The infrared spectrum of this picrate was identical with that of an authentic specimen.[6]

B. Direct Method.—To a solution of V (288 mg, 2 mmoles) in reagent grade methanol (50 ml) was added methanol-washed, activated Raney nickel (*ca.* 5 g) and the mixture was stirred for 2 hr. The Raney nickel was filtered and washed with water (30 ml). The combined filtrate and washings were adjusted to pH 1 with 1 *N* hydrochloric acid, then evaporated to dryness under reduced pressure. A slightly yellow, crystalline residue was obtained which was recrystallized from ethanol. Pale yellow needles of the dihydrochloride of VIII (248 mg, 58%) were obtained, mp 302°.

The picrate of VIII, mp 205–207°, was readily obtained by addition of a methanolic solution of picric acid to the aqueous solution of the dihydrochloride. The infrared spectra and melting points of the dihydrochloride and picrate of VIII were identical with those of authentic samples prepared from 1,3-dibromopropane and dimethylamine.[6] The melting points of these salts were not depressed by admixture with the authentic samples[6] of the corresponding salts.

β-Methylaminopropionic Acid (X) from V.—Compound V (633 mg, 4.4 mmoles) was dissolved in 130 ml of a 1:1 mixture of ethanol and 0.1 *N* hydrochloric acid. Hydrolysis of IX was followed spectrophotometrically. Within 15 min the absorption maximum at 337 mμ completely disappeared. Raney nickel (30 g) was then added and the mixture was stirred for 30 min. The catalyst was filtered and washed with a 1:1 mixture of ethanol and water (50 ml). The filtrate and washings were combined and evaporated to dryness. The residue was dissolved in 100 ml of water and treated with 1.2 g of potassium permanganate and 5 ml of 1 *N* sodium hydroxide. The mixture was shaken for 2 hr after which it was treated with methanol until the red color of permanganate disappeared. Precipitated manganese dioxide was removed by filtration through a pad of diatomaceous earth. The filtrate was evaporated to dryness to a white solid. The solid was dissolved in 10 ml of water followed by addition of ethanol (20 ml). Precipitated inorganic material was removed by filtration. The filtrate was evaporated to a glass, which still contained considerable amount of impurities and could not be crystallized. The glass was subjected directly (Table I) to paper chromatographic examination (Whatman No. 1, descending method) and was identical in $R_{sarcosine}$ values with authentic X.

TABLE I

Solvent system[a]	$R_{sarcosine}$: Glassy product (X)	$R_{sarcosine}$: Authentic (X)[b]	$R_{sarcosine}$: β-Dimethylaminopropionic acid[c]
A	2.0	2.0	4.1
B	1.5	1.5	1.6
C	Front	Front	Front

[a] Solvent system A = 2,6-lutidine, ethanol, water, and diethylamine (55:25:20:2); B = upper layer of the following mixture: *n*-butanol, water, and acetic acid (50:50:6); C = phenol (400 ml), water (100 ml), and 8-hydroxyquinonoline (50 mg). [b] Prepared by condensation of β-bromopropionic acid with methylamine [P. Handler, M. L. C. Bernhein, and J. R. Klein, *J. Biol. Chem.*, **138**, 215 (1941)]. [c] Prepared by reaction of β-bromopropionic acid with dimethylamine [U. S. Patent 2,203,009 (1937)].

1-Methyl-4-dimethylamino-2(1H)-pyrimidinone.[19]—A mixture of 1-methyl-4-thiouracil[18] (2.0 g, 0.014 mole) in 20% methanolic dimethylamine was heated at 115° for 19 hr in a sealed glass tube. The almost colorless reaction mixture was evaporated *in vacuo* to dryness to a solid which was crystallized from ethyl acetate. Colorless needles (0.85 g) deposited, mp 175–177° [not lowered on admixture with 1-methyl-4-dimethylamino-2(1H)-pyrimidinone which was prepared by the procedure of Kenner, *et al.*[19]] The ultraviolet absorption spectral characteristics were also identical with those reported.[19] An additional 500 mg of this product was obtained from the mother liquors (total yield 1.35 g, 63%).

Acknowledgment.—The authors are indebted to Dr. George B. Brown for his warm and continued interest.

Synthesis of 5-Hydroxyalkylpyrimidines from Lactones. II. 5-Monohydroxycyclopentylpyrimidines[1]

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The synthesis of 5-hydroxycyclopentylpyrimidines, including those of uracil and cytosine, is described. Their stereochemistry and the significance of their spectra with respect to those of other hydroxyalkylpyrimidines are discussed.

We have reported[2] the synthesis of a number of 5-hydroxyalkylpyrimidines from γ-lactones, and have now extended this synthesis to a group of pyrimidines possessing a monohydroxycycloalkyl group at the 5 position. Of these compounds the 5-hydroxycyclopentyluracil (7) bears structural similarity to pseudouridine. It also serves as a model for the several 5-hydroxyalkyluracils which have been obtained as degradation products of pseudouridine.[3] In these cycloaliphatic model compounds the number of conformations possible is considerably fewer than in those with an acyclic 5 substituent. Consequently a study of its physical properties may serve to elucidate the role of hydrogen bonding in the previously observed[4] spectral differences between thymine and 5-hydroxymethyluracil and between α- and β-pseudouridines.

