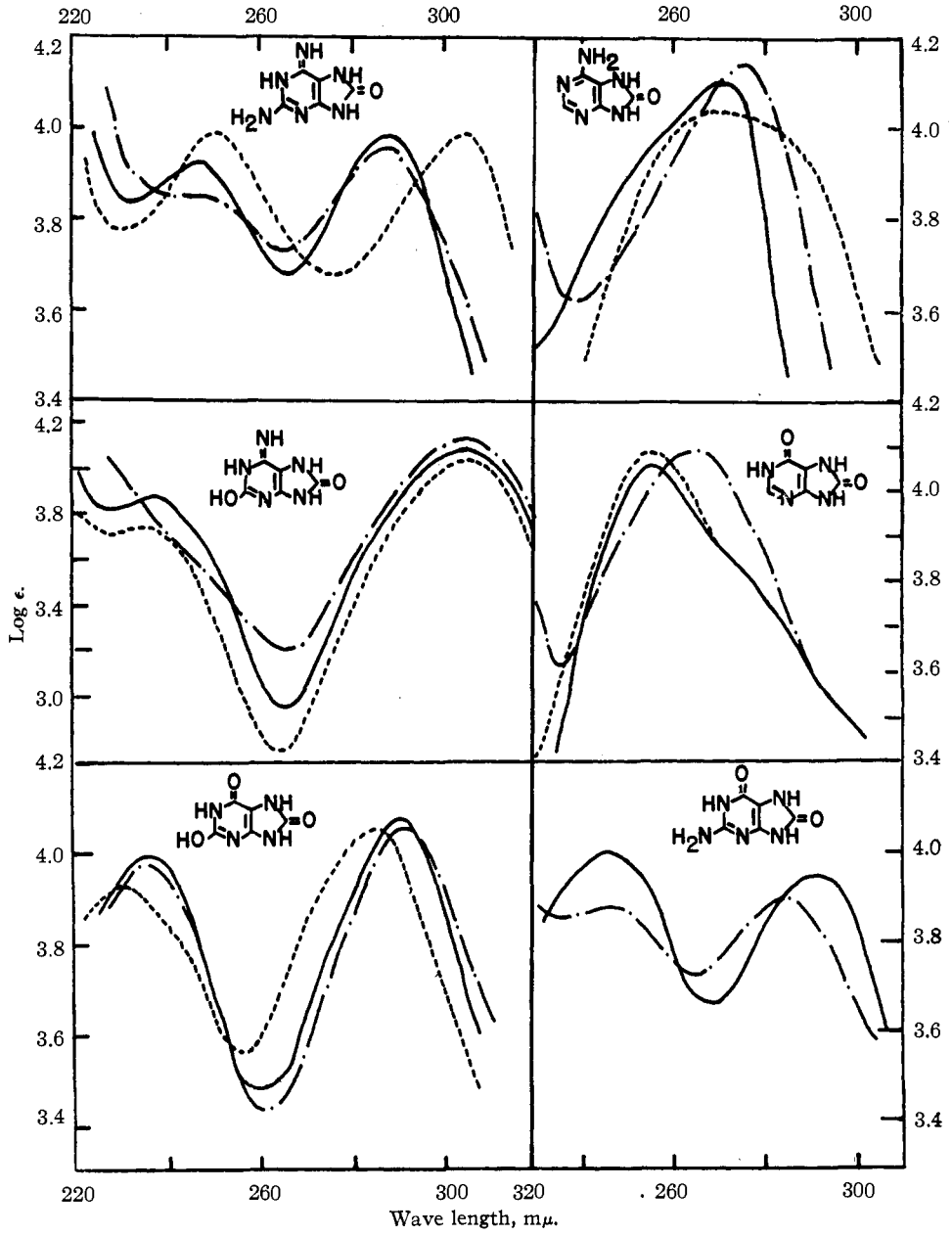
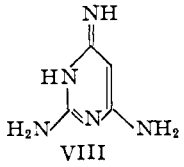
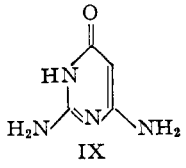


Fig. 3.—*p*H 2, - - - - - - - -; *p*H 6, ———; *p*H 9, — — — —.

