Hydrolysis of 6-Methyl-4-phenylpyrimidine 1-Oxide (VIII)[10] with Sulfuric Acid.—A solution of 6-methyl-4-phenylpyrimidine 1-oxide (VIII) (1.9 g) in 30% sulfuric acid (15 ml) was refluxed for 7 hr. In a fashion similar to the above, the reaction mixture was treated with ether and chloroform. From the ether fraction 0.5 g (30%) of 3-methyl-5-phenylisoxazole (X)[11] was obtained, bp 152° (19 mm), mp 67–68° (lit. 67–68°). From the chloroform extract, 1.1 g (58%) of the starting material (VIII) was recovered.

Hydrolysis of 6-Methyl-4-methoxypyrimidine 1-Oxide (II)[12] with Hydrochloric Acid.—A solution of II (1.4 g) in 10% hydrochloric acid (20 ml) was refluxed for 1 hr, during which time carbon dioxide was identified as barium carbonate by passing the gas evolved from the top of the refluxing condenser to a barium hydroxide solution.

A part of the reaction mixture was treated with tin, and then chromotropic acid–sulfuric acid was added, and on warming in a water bath blue coloration appeared (formic acid positive).

Another part of the reaction mixture was distilled, and 2,4-dinitrophenylhydrazine was added to the distillate, giving orange crystals. Recrystallization from methanol afforded orange leaves, mp 128° (undepressed on admixture with an authentic sample of acetone 2,4-dinitrophenylhydrazone). The residue was identified as ammonium chloride.

Registry No.—IV, 14161-40-1; V, 1006-67-3; VII, 14161-42-3; VIII, 14161-43-4.

Acknowledgment.—We wish to express our sincere appreciation to Miss. A. Sato, N. Nanjo, R. Oikawa, and Y. Tadano of the Analytical Laboratories, of this institute, for the microanalyses and infrared and nmr spectral measurements.

(10) H. Bredereck, R. Gompper, and H. Herlinger, *Chem. Ber.*, **91**, 2832 (1958).
(11) L. Claisen, *ibid.*, **59**, 194 (1926).
(12) E. Ochiai and H. Yamanaka, *Pharm. Bull.* (Tokyo) **3**, 173 (1955).

Synthesis of 5-Hydroxyalkylpyrimidines from Lactones. III. 5-Dihydroxycyclopentylpyrimidines[1]

JOHN D. FISSEKIS AND BARBARA MARKERT CREEGAN

Division of Biological Chemistry, Sloan-Kettering Division, Graduate School of Medical Sciences, Cornell University Medical College, New York, New York 10021

Received May 3, 1967

Syntheses of several 5-(*trans*-2′,3′-dihydroxycyclopentyl)pyrimidines, including those of uracil and cytosine, are described. From the α-hydroxymethylene(*trans*-2-hydroxy-3-methoxycyclopentyl)acetic acid γ-*cis*-lactone, 4-hydroxy-5-(*trans*-2′-hydroxy-3-methoxycyclopentyl)-2-mercaptopyrimidine (**13**), 2,4-dihydroxy-5-(*trans*-2′,3′-dihydroxycyclopentyl)pyrimidine (**14**), and 2,4-dihydroxy-5-(*trans*-2′,3′-dihydroxycyclopentyl)-3-methylpyrimidine (**15**) were prepared. The cytosine analog 4-amino-2-hydroxy-5-(*trans*-2′,3′-dihydroxycyclopentyl)pyrimidine (**19**) was synthesized from **14** *via* acetylation and thiation of the 4 position. Evidence is presented that intramolecular hydrogen bonding occurs in 5-hydroxyalkyluracils.