These hydroxycycloalkylpyrimidines may also be useful in biological studies, as have similar analogs of purine nucleosides where 9-hydroxycyclopentyl or cyclohexyl derivatives have been used successfully in obtaining information concerning the nature of the functional group which is required for binding to the active site of various enzymes.[5] Such studies with adenosine deaminase led to the conclusion that the hydroxyl group at C′-2 makes a significant contribution to the binding whereas the hydroxy groups at C′-3 and the hydroxymethyl group at C′-4 make only a small contribution to binding to that enzyme. An unexpected finding[5a] was that the stereochemistry of the hydroxyl group at the 2′ position of the cycloaliphatic ring is not critical to the binding. On the other hand

(1) This investigation was supported by Public Health Service Research Grant No. CA-03190-09 and the Maude K. Irving Memorial Grant for Cancer Research from the American Cancer Society.

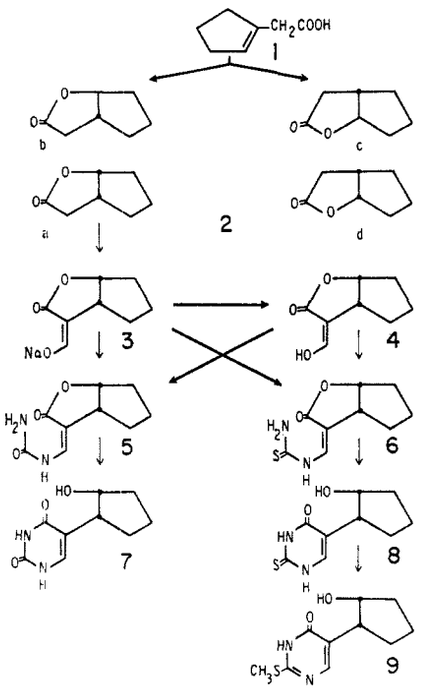
(2) J. D. Fissekis, A. Myles, and G. B. Brown, *J. Org. Chem.*, **29**, 2670 (1964): manuscript I of this series.

(3) R. W. Chambers and V. Kurkov, *Biochemistry*, **3**, 326 (1964).

(4) R. W. Chambers, V. Kurkov, and R. Shapiro, *ibid.*, **2**, 1192 (1963).

(5) (a) H. J. Schaeffer, S. Marathe, and V. Alks, *J. Pharm. Sci.*, **53**, 1368 (1964); (b) H. J. Schaeffer, K. K. Kaistha, and S. K. Chakraborti, *ibid.*, **53**, 1371 (1964).

SCHEME I



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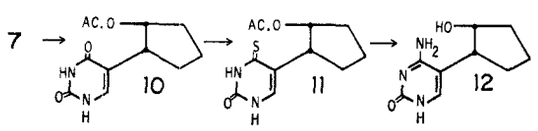

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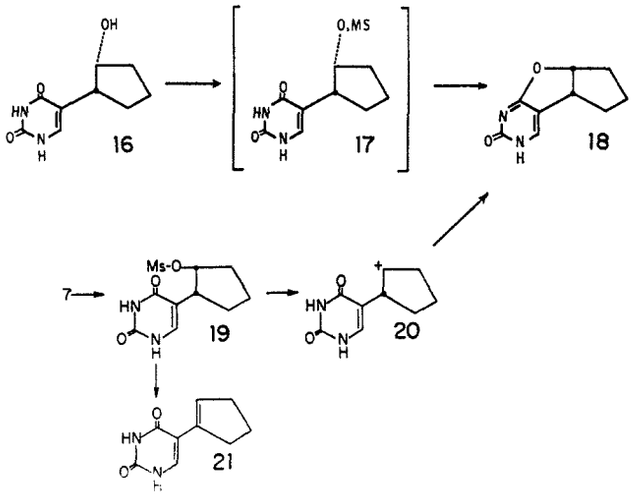
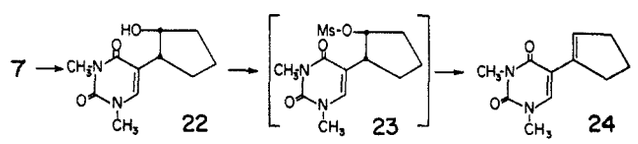


SCHEME IV



various cyclopentyl thymines, including a cyclopentane isostere of thymidine, have shown no activity against a wide assortment of bacteria and fungi.[6]

1-Cyclopentenylacetic acid (**1**) was first synthesized by the method of Linstead and Meade[7] through the route cyclopentanone → ethyl (1-hydroxycyclopentyl)-1-acetate → ethyl (1-cyclopentenyl)-1-acetate → **1**. The procedure of Harding and Haworth[8] whereby cyclopentylidenecyanoacetic acid is decarboxylated to 1-cyclopentenylacetonitrile which is then hydrolyzed in two steps to the corresponding acid **1**, when modified by preparing the first two intermediates by the method of Cope, *et al.*,[9] was more convenient.

The lactone **2** was prepared from the unsaturated acid **1** with 60% sulfuric acid according to the procedure of Linstead and Meade.[7] This lactone, the stereochemistry of which must be considered in terms of either one or two *pairs* of enantiomorphs, is depicted as **2a–d**. Subsequent formulas in Schemes I–IV are depicted only in terms of derivatives of isomers **a** or **b**.