and IX are best represented by the following (asymmetrical) structures.[12]

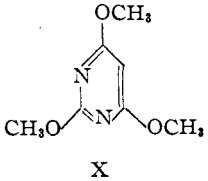


VIII

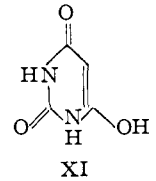


IX

The symmetrical molecule 2,4,6-trimethoxypyrimidine (X) exhibits a low extinction (ϵ = 7620, λ = 248 mμ) as compared to barbituric acid (ϵ = 25,000, λ = 262 mμ) which probably has the asymmetrical structure (XI).[3,13]



X



XI

(12) Polarographic evidence indicates that the compounds in question exist in the forms VIII and IX, Cavalieri and Lowy, unpublished results.

(13) That barbituric acid does not exist as the tricarbonyl form is shown by the lack of selective absorption of 5,5-diethylbarbituric acid.[3]

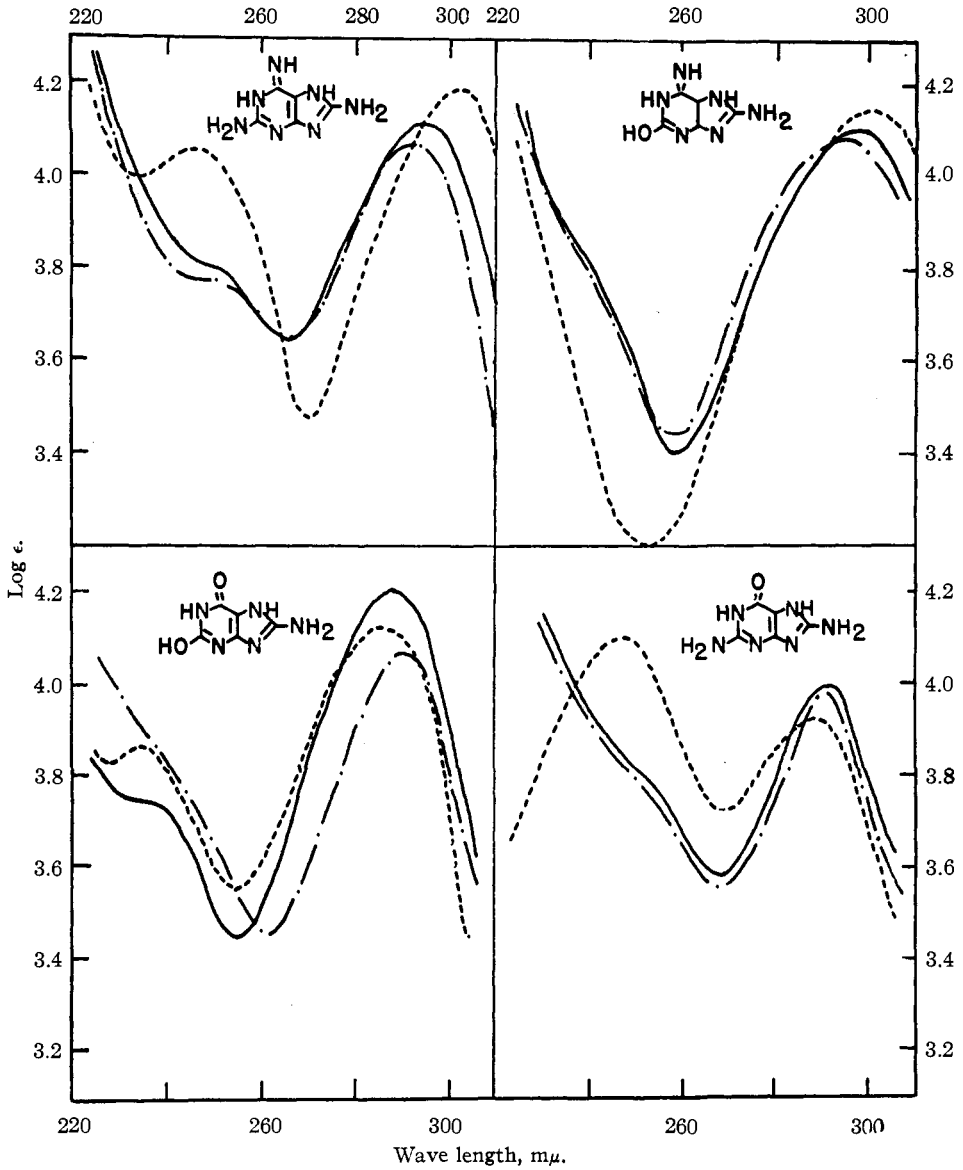


Fig. 4.—*p*H 2, - - - - - - - -; *p*H 6, ———; *p*H 9, — — — —.