The ultraviolet spectral shifts in the high alkaline region (pH 12–14) have been proposed as evidence for significant intramolecular hydrogen bonding in pyrimidine derivatives. However, a study of such shifts in 5-(2-hydroxyethyl)uracil (**29**)[2] and of 5-(2-hydroxycyclopentyl)uracil (**31**)[3] has raised certain questions regarding this interpretation. Such changes in the spectrum of N-1-glycosylpyrimidines[4,5] were regarded to involve primarily, a C′-2 hydroxyl to C-2 carbonyl hydrogen bond which is broken by ionization of the sugar alcohol at pH 12–14. By analogy it was postulated[6] that 5-hydroxyalkylpyrimidines such as 5-hydroxymethyluracil and the pseudouridine C isomer have a hydrogen bond between the 5-hydroxyalkyl side chain or the 5′-hydroxymethyl group of the 5-ribosyl moiety and the C-4 carbonyl. A ratio, at pH 12, of the absorption at 280 mμ to that at 260 mμ of 1.8 or higher was proposed[6] as the criterion for the presence of the latter hydrogen bond. Compounds such as 5-methoxy-, ethoxy-, and *n*-butoxymethyluracil[7] still show the high ratio proposed as characteristic of the presence of the hydrogen bond whereas 2′-O-methylpseudouridine[8] shows a low ratio. In the former three the hydrogen bond is blocked, although in the latter the 5′-hydroxymethyl group is still available for hydrogen-bond formation. Both the A_S (β-ribopyranosyl) and A_F (α-ribopyranosyl) isomers of pseudouridine are capable of forming a hydrogen bond between the C-4 carbonyl and the C′-3 hydroxyl; yet they show $A_{280}:A_{260}$ ratios of 2.1[9] and 1.4.[6] No interpretation has been offered for that difference.

The recent results of Asbun and Binkley[10] are of interest. The high ratio (*ca.* 2.22) exhibited by the 5-β-D-xylofuranosyluracil (xylo analog of pseudouridine C) is in agreement with the proposed hydrogen-bond theory. The low ratios (1.46 and 1.68) shown by the other two analogs, *i.e.*, 5-α-D-arabinitol- and 5-α-D-ribitoluracil are more difficult to interpret. In these compounds, regardless of the anomeric configuration of the C-5,C′-1 bond, there are several possibilities of hydrogen bonding to the C-4 carbonyl. Also the electromeric effect of the side chain should be similar to that of the CH_2OH in 5-hydroxymethyluracil as both these compounds are substituted derivatives of the latter. Of course, extensive intramolecular bonding among the hydroxyls might restrict the side chain to a conformation prohibiting any bonding to the C-4 carbonyl.

(1) This investigation was supported in part by funds from the Maude K. Irving Memorial Grant for Cancer Research from the American Cancer Society and National Cancer Institute, National Institutes of Health, U. S. Public Health Service Research Grant No. CA 08748.
(2) J. D. Fissekis, A. Myles, and G. B. Brown, *J. Org. Chem.*, **29**, 2670 (1964).
(3) J. D. Fissekis and B. A. Markert, *ibid.*, **31**, 2945 (1966).
(4) J. J. Fox, L. F. Cavalieri, and N. Chang, *J. Am. Chem. Soc.*, **75**, 4315 (1953).
(5) J. J. Fox, J. F. Codington, N. Chang Yung, L. Kaplan, and J. O. Lampen, *ibid.*, **80**, 5155 (1958).
(6) R. W. Chambers, V. Kurkov, and R. Shapiro, *Biochemistry*, **2**, 1192 (1963).
(7) R. E. Cline, R. M. Fink, and K. Fink, *J. Am. Chem. Soc.*, **81**, 2521 (1959).
(8) R. H. Hall, *Biochemistry*, **3**, 876 (1964).
(9) R. W. Chambers, *Progr. Nucleic Acid Res. Mol. Biol.*, **5**, 377 (1966).
(10) W. Asbun and S. B. Binkley, *J. Org. Chem.*, **31**, 2215 (1966).

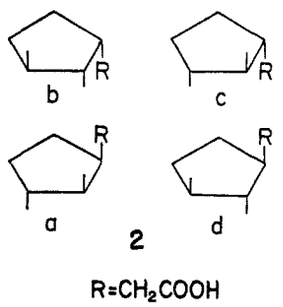


Figure 1.—Possible isomers of 2,3-*trans*-dihydroxy-1-acetic acid.