The sodium derivative **3** was prepared from the lactone **2** and methylformate in dry ether in the presence of sodium methoxide. Its enolic nature is indicated by the strong ultraviolet absorption of an aqueous solution of the sodium salt (λ_{max} 278 mμ). In acid the absorption is greatly depressed and shifted toward lower wavelength (λ_{max} 247.5 mμ). Continuous ether extraction of an acidified, cold, aqueous solution of **3**, permitted the isolation of **4** in crystalline form. Either **3** or **4** readily yields a 2,4-dinitrophenylhydrazone in 2 *N* hydrochloric acid solution. Attempted condensation of **3** with thiourea in a saturated aqueous solution of the latter[10] failed. The ureido compounds **5** and **6** were prepared from **3** or **4** with urea and thiourea in 3 *N* hydrochloric acid. The products precipitate readily from the reaction mixtures. From a comparison of the yields from **3** with those obtained when **4** was employed, it was concluded that **3** was about 70% pure.

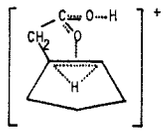
The cyclizations to the pyrimidines **7** and **8** were readily effected by refluxing the corresponding ureido derivatives (**5** and **6**) with 2 equiv of sodium ethoxide. **8** was methylated with CH_3I in sodium hydroxide solution to **9**. Attempted substitution of the 2-methylmercapto group by ammonia was unsuccessful. From a solution of **9** in liquid ammonia, heated at 60° over night, most of the starting material was recovered unchanged and heating to 180° of a solution of **9** in methanol saturated with NH_3 at 0° led to extensive decomposition.

The 5-hydroxycyclopentyluracil (**7**) served as starting material for the synthesis of the corresponding cytosine derivative. When the hydroxyl group in the side chain was protected by acetylation, the 4 position of **10** could be thiated[11] to **11** under the controlled conditions of Mizuno, *et al.*[12] The mercapto compound (**11**) was then treated with ammonia in methanol at 100° to yield 5-hydroxycyclopentylcytosine (**12**).

The stereochemistry of the lactone **2** determines the configuration of the pyrimidine derivatives. The lactonization process has introduced two asymmetric centers, with the four isomers, **2a–d**, possible. Linstead and Meade[7] have argued in favor of a predominance of the *cis*-lactones (**a** and **d**) on the basis of the

(6) K. C. Murdock and R. B. Angier, *J. Am. Chem. Soc.*, **84**, 3758 (1962).
(7) R. P. Linstead and E. M. Meade, *J. Chem. Soc.*, 935 (1934).
(8) V. J. Harding and W. N. Haworth, *ibid.*, **97**, 486 (1910).
(9) A. C. Cope, A. A. D'Addieco, D. E. Whyte, and S. A. Glickman, in "Organic Syntheses," Coll. Vol. IV, N. Rabjohn, Ed., John Wiley and Sons, Inc., New York, N. Y., 1963, p 234.
(10) H. L. Wheeler and L. M. Liddle, *Am. Chem. J.*, **40**, 547 (1908).
(11) J. J. Fox, D. Van Praag, I. Wempen, I. L. Doerr, L. Cheong, J. E. Knoll, M. L. Eidinoff, A. Bendich, and G. B. Brown, *J. Am. Chem. Soc.*, **81**, 178 (1959).
(12) Y. Mizuno, M. Ikehara, and K. A. Watanabe, *Chem. Pharm. Bull. (Tokyo)*, **10**, 647 (1962).

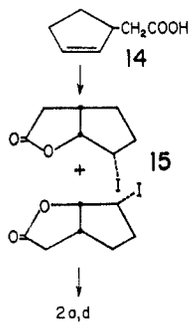
stability towards water and alkali, although they did not exclude the presence of some of the *trans* modification. In addition the probable stereochemical configuration of the lactone can be derived from mechanistic considerations. The steric course of lactonizations (in the presence of a strong acid catalyst) is consistent with a concerted or near-concerted mechanism[13] which in this case should involve the transition state structure **13**.



13

The steric consequence of such a transition state would be the formation of the *cis*-lactone.[14] Formation of diastereoisomeric lactones from *cis* and *trans* isomers of an alkenoic acid has been observed, yet it has been shown that the product isolated may (especially if a strong acid catalyst is used) be that expected from a *cis* addition.[15]

The stereochemistry of the lactone **2** was elucidated by an unequivocal synthesis of the *cis* isomers (**2a** and **2d** from 2-cyclopentenyl-1-acetic acid (**14**) through a related iodolactonization reaction. It has been conclusively shown that the formation of a *cis*-fused γ-lactone is the expected result when an appropriate cycloalkenylacetic acid is subjected to iodolactonization.[14,16] This reaction involves an initial attack by I^+ to form a transition state structure analogous to **13**, which is then opened *trans* through an intramolecular attack of the carboxymethyl ion to give **15**. Due to the steric



effect of the angular carboxymethyl group, the I^+ attack occurs at the less hindered site, thus leading to an iodo-*cis*-γ-lactone. This lactone was subjected to hydrogenolysis with Raney nickel and the *cis*-lactone **2a,d** was isolated in small yield.