It is of further interest to compare the spectra of the trisubstituted pyrimidines with those of the tetrasubstituted pyrimidines.[2] The introduction of the 5-amino group results in about a 50% decrease in extinction values while the bands are displaced 8–10 mμ toward the visible. When a formyl group is introduced on the 5-amino group, providing a sink for the electrons of the 5-amino group, the resulting formamido derivatives are found to absorb in the same region and with approximately the same intensities as the trisubstituted pyrimidines. The formyl unit, therefore, virtually eliminates the effect of the 5-amino group.

The most complex molecules included in this study are the 8-hydroxy- and 8-aminopurines the spectra of which are shown in Figs. 3 and 4.

TABLE I

SPECTRAL DATA

Pyrimidine	mμ	log
2,6-Dihydroxy- (uracil)[a]	260	3.954
6-Amino-2-hydroxy- (cytosine)[b]	267	3.799
2-Amino-6-hydroxy- (isocytosine)[c]	265	3.653
	285	3.716
2,6-Diamino-	267[d]	3.733
4,6-Diamino-	260[d]	3.806
4-Amino-6-hydroxy-	257[d]	3.903

[a] Taken from the data of Heyroth and Loofbourow, THIS JOURNAL, **56**, 1728 (1934). [b] Bendich, Getler and Brown, *J. Biol. Chem.*, **177**, 565 (1949). [c] Taken from the data of Stimson and Reuter, THIS JOURNAL, **67**, 2191 (1945). [d] Determined in 0.1 *M* phosphate buffer, *p*H 6.5.