Sterically the 5-(2-hydroxyethyl)- and the *cis*-5-(2-hydroxycyclopentyl)uracils can form an hydrogen bond with the C-4 carbonyl; yet by the criterion of their low ratios at pH 12 they do not appear to hydrogen bond.

It is obvious that the $A_{280}:A_{260}$ ratio at pH 12 is not an adequate criterion for hydrogen bonding in all these cases, and that the inductive effect of the substituents, and other types of hydrogen bonding, must be considered separately. Toward this goal we have begun a systematic extension of studies of hydrogen bonding and its effect on the ultraviolet spectra and fine structure of various 5-hydroxyalkylpyrimidines.

In no case where hydrogen bonding has been considered was there direct evidence for its occurrence. This report presents the syntheses of the 5-(2′,3′-dihydroxycyclopentyl) derivatives of uracil and cytosine, and direct evidence of the existence of hydrogen bonding in 5-hydroxyalkyluracils. The effect of such hydrogen bonding as well as that of the inductive effect of substituents upon the ultraviolet spectra of these pyrimidines is considered. In the earlier reports attention was paid to the C-4 carbonyl in pseudouridines and 5-hydroxymethyluracil as the hydrogen-bond receptor site. However, one must consider other potential basic regions in the pyrimidine ring of uracil, *i.e.*, the π clouds of the carbonyl[11] and C-5,C-6 double bond. In the 5-hydroxycycloalkylpyrimidines, the possibility of intramolecular hydrogen bonding to the π electrons, especially those of the carbon–carbon double bond, is specifically considered.[12] The possibility of such a bonding deserves serious consideration since studies of infrared spectra have demonstrated the presence of a hydrogen bond with either an aromatic or a single double-bond π system as the receptor in a variety of phenyl alkyl alcohols[13-15] and aliphatic unsaturated alcohols.[13]

In pseudouridine C and B, each of the following individual groups is a potential hydrogen-bond donor: C′-2 hydroxyl, C′-3 hydroxyl, and C′-5 hydroxymethyl group. In considering the inductive effects, however, the tetrahydrofuran ring of the furanose should also be taken into account. The contribution of each of these groups to the ultraviolet spectrum of uracil can be studied in hydroxyalkyl analogs of pseudouridine, such as **14** and **31**. Substitution of the cyclopentane ring for the furanose ring of pseudouridine leaves the stereochemical arrangement of the individual groups essentially unchanged. These monohydroxy and dihydroxy derivatives (**31** and **14**) permit comparison with the 2′- and/or 3′-hydroxyls of pseudouridine as potential donors to a hydrogen bond.

(11) A. T. Shulgin and H. O. Kerlinger, *Chem. Commun.* (London), 249 (1966).

(12) The C-4 carbonyl double bond was considered an unlikely receptor as the C-4 carbonyl oxygen, being the more electronegative component, affords a stronger base.

(13) P. von R. Schleyer, D. S. Trifan, and R. Bacskai, *J. Am. Chem. Soc.*, **80**, 6691 (1958).

(14) P. von R. Schleyer, C. Wintner, D. S. Trifan, and R. Bacskai, *Tetrahedron Letters*, 1 (1959).

(15) I. M. Goldman and R. O. Crisler, *J. Org. Chem.*, **23**, 751 (1958).

Discussion and Results

A. Syntheses and Structural Considerations.—The hydroxylactone **3** was prepared in one operation from the unsaturated acid **1** by oxidation with performic acid.[16a] The stereochemistry of the lactone **3** is critical since it determines the configuration of the pyrimidine derivatives. The hydroxylation procedure involves a *cis* epoxidation which is followed by a *trans* opening leading to the four possible *trans*-diols **2a–d** (Figure 1). The pair **2a,b** can only give a *cis*-γ-lactone while the other (**2c,d**) could only lead to a *cis*-δ-lactone. Formation of a *trans*-γ-lactone in the latter case is quite unlikely. Vapor phase chromatography[17] of the lactone **3** showed a single peak. The lactone also revealed a carbonyl absorption in the infrared (1776 cm^{-1}) consistent with a γ-lactone structure, and thus structure **3a,b** was assigned to this lactone.