The boiling point, refractive index, and infrared absorption spectrum of this product were identical with those of the lactone obtained by cyclization of the 1-cyclopentenyl-1-acetic acid with 60% sulfuric acid. The identity of the two samples was also confirmed by gas chromatography employing columns packed with SE-30 silicone gum rubber on Chromosorb W and XE-60 silicone gum on Chromosorb W. The latter system has been used successfully in partially resolving a mixture of *cis* and *trans* isomers of a lactone.[16] In addition each of the two samples of lactone gave similar yields of compounds **5** and **7** and on comparison these products were found to have identical melting and mixture melting points. Therefore it was concluded that the lactone **2** was a mixture only of the *cis* isomers **2a** and **2d**.

Consequently, structure **7** (and its mirror image) was assigned as the only permissible structure for the 5-hydroxycyclopentyluracil obtained. In an attempted inversion of C′-2 to the other possible isomers (**16** and its mirror image) in which the hydroxyls are *trans* to the pyrimidine, a facile elimination reaction was encountered. A crude O-methylsulfonyl derivative of 5-hydroxycyclopentyluracil was obtained. This was unstable, and in hot ethanol alone it gave a sulfur-free solid. Structure **18** was tentatively assigned to that product since it showed an ultraviolet absorption pattern in which the maximum of the uridyl group at 264 mμ had disappeared and a pair of new maxima were present at 242 and 294 mμ. The curves and shifts at neutral and alkaline pH resembled those reported for isopropylidene cyclouridine.[17] It proved extremely resistant under hydrolytic conditions as, *e.g.*, heating for 24 hr in 0.01 *N* H_2SO_4 or 1 *N* NaOH as well as treatment with CF_3COOH and NH_4OH.[18] It was also inert toward potassium *t*-butoxide–DMSO.[19] The formation of such a derivative could be rationalized in terms of an SN2 mechanism from **16** or an SN1 mechanism from **7** and/or **16**.

To get a better understanding of the nature of the reaction, and to elucidate the structure of the product, the 1,3-dimethylderivative (**22**) was prepared.[20] From this a crude O-methanesulfonate (**23**) was obtained. When the latter was treated under the same experimental conditions, elimination of methanesulfonic acid to yield a sulfur free product also occurred. The ultraviolet absorption spectrum of this compound at neutral and acidic pH's was very similar to that of the product that was obtained under the same conditions from the nonmethylated pyrimidine **7**. Yet in the second case a structure analogous to **18** was impossible.

Conclusive proof that the two products are 5-cyclopentenylpyrimidine derivatives was obtained from nmr spectra and thus structures **21** and **24** were assigned to them. For **21**, the spectrum shows two vinyl protons, one identified as a doublet at δ 7.28 with a coupling constant $J_{H_6,H_1} = 5.5$ cps, and another poorly resolved at δ 6.71. The two amide H's which are in the δ ~11 region are exchanged in D_2O. For **24** (also in DMSO) the two vinyl protons appear at δ 7.55 (H-6) and δ 6.69 (H′-2), and the two N-methyl groups at δ 3.36 and δ 3.20.

Although it has been demonstrated that sulfonate esters of cyclic and secondary acyclic alcohols afford alkenes on treatment with potassium *t*-butoxide in dimethyl sulfoxide,[19,21] this is the first case where such a reaction was observed to proceed under mild experimental conditions and in the absence of a strong base.

Spectral Studies.—Pyrimidine nucleosides exhibit spectral shifts between pH 12 to 14 which are primarily

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(18) K. C. Murdock and R. B. Angier, *J. Am. Chem. Soc.*, **84**, 3748 (1962).
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(20) D. Davidson and O. Bandisch, *J. Am. Chem. Soc.*, **48**, 2379 (1926).
(21) C. H. Snyder and A. R. Soto, *J. Org. Chem.*, **29**, 742 (1964).

TABLE I

Compd	Spectral data: 0.1 N HCl mμ	0.1 N HCl ε × 10⁻³	0.1 N NaOH mμ	0.1 N NaOH ε × 10⁻³	$A_{280}:A_{260}$[a] at pH 12	R_f in solvents: A	B	C
5	273, max	22.3	Unstable					
	224, min	0.93						
7[b]	262, max	7.4	289, max	5.5	1.41	0.72	0.59	0.68
	237, min	2.1	246, min	2.2				
8	280, max	16.8	260, max	13.2		0.80	0.79	0.61
	217	13.5						
	241, min	3.1	244, min	10.2				
9	274, max	10.4	280, max	7.9		0.89	0.86	0.76
	253	9.7	248	9.2				
	229	9.2						
	260, min	9.5	264, min	5.9				
	239.5	8.4	237	7.9				
10	264, max	7.5	289, max	5.6		0.85	0.80	0.81
	235, min	2.1	246, min	2.1				
11	334, max	15.1				0.90	0.88	0.79
	243	3.8	Unstable					
	277, min	3.2						
12[c]	285, max	9.2	286.5, max	6.5	3.26	0.54	0.35	0.59
	244, min	0.85	254, min	1.4				
21	295, max	7.2	308, max	8.4			0.79	0.75
	243.5	10.2	253.5	10.2				
	270, min	5.3	279, min	5.3				
	214	5.6	229	7.0				
22	271, max	8.2	No change			0.88	0.85	0.91
	239, min	1.9						
24	299, max	8.7				0.93	0.88	0.94
	246	11.5	No change					
	272, min	5.1						
	217	6.3						