TABLE II

No.	Compound	Absorption[a] mμ	log ε	mμ	log ε	mμ	log ε	Formula	Nitrogen, % Calcd.	Found	Sulfur, % Calcd.	Found	Distribution constant[b]
	PYRIMIDINE												
1	2,4-Diamino-6-hydroxy-[c,14]	265	4.268	267	4.171			$C_4H_6ON_4 \cdot H_2SO_4$			14.2	14.0	0.36
2	4,6-Diamino-2-hydroxy-[15]	271	4.428	272	4.369			$C_4H_6ON_4 \cdot HCl$	34.5	34.5			.14
3	2,4,6-Triamino-[16]	272	4.222	270	4.159			$C_4H_7N_5 \cdot H_2SO_4$			14.4	14.8	.07
4	2,4,6-Trihydroxy-[d]	260	4.398					$C_4H_4O_3N_2$					
	5-FORMAMIDOPYRIMIDINE												
5	4,6-Diamino-	265	4.016	259	3.673			$(C_5H_7ON_5)_2 \cdot H_2SO_4 \cdot H_2O$			7.56	7.40	.16
6	4-Amino-6-hydroxy-	257	3.885	258	3.875			$C_5H_6O_2N_4$	36.4	36.9			.081
7	2,4-Diamino-6-hydroxy-	265	4.173	267	4.110			$(C_5H_7O_2N_5)_2 \cdot H_2SO_4$	32.1	31.9	7.33	7.30	.051
8	2,4,6-Triamino-	272	4.192	268	4.062			$(C_5H_8ON_6)_2 \cdot H_2SO_4 \cdot 2H_2O$	35.7	35.7	6.82	7.04	.028
9	4-Amino-2,6-dihydroxy-	262	4.270	264	4.192			$C_5H_6O_3N_4 \cdot H_2O$	29.8	29.5			.061
10	4,6-Diamino-2-hydroxy-	271	4.409	271	4.239			$(C_5H_7O_2N_5)_2 \cdot H_2SO_4 \cdot H_2O$	30.8	31.1	7.05	7.20	.025
	PURINE												
11	6-Amino-8-hydroxy-[e]	272	4.038	270	4.106	270	4.114	$(C_5H_5ON_5)_2 \cdot H_2SO_4$	35.0	35.2	8.00	8.22	1.44
12	6,8-Dihydroxy-	255	4.084	256	4.093	266	4.056	$C_5H_4O_2N_4 \cdot H_2O$	32.9	32.7			0.363
13	2-Amino-6,8-dihydroxy-[f]			245	3.996	245	3.878						
		292	3.941	285	3.890			$C_5H_5O_2N_5$	41.8	42.2			
14	2,6-Diamino-8-hydroxy-	250	3.939	246	3.907	(245)	(3.817)						
		305	3.981	287	3.982	289	3.953	$(C_5H_5ON_6)_2 \cdot H_2SO_4 \cdot 2H_2O$	36.1	36.0	6.87	6.68	.767
15	2,6,8-Trihydroxy-	231	3.930	235	3.990	235	3.982						
		283	4.060	291	4.074	292	4.066	$C_5H_4O_3N_4$	33.3	33.6			.11
16	6-Amino-2,8-dihydroxy-[17]	232	3.899	236	3.949	(237)	(4.165)						
		304	4.201	303	4.188	302	4.299	$(C_5H_5O_2N_5)_2 \cdot H_2SO_4$	32.5	32.7	7.42	7.10	
17	2,8-Diamino-6-hydroxy-[g]	247	4.106	(247)	(3.852)	(247)	(3.831)						
		287	3.928	291	4.000	290	3.988	$(C_5H_6ON_6)_2 \cdot H_2SO_4 \cdot H_2O$	37.4	37.6	7.13	7.13	.33
18	2,6,8-Triamino-	246	4.030	(250)	(3.808)	250	3.828						
		302	4.162	295	4.146	291	4.104	$C_5H_7N_7 \cdot H_2SO_4 \cdot H_2O$	34.9	35.1	11.4	11.4	.056
19	8-Amino-2,6-dihydroxy-[18]	233	3.854	(233)	(3.696)								
		285	4.125	288	4.198	290	4.071	$(C_5H_5O_2N_5)_2 \cdot H_2SO_4 \cdot H_2O$	31.1	30.9	7.12	6.96	.21
20	6,8-Diamino-2-hydroxy-			(245)	(3.778)								
		302	4.142	298	4.113	295	4.095	$(C_5H_6ON_6)_2 \cdot H_2SO_4 \cdot 2H_2O$	36.1	35.8	6.87	6.96	.056

[a] Of the log values for compounds 1–10, the first was determined at *p*H 2.3, the second at *p*H 6.5; for compounds 11–20 the third value was determined at *p*H 9.2. The values in parentheses represent inflection points. [b] Compounds 1, 2, 14 determined in *n*-butanol–0.1 *M* phosphate buffer, *p*H 6.5. Compounds 3, 5, 11, 12, 15 determined in *n*-butanol–1.0 *M* phosphate buffer *p*H 6.5. Compounds 6–10, 18, 20 determined in *n*-butanol–0.1 *M* phosphate buffer, *p*H 2.4. Some of these compounds appeared to be unstable at *p*H 6.5, and in order to obtain comparable values, the distributions were run at *p*H 2.4 at which value all compounds were stable. It is clear, however, that these low distribution constants involve some error; compounds 17 and 19 determined at *p*H 9.2. The solutions for distribution of compounds 17 and 19 were made up by dissolving the compounds in buffer containing 0.1 cc. of 12 *N* sodium hydroxide. These distribution coefficients are therefore subject to error since the first few tubes were at a higher *p*H. [c] For compounds 1–10, solutions were made up by dissolving 2 mg. of the compound in 10 cc. of water and diluting 1:10 with 0.1 *M* phosphate buffer. [d] Taken from the data of Heyroth and Loofbourow, footnote *a*, Table I. [e] For compounds 11, 12, 14, 15 solutions were made up by dissolving *ca.* 1.5 mg. of the compound in 10 cc. of hot water and diluting 1:10 with 0.1 *M* phosphate buffer. [f] For spectral data this compound (2 mg.) was dissolved in 4 cc. of 0.1 *N* potassium hydroxide and the solution diluted with 40 cc. of water. After neutralizing with 4 cc. of 0.1 *N* hydrochloric acid, the solution was made up to 50 cc. and finally diluted 1:5 with buffer of appropriate *p*H. [g] For compounds 17–20, solutions were made by dissolving 1.5 mg. of the compound in 2 cc. of 0.1 *N* potassium hydroxide, and then neutralizing with 2 cc. of 0.1 *N* hydrochloric acid. The resulting solution was made up to 10 cc. and diluted 1:10 with buffer.