It has been established that the hydroxylation of olefins by peracids proceeds through an epoxide.[16b] The relatively high yield of **3** suggests a specific rupture of one of the C–O bonds of the intermediate. Such stereoselective cleavage has been considered to be directed by conformational factors, and electronic and steric effects.[18] In the case of the lactone **3a,b** there is evidence that the major part of the lactonization occurred concurrently with the rupture of the epoxide ring. Indeed the infrared spectrum of an oil, presumably the monoformate of the diol, showed a split carbonyl peak at 1776 and 1718 cm^{-1}. The 1776-cm^{-1} absorption disclosed the presence of the lactone **3a,b**[19] in the mixture. This suggested a concerted hydroxylation–lactonization mechanism for the reaction. The *cis* epoxidation of the acid **1** occurs from the unsubstituted side and it is followed by the opening of the epoxide through a *trans* attack by the carboxymethyl group to give the lactone directly. It has been observed previously that the epoxidation of several olefinic acids yielded only hydroxylactones.[20]

Some lactonization did occur during the final distillation as manifested by the few milliliters of water eliminated at that stage, but it could not be ascertained whether the free diol was derived from the opening of the oxirane ring by formic acid and subsequent hydrolysis, or from partial hydrolysis of the lactone itself.

The direct formylation of **3** (Scheme I) with methyl formate in the presence of sodium methylate was complicated by the presence of the free hydroxyl group. The solid isolated appeared to contain a small amount of the anticipated product, from the facts that the

(16) (a) D. Swern, *Org. Reactions*, **7**, 398 (1953); (b) *ibid.*, **7**, 385 (1953).

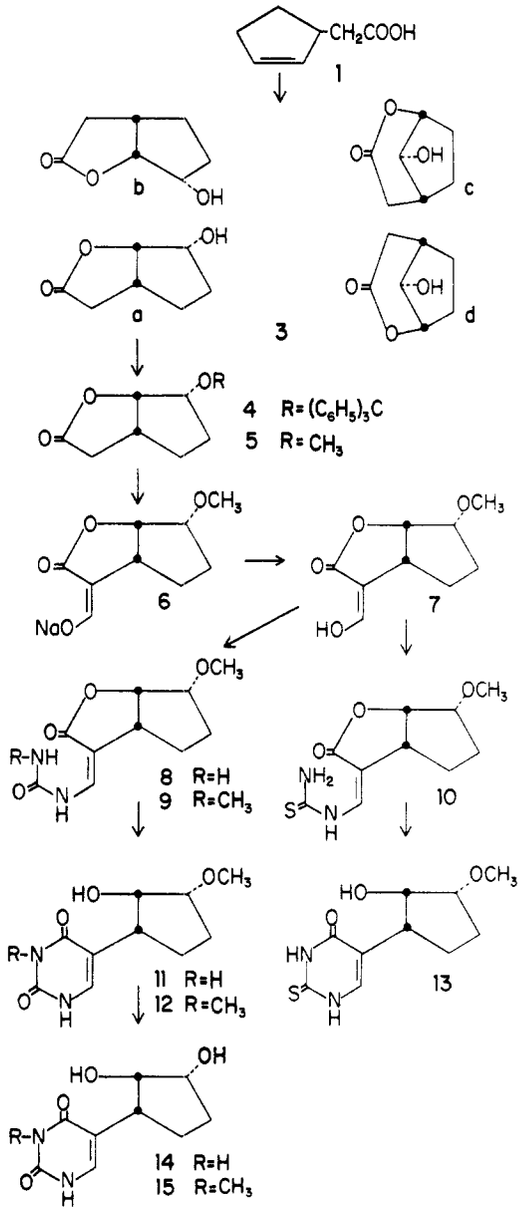
(17) 20% SE-30 silicone gum rubber on Chromosorb W.

(18) J. A. Franks, Jr., B. Tolbert, R. Steyn, and H. Z. Sable, *J. Org. Chem.*, **30**, 1440 (1965), and references therein.

(19) Distillation of this material without prior hydrolysis with water gave the lactone **3a,b** in 66.5% yield.