[a] The $A_{280}:A_{260}$ ratios of uracil, 1.4;[4] 5-hydroxymethyluracil, 1.8;[4] pseudouridine B, 1.5;[4] pseudouridine C, 2.0;[4] 5-methoxymethyluracil, 2.22,[24] 5-ethoxymethyluracil, 2.35;[24] 5-*n*-butoxymethyluracil, 2.28;[24] 5-hydroxyethyluracil, 1.59. [b] pK = 9.70 ± 0.05. [c] pK = 4.49 ± 0.05.

attributed *to ionization of the C′-2 hydroxyl group* of the sugar moiety, and a concomitant rupture of hydrogen bonding to the C-2 carbonyl of the pyrimidine. In a study of this effect with all four pentofuranosyl thymine isomers[22] it was observed that the alterations of the spectra in this high pH region appeared to be ones of degree rather than kind, and it was suggested that a general mechanism is operative by which ionization of the carbohydrate residue affects the aglycon.

In considering the spectral properties of the 5-(2′-hydroxycycloalkyl)uracils and cytosines we assume that the structural relationship between the C-4 carbonyl and C′-2 hydroxyl existing in these pyrimidines is analogous to that between the C-2 carbonyl and C′-2 hydroxyl in the pyrimidine nucleosides. Therefore, *regardless of the stereochemistry of the C′-2 hydroxyl* in the 5-hydroxycycloalkylpyrimidines, their spectra should yield additional information regarding a possible association through hydrogen bonding of the C′-2 hydroxyl and the C-4 carbonyl. Inspection of FMO models[23] of compound 7 and its mirror image supports this assumption.

Chambers and co-workers have previously proposed[4] that differences between the spectra of thymine and 5-hydroxymethyluracil at pH 12 could be attributed to a hydrogen bond between the latter's 5-hydroxymethyl and C-4 carbonyl groups. A ratio $A_{280}:A_{260}$ at pH 12 of about 1.8 or higher was their criterion of the presence of an H bond. By analogy the hydroxymethyluracil-like spectrum of pseudouridine C (β-furanosyl) was attributed to such H bonding, and that of thymine-like spectrum of pseudouridine B (α-furanosyl) was attributed to its stereochemical configuration, which renders such H bonding unlikely.

In the 5-(2-hydroxyethyl)uracil an H bond to the C-4 carbonyl is sterically permissible, yet its spectrum[2] is more similar to those of uracil and thymine than to that of 5-hydroxymethyluracil. In the case of 5-alkoxymethyluracils such hydrogen bonding is impossible, and if the $A_{280}:A_{260}$ ratio is a measure of such H bonding these should exhibit ratios of less than 1.8. Cline, *et al.*,[24] report the opposite in that 5-methoxymethyl-, 5-ethoxymethyl-, and 5-*n*-butoxymethyluracil show $A_{280}:A_{260}$ ratios in alkali of 2.2, 2.35, and 2.28. Certainly the electron-withdrawing 5-alkoxy groups could affect the $A_{280}:A_{260}$ ratio by altering the tautomer distribution compared to uracil, and it seems that in this aspect the inductive effect of these alkoxy groups would be opposite to that of the methyl group in thymine. O-Methylation of pseudouridine (C and A_s isomers) should disrupt any hydrogen bond between the C′-2 hydroxyl and the C-4 carbonyl, and reduce the value of the $A_{280}:A_{260}$ ratio. From the data of Hall[25] it can, indeed, be deduced that for his presumed C′-2 O-methylpseudouridine, the ratio does appear to be *ca.* 1.41. On the other hand 2′,3′-O-isopropylidene pseudouridine,

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(23) "Framework Molecular Orbital Models," distributed by Prentice-Hall, Inc., Englewood Cliffs, N. J.

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(25) R. H. Hall, *Biochemistry*, **3**, 876 (1964).

pseudouridine 2′-phosphate, and pseudouridine 3′-phosphate show A_{280}:A_{260} at pH 12 of 2.1, 1.9, and 1.9.[4]

The spectral properties and ionization constants of 5-hydroxycyclopentyluracil and cytosine (Table I) are generally similar to those of the corresponding 5-hydroxyethyl- and 5-hydroxymethyl deriyatives.[2] The spectrum of the 5-(2′-hydroxycyclopentyl)uracil at pH 12 shows a maximum at 289 mμ and a typical uracil-like shoulder at 265–270 mμ. The A_{280}:A_{260} ratio is 1.41 which on the basis of the H-bond theory discussed should exclude any H bond between the C-4 carbonyl and C′-2 hydroxyl. However in this pyrimidine (**7** and its mirror image) the hydroxy group is *cis* to the base, and the hydrogen bonding should be even more favored than in 5-hydroxyethyluracil (observed value 1.59) and its value should approach the value 1.8 of 5-hydroxymethyluracil.

Thus in view of the several discrepancies among the observations available it seems that hydrogen bonding to the ring carbonyl is not the only way to interpret the A_{280}:A_{260} ratios, and an unequivocal explanation of the spectral properties of the 5-hydroxyalkyluracils (including pseudouridine C) will require a greater understanding of the properties of this important group of compounds.