All but two of these derivatives exhibit bands in the region of 240 ± 5 mμ and 295 ± 7 mμ, while the purines containing no substituent in the 8-position possess bands at 243 ± 5 mμ and 280 ± 5 mμ.[2] In both the 8-substituted and unsubstituted derivatives, the appearance of only one band coincides with the absence of a 2-substituent. A similar situation obtains in the case of the tetrasubstituted pyrimidines. The similar extinction values and position of maxima in these three types of compounds suggests that the same chromophore is involved in all cases. However, contributions to the chromophore from the remainder of the molecule must be considered in any detailed analysis and undoubtedly these contributions will vary even among similar type compounds.

Experimental

Measurements.—All measurements were made with a Beckman ultraviolet spectrophotometer, Model DU. All compounds (except two) were tested for homogeneity by the countercurrent distribution method.[19] On the basis of this technique the samples were shown to be 98–100% homogeneous. In the regions of maximum extinction, readings were obtained at 1 mμ intervals.

Pyrimidine Mercuric Chloride.—Pyrimidine was obtained as the mercuric chloride salt by the method of Gabriel.[20] The procedure involves the reduction of trichloropyrimidine by means of zinc and hydrochloric acid. Pyrimidine may also be obtained by the dethiolation of dithiouracil using Raney nickel.

(14) Traube, *Ber.*, **33**, 1371 (1900); Plentl and Schoenheimer, *J. Biol. Chem.*, **153**, 205 (1944).

(15) Bendich, Tinker and Brown, THIS JOURNAL, **70**, 3109 (1948).

(16) Mallette, Taylor and Cain, *ibid.*, **69**, 1814 (1947).

(17) Fischer, *Ber.*, **30**, 2220 (1897).

(18) Fischer, *Z. physiol. Chem.*, **60**, 69 (1909).

(19) Tinker and Brown, *J. Biol. Chem.*, **173**, 585 (1948).

(20) Gabriel, *Ber.*, **33**, 3666 (1900).

Anal. Calcd. for $C_4H_4N_2 \cdot HgCl_2$: Cl, 20.1. Found: Cl, 19.9.

6-Aminopyrimidine.[21]—Thiourea (2.8 g., 0.037 mole) and 5 g. (0.035 mole) of cyanoacetaldehyde diethylacetal were refluxed for four hours in 15 cc. of *n*-butanol containing 3.3 g. (0.035 mole) of sodium butoxide. The mixture was cooled and the product (3.0 g.) collected by filtration. The 2-thio-6-aminopyrimidine was dissolved in water and precipitated by the addition of glacial acetic acid; yield, 2.0 g. One gram of 2-thio-6-aminopyrimidine was refluxed in 20 cc. of water containing about 3 g. of Raney nickel. The filtrate of this reaction mixture was evaporated to dryness and extracted with five 10-cc. portions of ethyl acetate; yield of 6-aminopyrimidine, 0.15 g. (20%).

Anal. Calcd. for $C_4H_5N_3$: N, 44.2. Found: N, 43.8.

6-Hydroxypyrimidine.[22]—2-Thio-6-hydroxypyrimidine was prepared by treating thiourea with ethyl formylacetate diethylacetal according to the procedure described for 2-thio-6-aminopyrimidine. In this case the condensation product was recrystallized from 2 *N* sulfuric acid; yield 0.76 g. One gram was dethiolated with Raney nickel and isolated as above; yield of 6-hydroxypyrimidine, 0.23 g. (30%).

Anal. Calcd. for $C_4H_4ON_2$: N, 29.2. Found: N, 29.8.