(20) G. Berti, *J. Org. Chem.*, **24**, 934 (1959).

SCHEME I



ultraviolet absorption of a concentrated solution of it showed the presence of an enolic component[21] and that, when it was condensed with urea and thiourea, the reaction mixtures showed the distinctive ultraviolet spectra of the anticipated ureido derivatives. On the basis of the condensations with ureas it was considered unlikely that the enolic component could be a self-condensation product of the lactone.

In order to obtain a suitably protected compound, the O-trityl (**4**) and O-methyl (**5**) derivatives of the lactone **3** were prepared. Trityl chloride normally reacts with primary hydroxy groups, but instances where it reacts with secondary hydroxy groups of carbohydrates are known,[22,23] and **4** was obtained, but in an impractical low yield (9%). For the preparation of **5**, Purdie's method[24] was used.

In the nuclear magnetic resonance (nmr) spectrum of **3** (in $CDCl_3$) the C-2 and C-3 protons, *trans* to the lactonized and free hydroxyls, appear as multiplets at *ca.* δ = 4.72 and 4.28 ppm, respectively. This order of assignment is based upon the phenomenon of "acylation shift;"[25] *i.e.*, protons attached to the α-carbon atom of esterified alcohols give rise to a signal at lower field compared to the same protons in the free alcohols. The hydrogen of the free hydroxyl group appears at *ca.* δ = 3.88 ppm and the signals of the other seven hydrogens are accumulated between δ = 3.2 and 1.3 ppm. In the methoxy derivative **5** the signals of the C-2 and C-3 protons appear at *ca.* δ = 4.78 and 3.84 ppm, and that of the methyl hydrogens show at *ca.* δ = 3.39 ppm. The signals of the remaining hydrogens are between *ca.* δ = 3.1 and 1.3 ppm. The upfield shift of the C-3 proton in the methoxy derivative **5** verifies the assignment made for the C-2 and C-3 protons in **3**.

The reaction of the lactone **5** with methyl formate in dry ether in the presence of sodium methoxide produced the sodium derivative **6**. This shows a strong ultraviolet absorption in water at λ_{max} 279 mμ. After acidification the absorption is greatly reduced and shifted toward lower wavelength (λ_{max} 248 mμ). Continuous ether extraction of an acidified, cold aqueous solution of **6**, permitted the isolation of **7** in crystalline form. This gives an intense violet color with ferric chloride and reacts readily with 2,4-dinitrophenylhydrazine to give the corresponding hydrazone. The enolic structure **7** is preferred, since in the low-field part of the nmr spectrum of the compound, the signal at *ca.* δ = 11 ppm (broad peak, disappearing upon deuterium exchange) is assigned to the hydroxyl proton. No other signal in the range 8–11 ppm could be detected. This excluded the presence of the aldehydic tautomer. The signal of only one vinyl proton (doublet $\delta \simeq 7.46$ ppm, allylic coupling constant J = 2 Hz) was observed between 8 and 5. This suggested the presence of only one of the two possible geometric isomers.[26] The infrared spectrum of **7** in the solid state (2.5 mg/600 mg of KBr) shows a sharp peak in the carbonyl region at 1730 cm^{-1} and a broad one at 1660 cm^{-1}. In the hydroxyl region there is broad absorption between 3000 and 3700 cm^{-1} with the maximum at 3420 cm^{-1}. The 1660- (absent in **5**) and 3420-cm^{-1} absorptions should be attributed to an intramolecularly associated carbonyl[27a] and hydroxyl group,[27b] respectively, as structure **7** suggests. The absorption due to the trisubstituted double bond should be weak[28] and it is likely that it is buried beneath the 1660-cm^{-1} peak. The 1740-cm^{-1} peak undoubtedly due to a nonbonded carbonyl may be composed of the absorption of a formyl group superimposed on that of the lactone carbonyl. Thus in the crystalline state the presence of the aldehydic tautomer of **7** can not be excluded.