Experimental Section

Melting Points.—All melting points were determined with a Mel-Temp apparatus and are uncorrected.

Paper Chromatography.—Ascending technique on Whatman No. 1 paper was used with the solvents: A, *n*-BuOH–HOAc–H_2O (12:3:5); B, *n*-BuOH–H_2O (85:15); and C, *i*-PrOH–H_2O–NH_4OH (7:2:1).

Cyclopentylidenecyanoacetic Acid and 1-Cyclopentenylacetonitrile.—A solution of 185 g (2.2 moles) of cyclopentanone, 170 g (2 moles) of cyanoacetic acid, and 6 g (0.08 mole) ammonium acetate in 150 ml of benzene was refluxed vigorously for about 10 hr while the water from the reaction was removed azeotropically. The mixture was then left at room temperature overnight. Crystalline solid had separated at this stage. After standing in the cold for a few hours, the mixture was filtered and the solid was washed well with petroleum ether (bp 30–60°) and then dried on a porous plate; yield 252 g (84%). A few more grams of product could be recovered from the concentrated mother liquors. After recrystallization from benzene, the obtained cyclopentylidenecyanoacetic acid melted at 128.5–130.5°.[26a]

The above product was decarboxylated in a flask fitted with a condenser by heating it slowly up to 180° with stirring. The temperature was maintained at that level for about 3 hr until the decomposition was completed. The crude mixture was fractionated and the nitrile was collected at 122–125° (88 mm); yield 149 g (83%). On redistillation, it boiled at 126–127° (100 mm);[26b] $n^{20}D$ 1.4672.

Racemic *cis*-2-Hydroxycyclopentylacetic Acid Lactone (2).—1-Cyclopentenylacetic acid (50 g) dissolved in 200 ml of 60% sulfuric acid was heated on a steam bath for *ca.* 30 min. Ice was added to the cold solution (total volume *ca.* 400 ml), the mixture was ether extracted overnight, and the extract was dried over Na_2SO_4 and fractionated. The product was collected as a colorless liquid; bp 110–112° (10 mm); $n^{20}D$ 1.474;[7] yield 29.2 g (58.3%).

Iodo Lactone 15.—A solution of 37.8 g (0.33 mole) of 2-cyclopentenyl-1-acetic acid and 79.6 g (0.94 mole) of sodium bicarbonate in 1250 ml of H_2O was mixed with a solution of 159.5 g (0.63 g-atom) of iodine and 314 g (1.9 moles) of potassium iodide in 2500 ml of water. The mixture was stirred over the weekend at room temperature. An oily precipitate had separated at this stage. The supernatant was decolorized with 1 *N* sodium bisulfite solution and extracted twice with ether. The ether extracts were combined with the oily precipitate and the solution was first shaken again with 1 *N* sodium bisulfite solution until it was colorless and then was extracted with a small volume of cold 5% sodium bicarbonate solution and dried over sodium sulfate. After the solvent had been removed *in vacuo*, *ca.* 50 ml of petroleum ether (bp 50–60°) was added to the residue, the mixture was seeded and cooled to give a crystalline mass; yield 72.3 g (95.6%). The crude product was purified by recrystallization from ether–petroleum ether giving large prismatic crystals, mp 35–36°.

Anal. Calcd for $C_7H_9IO_2$: C, 33.35; H, 3.60; I, 50.35. Found: C, 33.45; H, 3.51; I, 50.40.

Hydrogenolysis of 15.—To a solution of 37.5 g of the iodolactone **15** and 30.1 g of diethylamine in *ca.* 230 ml of dry methanol, *ca.* 7.5 g of Raney nickel was added and the mixture was hydrogenated at room temperature and 3 atm for 20 min. The mixture was filtered and the solvent was removed *in vacuo*. The magma was extracted well with ether, dissolved in water and this aqueous solution was again continuously extracted with ether. The combined ether extracts were dried with sodium sulfate and distilled. The fraction boiling between 102–115° (10 mm) was dissolved in 10% sodium hydroxide solution which was first extracted with ether, and then was carefully acidified and extracted again with ether. This ether extract was fractionated to give a few grams of product (**2a**, **2d**) that boiled at 114–115° (10 mm); $n^{20}D$ 1.475.

Anal. Calcd for $C_7H_{10}O_2$: C, 66.64; H, 7.99. Found: C, 66.53; H, 7.81.

α-Hydroxymethylene(2-hydroxycyclopentyl)acetic Acid Lactone, Sodium (3).—To a stirred suspension of 12.9 g (0.25 mole) of CH_3ONa in *ca.* 1 l. of dry ether, a mixture of 30 ml (0.49 mole) of methyl formate and 29.2 g (0.23 mole) of **2** was added dropwise over a 2-hr period; the stirring was continued overnight. The cream-colored solid product was collected, washed with dry ether, and dried *in vacuo*. Yield varied from 27.6 to 34.5 g.