2,6-Diaminopyrimidine Sulfate.[21]—Sodium (1.01 g.) was dissolved in 35 cc. of *n*-butanol. To this was added 6.0 cc. of cyanoacetaldehyde diethylacetal and 3.8 g. of guanidine hydrochloride and the mixture refluxed while stirring for two and three-quarter hours. The sodium chloride was removed by filtration and washed with one volume of ethanol and one volume of ether. The combined filtrate and washings were acidified with 6 *N* sulfuric acid until precipitation was complete. The crude sulfate obtained on filtration weighed 6.5 g. Recrystallization from two volumes of ethanol and one of 2 *N* sulfuric acid gave 5.2 g. of 2,6-diaminopyrimidine sulfate.

Anal. Calcd. for $(C_4H_6N_4)_2 \cdot H_2SO_4 \cdot H_2O$: N, 33.4; S, 9.53. Found: N, 33.6; S, 9.87.

4-Amino-6-hydroxypyrimidine.—4-Amino-6-hydroxy-2-thiopyrimidine (4.0 g., obtained by the reaction of thiourea with ethyl cyanoacetate in ethanol and sodium ethylate) was taken up in 70 cc. of water containing 1.0 g. of sodium acetate and refluxed in the presence of several grams of Raney nickel for one and one-half hours. The mixture was filtered and concentrated *in vacuo* to about 10 cc. to yield 0.49 g. of 4-amino-6-hydroxypyrimidine (16%). The product was recrystallized from water.

Anal. Calcd. for $C_4H_5ON_3$: N, 37.8. Found: N, 37.7.

4,6-Diaminopyrimidine Sulfate.[21]—4,6-Diamino-2-thiopyrimidine (3.0 g.) in 50 cc. of water was refluxed with several grams of Raney nickel for two hours. The filtrate was made approximately 2 *N* in sulfuric acid and 100 cc. of ethanol was added. 4,6-Diaminopyrimidine sulfate (1.0 g., 24%) was obtained which was recrystallized from one volume of 2 *N* sulfuric acid and two volumes of ethanol.

Anal. Calcd. for $C_4H_6N_4 \cdot H_2SO_4 \cdot {}^1/_2H_2O$: N, 25.8; S, 14.8. Found: N, 25.8; S, 15.1.

2,4,6-Trisubstituted Pyrimidines.—The compounds listed in Table II were prepared according to methods previously described.

5-Formamidopyrimidines.—The formamidopyrimidines were prepared by dissolving 0.5 g. of the appropriate pyrimidine in the minimum amount (*ca.* of 10 cc.) of boiling 98% formic acid. In three cases (2,6-dihydroxy-4-amino-5-formamidopyrimidine, 4-amino-6-hydroxy-5-formamidopyrimidine and 2,4-diamino-6-hydroxy-5-formamidopyrimidine) the product was obtained by precipitation with ethanol (15 cc.). The others were obtained by evaporation of the reaction mixture to dryness. In all cases, the formamidopyrimidines were recrystallized from water; yields, about 50%.

Hydroxypurines.—8-Hydroxypurines could be prepared either by the fusion of the appropriate pyrimidine with urea[23] or by the action of phosgene.

6-Amino-8-hydroxypurine Sulfate.—4,5,6-Triaminopyrimidine sulfate[24] (1.0 g., 0.0041 mole) was dissolved in 40 cc. of 10% sodium hydroxide and phosgene was passed in for two hours. A precipitate appeared which later dissolved. To the reaction mixture was added 5 cc. of 2 *N* sulfuric acid. The solution was heated and decolorized. On cooling, 472 mg. of 6-amino-8-hydroxypurine sulfate separated. This material was recrystallized from 2 *N* sulfuric acid; yield, 325 mg. (39%).

6,8-Dihydroxypurine.—4,5-Diamino-6-hydroxypyrimidine sulfate[25] (1.0 g., 0.0057 mole) was dissolved in 25 cc. of 10% sodium hydroxide and phosgene passed in for two hours. The mixture was heated until the solid had dissolved and the solution decolorized. On cooling 310 mg. of product separated. This material was recrystallized from water; yield, 290 mg. (30%).

6-Amino-2,8-dihydroxypurine Sulfate.—4,5,6-Triamino-2-hydroxypyrimidine sulfate[15] (0.8 g., 0.0033 mole) was dissolved in 25 cc. of 10% sodium hydroxide and phosgene passed in for two hours. The product was filtered and recrystallized twice from 2 *N* sulfuric acid; yield, 210 mg. (29%).