The ureido derivatives **8**–**10** precipitate from the reaction mixtures of **7** (formed *in situ* from **6**) with urea, N-methylurea, or thiourea in 3 *N* hydrochloric acid. In the nmr spectrum of **8** the easily identifiable vinyl proton

(21) The ultraviolet spectrum of this material showed a peak at 277 mμ, suppressed and shifted to 247 mμ when the solution was acidified.

(22) G. R. Barker, *Methods Carbohydrate Chem.*, **2**, 168 (1963).

(23) N. C. Yung and J. J. Fox, *J. Am. Chem. Soc.*, **83**, 3060 (1961).

(24) E. L. Hirst and E. Percival, *Methods Carbohydrate Chem.*, **2**, 146 (1963).

(25) C. C. J. Culvenor, *Tetrahedron Letters*, 1091 (1966).

(26) In the similar case of formyl camphor where both geometric isomers were present, the signals of the two vinyl protons appeared at δ = 7.39 and 6.79 ppm. E. W. Garbisch, Jr., *J. Am. Chem. Soc.*, **85**, 1696 (1963).

(27) (a) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1959, p 141; (b) p 103.

(28) K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, Inc., San Francisco, Calif., 1964, p 24.

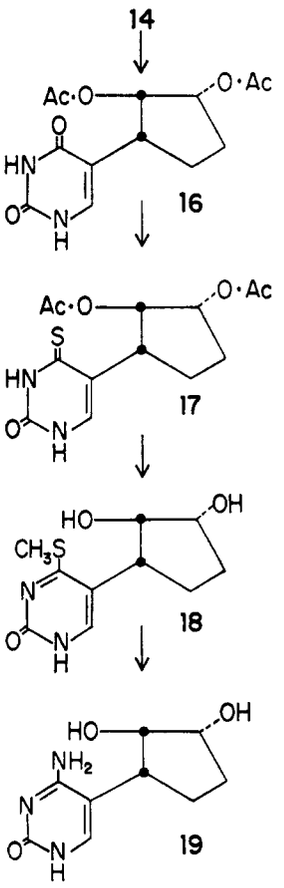
shows as a quartet at $\delta = 7.63$ ppm (coupling constant with the neighbor amide hydrogen $J = 12$ Hz, allylic coupling constant $J = 2$ Hz). The signal of the secondary amide itself appears at $\delta = 9.01$ ppm (doublet, $J = 12$ Hz) and the two hydrogens of the primary amide group show at $\delta = 6.30$ ppm. Upon deuterium exchange all the amido signals disappear and the vinyl proton shows a doublet ($J = 2$ Hz). Similarly for **9** the vinyl proton shows as a quartet, coupled to both the neighbor amido hydrogen ($J = 12$ Hz) and the allylic hydrogen ($J = 2$ Hz). The middle and terminal secondary amido hydrogens appear as a doublet ($\delta = 9.03$ ppm, $J = 12$ Hz) and quartet ($\delta = 6.51$ ppm, $J = 4.5$ Hz), respectively. The hydrogens of the CH_3N group are found as a doublet at $\delta = 2.70$ ppm ($J = 4.5$ Hz). These data verify the structures assigned to these compounds, especially that for **9** as in this case the methyl group of the urea could appear on either the middle or the terminal nitrogen. By analogy to similar condensations,[29] the hydroxymethylene function of **7** reacts with the unsubstituted NH_2 rather than with the $NHCH_3$ group of N-methylurea. Compounds **8** and **9** show very similar ultraviolet absorption in neutral and alkaline solutions. The corresponding curves of both compounds resemble those of 3-methyluracil except that they are shifted to higher wavelengths (see Table I). Absorption in alkali changes with time; *e.g.*, for **8** the absorption at λ 320 mμ after 3 hr was reduced to almost zero while a new maximum at λ 258 mμ had appeared. These changes do not reflect cyclization to **11** but rather decomposition of the ureido moiety and hydrolysis of the lactone. The spectral similarity to 3-methyluracil could be attributed to some delocalization of the π-electron density along the bond system (O=C=C=C=N=C=O)$^-$ from the lactone to the urea carbonyl. The hydrogen of the middle rather than the terminal amido group is the more acidic one, because in all three nmr spectra of **8–10** it is found at lower field than the terminal amido protons. Therefore it must be involved in the dissociation.