α-Hydroxymethylene(2-hydroxycyclopentyl)acetic Acid Lactone (4).—**3** (2 g, 11.3 mmoles) was dissolved in 50 ml of ice-cold water, and the solution was acidified (*ca.* pH 1) with concentrated hydrochloric acid. The mixture was diluted to 100 ml with water and extracted overnight with ether. The extract was dried with Na_2SO_4 and concentrated *in vacuo* to a yellowish semicrystalline residue. This was redissolved in ether; the solution was treated with Norit, concentrated to a small volume (2–3 ml), and placed in the deep freezer. [The addition of a few drops of petroleum ether (bp 30–60°) to the above ether solution, sometimes facilitated the crystallization.] The short, white needles thus obtained were collected, washed with light petroleum ether and dried *in vacuo*. Yield varied between 34 and 53%, mp 124–126°.

Anal. Calcd for $C_8H_{10}O_3$: C, 62.32; H, 6.54. Found: C, 62.28; H, 6.43.

2,4-Dinitrophenylhydrazone.—A small sample of **4** dissolved in a few drops of methanol was added to a solution of 2,4-dinitrophenylhydrazine in 2 *N* hydrochloric acid. Separation of a yellow derivative occurred immediately. After standing in the cold for a few hours it was filtered, washed well with water, and dried *in vacuo*. Recrystallization from ethanol gave small yellow crystals, mp 180–181°.

Anal. Calcd for $C_{14}H_{14}N_4O_6$: N, 16.00; Found: N, 16.07.

α-Carbamyliminomethylene(2-hydroxycyclopentyl)acetic Acid Lactone (5) and α-Thiocarbamyliminomethylene(2-hydroxycyclopentyl)acetic Acid Lactone (6).—**3** (10 g) was added in small portions to a solution of urea (8 g) or thiourea (10.1 g) in 100 ml of cold 3 *N* hydrochloric acid. After stirring in the cold overnight, the precipitated product was collected, washed well with water, and dried *in vacuo*.

Compound **5** yielded 7.0 g (63.5%). It was recrystallized twice from a small volume of methanol, mp 235–237°.

Anal. Calcd for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.16; N, 14.28. Found: C, 55.13; H, 6.30; N, 14.06.

Compound **6** yielded 7.0 g (58%). It was recrystallized twice from ethanol, mp 235–237°.

Anal. Calcd for $C_9H_{12}N_2O_2S$: N, 13.20; S, 15.10. Found: N, 13.12; S, 15.16.

In similar small-scale experiments in which **4** was used instead of **3**, the yield of **5** and **6** was correspondingly 81.5 and 89.5%.

2,4-Dihydroxy-5-(2′-hydroxycyclopentyl)pyrimidine (7) and 4-Hydroxy-2-mercapto-5-(2′-hydroxycyclopentyl)pyrimidine (8).—Compound **5** or **6** was refluxed with a solution of 2 equiv of sodium in dry ethanol for 4–6 hr. The sodium salt of **7** precipitated during the course of the reaction, while the corresponding derivative of **8** remained in solution. In either case, the solvent was removed *in vacuo;* the residue was dissolved in a small volume of cold water and the solution was filtered and acidified with

(26) (a) Lit.[8] mp 129°. (b) Lit. bp 124° (100 mm) or 150° (200 mm).

glacial acetic acid. The product that precipitated was left in the cold for several hours and then filtered, washed well with cold water, and dried *in vacuo*.

Compound **7** yielded 80–90%; recrystallization from methanol gave white needles, mp 286–291°.

Anal. Calcd for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.16; N, 14.28. Found: C, 54.67; H, 6.38; N, 13.70.

Compound **8** yielded 88%; recrystallization from 1-propanol gave plates, mp 303–304°.

Anal. Calcd for $C_9H_{12}N_2O_2S$: N, 13.20; S, 15.10. Found: N, 13.05; S, 15.10.

4-Hydroxy-2-methylmercapto-5-(2′-hydroxycyclopentyl)pyrimidine (9).—**8** (1.06 g, 5 mmoles) was dissolved in 25 ml of water containing 5.5 mmoles of NaOH and 0.36 ml (5.5 mmoles) of CH_3I was added. The mixture was stirred in the cold for 24 hr. The white solid which precipitated was collected, washed with cold water and dried *in vacuo;* yield 670 mg (59%). The combined mother liquors were concentrated to about 25 ml and recycled yielding 260 mg more of product (total yield 930 mg 82%). An analytical sample was recrystallized from acetone as white needles, mp 180–181°.

Anal. Calcd for $C_{10}H_{14}N_2O_2S$: N, 12.38; S, 14.15. Found: N, 12.36; S, 14.19.

2,4-Dihydroxy-5-(2′-acetoxycyclopentyl)pyrimidine (10).—**7** (402 mg, 2.0 mmoles) was acetylated with 2 ml of acetic anhydride in *ca.* 15 ml of dry pyridine. After stirring for 24 hr at room temperature, the mixture was treated with a few drops of water, and then concentrated to dryness *in vacuo*. Water was added to the residue. After standing in the cold for several hours, the product was filtered, washed with cold water and dried *in vacuo*. Occasionally the acetylation procedure had to be repeated at this stage to complete the reaction. Finally the product was recrystallized from methanol; yield 89% of white, small, fine needles, mp 258°.

Anal. Calcd for $C_{11}H_{14}N_2O_4$: C, 55.50; H, 5.91; N, 11.78. Found: C, 55.68; H, 5.96; N, 12.05.