2,6-Diamino-8-hydroxypurine Sulfate.—2,4,5,6-Tetraminopyrimidine sulfate[16] (1.0 g., 0.0042 mole) and 2.5 g. of urea were mixed intimately and fused at 180° for one hour. The cooled melt was extracted with 2 *N* sulfuric acid. The solution was cooled and the product collected by filtration. This was recrystallized four times from 2 *N* sulfuric acid; yield, 390 mg. (40%).

2-Amino-6,8-dihydroxypurine.—2,4,5-Triamino-6-hydroxypyrimidine sulfate[14] (1.0 g., 0.0042 mole) and 2.5 g. of urea were mixed intimately and fused at 180° for one hour. The cooled melt was extracted with 20 cc. of 12 *N* sodium hydroxide, while warming. The mixture was filtered and acidified with glacial acetic acid. The product[26] was reprecipitated from sodium hydroxide with acetic acid; yield, 140 mg. (20%).

Uric Acid.—Uric acid was synthesized according to directions given in a previous communication.[27]

8-Aminopurines.—Four 8-aminopurines were prepared by coupling the parent purine with 2,4-dichlorobenzenediazonium chloride and reducing the diazo compound with sodium hydrosulfite.[28,29] All products were recrystallized four times from 2 *N* sulfuric acid; yields *ca.* 10%.

Correction.—"Ultraviolet Absorption Spectra of Purines, Pyrimidines and Triazolopyrimidines" (Ref. 2 of this paper)—for guanine sulfate, *p*H 8.8 at 275 mμ, log ε should read 3.877; for 7-amino-5-hydroxy-1-v-triazolo-[d]pyrimidine at *p*H 2.08, log ε should read 3.868.

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(21) Wheeler prepared 6-aminopyrimidine by the reduction of 2-chloro-6-pyrimidine, *J. Biol. Chem.*, **3**, 287 (1907); *cf.* Büttner, *Ber.*, **36**, 2232 (1903).

(22) 6-Hydroxypyrimidine may also be prepared by the reduction of 2-chloro-6-hydroxypyrimidine.[21]

(23) Levene and Senior, *J. Biol. Chem.*, **25**, 618 (1916).

(24) Cavalieri, Tinker and Bendich, THIS JOURNAL, **71**, 533 (1949).

(25) Roblin, Lampen, English, Cole and Vaughan, *ibid.*, **67**, 290 (1945).

(26) Karrer, Manunta and Schwyzer, *Helv. Chim. Acta*, **31**, 1214 (1948); Fischer, *Ber.*, **30**, 559 (1897).

(27) Cavalieri, Blair and Brown, THIS JOURNAL, **70**, 1240 (1948).

(28) Spies and Harris, *ibid.*, **61**, 351 (1939).

(29) Attempts to prepare 6,8-diaminopurine and 8-amino-6-hydroxypurine by this method were unsuccessful. In some experiments the starting material was recovered. In one coupling experiment adenine resulted in a compound which had the spectrum of 2,6,-8-triaminopurine.

Summary

The ultraviolet absorption spectra of a variety of hydroxy- and aminopyrimidines and purines are recorded. These data further substantiate the interpretation that the major chromophore of pyrimidines and purines is the $-C=C-C=N-$ or $-C=C-C=O$ system.

A correlation of the intensities of absorption with the symmetry of substituted pyrimidines has been made.

New methods for the synthesis of 6-hydroxy-, 6-amino-, 2,6-diamino-, 4-amino-6-hydroxy-, and 4,6-diaminopyrimidines are presented.

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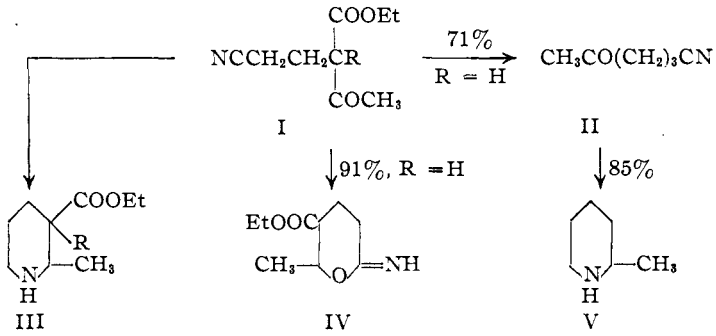
[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Piperidines and Azabicyclo Compounds. I. *Via* Michael Condensations