The cyclizations to the pyrimidines **11–13** were effected by refluxing the corresponding ureido derivatives (**8–10**) with 2 equiv of sodium ethoxide. The structure of **12** was deduced from its ultraviolet absorption properties, which resemble those of 3-methyluracil. Removal of the O-methyl group with hydrogen bromide in water[30] gave the 5-dihydroxycyclopentyluracils **14** and **15**. After the free hydroxyls of **14** (Scheme II) were protected by acetylation, the 4 position was thiated and compound **17** was methylated to yield **18**. This was subsequently treated with ammonia in methanol to yield 5-dihydroxycyclopentylcytosine (**19**). Compound **11** was mesylated with methanesulfonyl chloride in pyridine to give **20**.

TABLE I
ULTRAVIOLET ABSORPTION AND CHROMATOGRAPHIC PROPERTIES OF PYRIMIDINES

	Spectral data							
	0.1 *N* HCl		0.1 *N* NaOH		$A_{280}:A_{260}$	R_f in solvents		
Compd	mμ	ε × 10^{-3}	mμ	ε × 10^{-3}	at pH 12	A	B	C
8	276 max		318 max					
9	278 max		322.5 max					
10	301 max		346 max					
	259		268					
	276 min		293 min					
	233							
11	264 max	7.7	289 max	6.0	1.52	0.67	0.51	0.66
	234.5 min	2.15	246 min	2.25				
12	263 max	7.0	288 max	10.6	4.48	0.79	0.73	0.81
	236 min	2.05	249 min	0.92				
13	281 max	17.0	261 max	13.0		0.77	0.70	0.70
	241 min	3.15	245 min	10.0				
14	264 max	7.6	289 max	5.7	1.57	0.44	0.28	0.53
	235 min	2.15	246 min	2.15				
15	264 max	7.0	289 max	10.5		0.67	0.55	0.73
	236 min	2.35	250 min	0.98				
16	263 max	8.3	286 max	6.3	1.51	0.85	0.75	0.77
	234 min	2.25	246 min	2.75				
17	332 max	14.7	342 max	11.2		0.87	0.83	0.82
	278 min	1.6	284 min	2.50				
	243 max	3.55						
18	338 max		309 max			0.72	0.51	0.63
	328 min		269 min					
	311 max		246 sh					
	286 min							
	270 max							
	247 min							
	227.5 max							
	223 min							
	212.5 max							
19	286 max	9.2	288 max	7.0		0.43	0.25	0.52
	245 min	0.9	255 min	1.6				
20	263 max	7.8	Unstable			0.72	0.62	0.69
	233 min	2.12						
22	287 max	10.3				0.74	0.61	0.67
	265 min	6.9	In water					
	244 max	13.8						
24	266 max	7.7	291 max	5.6	1.59	0.86	0.83	0.82
	236 min	1.94	247 min	2.07				
27	268 max	8.8				0.76	0.65	0.82
	237 min	1.89						
30	272 max	8.6				0.81	0.71	0.86
	237 min	1.88						

SCHEME II

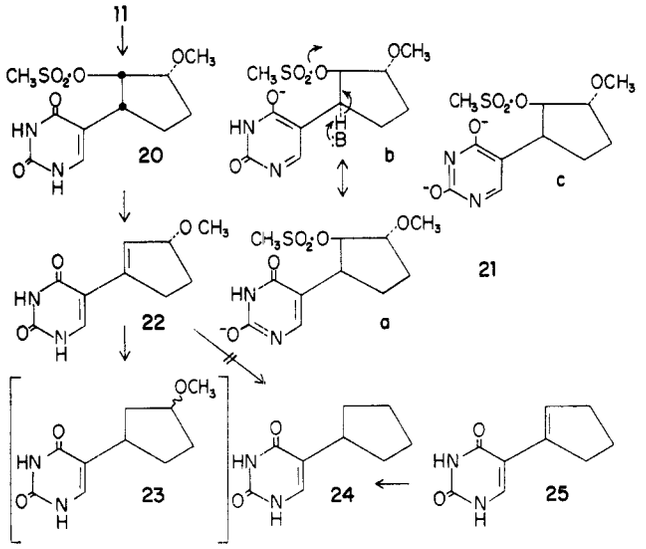


(29) D. J. Brown, "The Pyrimidines," The Chemistry of Heterocyclic Compounds, Vol. 16, John Wiley and Sons, Inc., New York, N. Y., 1962, pp. 42, 43, and 48.