2-Hydroxy-4-mercapto-5-(2′-acetoxycyclopentyl)pyrimidine (11).—**10** (78 mg, 2 mmoles) was dissolved in 20 ml of dry pyridide, 240 mg of P_2S_5 (1.1 mmoles) was added, and the mixture was refluxed for 8 hr. The dark yellow solution was taken to dryness *in vacuo*, and the residue was treated with water. After cooling for a few hours the product was filtered and washed several times with water. It was recrystallized from methanol–water as small yellow needles; yield 47%, mp 230–231°.

Anal. Calcd for $C_{11}H_{14}N_2O_3S$: N, 11.02; S, 12.62. Found: N, 10.90; S, 12.81.

4-Amino-2-hydroxy-5-(2′-hydroxycyclopentyl)pyrimidine (12).—A solution of 507 mg (2 mmoles) of **11** in *ca.* 40 ml of dry methanol saturated with ammonia at 0° was heated in a sealed tube at 100° for *ca.* 16 hr. The reaction mixture was concentrated until most of the excess ammonia had been expelled and then refrigerated. The separated solid was filtered, washed with small volume of cold methanol, dried *in vacuo*, and finally recrystallized from methanol as white plates; yield 151 mg (38%), mp 244–245° dec.

Anal. Calcd for $C_9H_{13}N_3O_2$: C, 55.37; H, 6.71; N, 21.53. Found: C, 55.45; H, 6.62; N, 21.52.

2,4-Dihydroxy-5-(1′-cyclopentenyl)pyrimidine (21).—A suspension of 980 mg (5 mmoles) of **7** in *ca.* 10–15 ml of dry pyridine was cooled in an ice bath and 1.72 g (1.15 ml, 15 mmoles) of methane sulfonyl chloride was added. The mixture was stirred in the cold overnight. Then 2 drops of water was added and after standing in the cold for 1 hr the solvent was removed *in vacuo* at 30° and the residue was treated with 25 ml of water. The mixture was refrigerated overnight to yield 1.23 g (90%) of a brown, crystalline precipitate which was filtered, washed with water, and dried *in vacuo* at room temperature (λ_{max}^{KBr} 8.55 μ, sulfonic ester). The crude material was dissolved in 175 ml of hot ethanol. After prolonged refluxing and cooling, 300 mg of a white solid had separated. It was collected, washed with cold methanol, and dried *in vacuo*. The mother liquor was neutralized with Amberlite IR-45 and concentrated on the steam bath to give another 160 mg of product. Repetitions of this treatment raised the total yield to 535 mg. It was dissolved in concentrated ammonium hydroxide and the solution was filtered through Darco and then allowed to stand at room temperature for several days. The product separates as small, white needles. It decomposes slowly above 300° and melts at 335°.

Anal. Calcd for $C_9H_{10}N_2O_2$: C, 60.71; H, 5.66; N, 15.72. Found: C, 60.60; H, 5.75; N, 16.01.

2,4-Dihydroxy-5-(2′-hydroxycyclopentyl)-1,3-dimethylpyrimidine (22).—Hydroxycyclopentyluracil (**7**, 1.59 g, 8.1 mmoles) was dissolved in 19.4 ml of 1 *N* sodium hydroxide (19.4 mmoles of base), the solution was cooled in an ice bath and 2.45 g (1.84 ml, 19.4 mmoles) of methyl sulfate was gradually added with stirring. The mixture was then heated to boiling (one phase was formed at this stage, and the pH was neutral), then cooled and extracted five times with an equal volume of chloroform. The chloroform extract was dried with sodium sulfate, filtered, and evaporated under reduced pressure, yielding 1.6 g (88%) of a white solid, which upon recrystallization from ether–methanol gave white needles, mp 132–133°.

Anal. Calcd for $C_{11}H_{16}N_2O_3$: C, 58.91; H, 7.19; N, 12.49. Found: C, 59.00; H, 7.19; N, 12.36.

2,4-Dihydroxy-5-(2′-cyclopentenyl)-1,3-dimethylpyrimidine (24).—**22** (673 mg, 3 mmoles) was suspended in *ca.* 10 ml of dry pyridine, the mixture was cooled in an ice bath, and 1.15 ml (15 mmoles) of methanesulfonyl chloride was added with stirring. Stirring was continued overnight in the cold. The excess of the chloride was then decomposed with a few drops of water and the mixture was evaporated to near dryness at room temperature under reduced pressure. The residue was treated with *ca.* 25 ml of cold water and after standing in the cold for a few hours the crystalline precipitate was collected, washed well with water, and dried *in vacuo* at room temperature (λ_{max}^{KBr} 8.55 μ, sulfonic ester), yield 700 mg.

The above crude sulfonate (302 mg, 1 mmole) was dissolved in *ca.* 25 ml of ethanol and the solution refluxed for 4 hr. The solvent was then removed in a stream of air, the residue was suspended in a few milliliters of cold water, and the mixture was neutralized with a few drops of cold, dilute ammonium hydroxide. After cooling for a few hours the product was filtered, washed well with cold water, and dried *in vacuo*, yield 130 mg (63%). The crude product was dissolved in hot methanol and the solution was treated with Norit, concentrated on the steam bath, and cooled to give small white needles that sintered at 146° and melted at 149–150°.

Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 64.19; H, 6.81; N, 13.76.

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