BY NOEL F. ALBERTSON

It has been known for a long time that δ-ketonic nitriles could be reduced to piperidines.[1] Since so many compounds of marked physiological activity contain the piperidine ring, it seemed worthwhile to reinvestigate this method of synthesis of piperidine compounds in light of the recent development of the chemistry of acrylonitrile. Accordingly, such a research program was initiated in this Laboratory a number of years ago. Publication at this time of some of the results of this investigation is prompted by the recent appearance of three papers[2] indicating an overlapping of interest in this and two other laboratories. Reference by Henecka in his *Berichte* article to a French Patent applied for in 1942[3] indicates clearly his priority in this method of synthesis. However, our results (performed independently) differ from those of Henecka in some respects and extend the general method to compounds not prepared by Henecka.



The δ-ketonitriles used in the present work were prepared by Michael condensations between vinyl ketones and cyanoacetic esters, or acrylonitrile and β-ketoesters.

The simplest δ-ketonic nitrile, 5-oxocapronitrile-(II) may be prepared from acetone and acrylonitrile, but the yield is very low,[4] owing to polycyanoethylation. Since β-keto esters give much higher yields of monocyanoethyl derivatives than can be obtained from ketones, a better yield of II was realized by starting with acetoacetic ester. The condensation of acrylonitrile with ethyl acetoacetate gave a 63% yield of ethyl (2-cyanoethyl)-acetoacetate, I (R = H).[5] It was found that aqueous carbonate readily converted I (R = H) to pure II in 71% yield (44% over-all based on acrylonitrile).

Reduction of II with Raney nickel catalyst yielded 2-methylpiperidine (V) in 85% yield. Reduction of I (R = H) may be stopped after the uptake of one mole of hydrogen to give a basic compound the analytical data for which agrees with the formula $C_9H_{15}NO_3$. Since this compound lost nitrogen as ammonium chloride on refluxing with hydrochloric acid, it is most probably 5-carbethoxy-6-methyltetrahydro-2-pyroneimine (IV).[6] This compound is undoubtedly identical with Henecka's compound XX[2c] (1-cyanopentanol-(4)-carbonsäure-(3)-ester) although Henecka gives no properties or experimental details.

Since Koelsch has shown that reduction of γ-cyano esters with Raney nickel catalyst yields piperidones,[7] one might expect that reduction of I would lead to either a piperidine or a piperidone or both. Actually, only piperidines, III, have been isolated, usually in high yield.

Complete reduction of I (R = H) using Raney nickel catalyst gave an 86% yield of 2-methyl-

(1) (a) Wohl and Maag, *Ber.*, **43**, 3280 (1910); (b) Rupe and Heckendorn, *Helv. Chim. Acta*, **9**, 980 (1926); (c) Rupe and Stern, *ibid.*, **10**, 859 (1927).

(2) (a) Henecka, *Angew. Chem.*, **60**, 59 (1948); received Feb. 1949, (b) Boekelheide and Rothchild, THIS JOURNAL, **71**, 879 (1949); (c) Henecka, *Ber.*, **82**, 104 (1949).

(3) French Patent 881,360. To the best of our knowledge the contents of this patent have not yet appeared in the abstract literature.

(4) Shannon, U. S. Patent 2,381,371 (1945). An 8.6% yield of product boiling over a thirty degree range is reported.

(5) (a) Keimatsn and Sugasawa, *J. Pharm. Soc. (Japan)*, **48**, 755 (1928); (b) Bruson, U. S. Patent 2,394,962 (1946); (c) Wiest and Glaser, U. S. Patent 2,396,626 (1946).

(6) We are indebted to Dr. A. A. Larsen of these laboratories for first suggesting this structure and pointing out the analogy between our compound and the 2-furanoneamine obtained by Schultz, Robb, and Sprague, THIS JOURNAL, **69**, 2454 (1947), and by Easton, Gardner and Stevens, *ibid.*, **69**, 2941 (1947).

(7) Koelsch, *ibid.*, **65**, 2458 (1943).