(30) L. Hough and R. S. Theobald, *Methods Carbohydrate Chem.*, **2**, 204 (1963).

In contrast to our previous experience[31] this product proved to be relatively stable and could be recrystallized from hot ethanol. The conversion of **20** (Scheme III) to the olefin **22** was effected by potassium *t*-butoxide (*t*-BuOK) in dimethyl sulfoxide (DMSO).[32] With 2 equiv of base, the reaction required 1 week to reach maximum yield. This slow rate can be rationalized as follows. It has been suggested that the elimination of the sulfonyloxy group is of the E2 variety.[32] Thus only the initial abstraction of the allylic C′-1 hydrogen (as in **21a,b**) could lead to the desired product. However, the formation of the stable pyrimidine dianion (**21c**) as well as the competing favored proton removal from the two methylene carbons C′-4 and C′-5 rather than the C′-1,[33] hinder the reaction. Because facile prototropic rearrangement of allyl ethers to their propenyl analog[34] can occur with *t*-BuOK in DMSO, the position of the double bond in **22** was established by a study of its nmr spectrum. It revealed that the methoxy group as well as the proton on the C′-3 of the alicyclic ring had been retained [shown at δ = 4.5 (broad peak) and 3.23 ppm, respectively] while the signal of the C′-2 proton had shifted downfield (doublet J = 2 Hz, δ = 6.76 ppm). In contrast, if in **22** the double bond were between C′-2 and C′-3 (methyl vinyl ether structure) the C′-2 proton should give rise to a signal at much higher field (*ca.* δ = 4.0 ppm)[35,36] because of the reduction of double-bond character in the vinyl grouping. In addition the ultraviolet spectrum of this compound should be similar to that of uracil. Actually the spectrum of **22** resembles that of **25**.[37] All the evidence is thus consistent with the diene structure for **22**.

SCHEME III



The reduction of **22** was explored as a method for the preparation of **23**.[38] Conceivably the hydrogenolysis of the allylic CH_3O group[39] in **22** could proceed concurrently with the reduction of the alicyclic unsaturated bond leading to **24**. In order to curtail this undesirable side reaction the reduction was carried out with Adams catalyst in the presence of $NaNO_3$ as described by Dart and Henbest.[40] The crude reduction mixture, chromatographed on paper gave a single ultraviolet-absorbing spot different from that of **24**. The ultraviolet spectrum of the water eluent of this spot resembled that of uracil indicating the presence in the reduction mixture of the 5-(3′-methoxycyclopentyl)-uracil(s). A comparison sample of **24** was prepared by hydrogenation of **25**[3] with Raney nickel. The slow reduction was carried out overnight in 10% sodium hydroxide solution. Under those conditions no 1,4 addition of hydrogen to the conjugated system was observed. The ultraviolet properties of the isolated product were similar to those of uracil and in its nmr spectrum the vinyl C-6 proton appeared at the expected range (δ = 7.15 ppm). In contrast the structure of the potential product from 1,4 addition (5,6-dihydro-5-cyclopentylideneuracil) lacks any vinyl protons, although the ultraviolet spectrum of such a compound might still be similar to that of uracil.

The methylated derivatives **27** and **30** were prepared according to the method of Davidson and Baudisch.[41] In an attempt to improve the yield of **27**, the partially methylated products recovered from the reaction mixture was subjected to remethylation. However, only the trimethyl derivative **28** was thus isolated.

B. Infrared Spectra and Interpretations.—Intramolecular hydrogen bonding between hydroxyl groups and a variety of acceptor sites, including weak basic ones such as the π electrons of aromatic or olefinic systems, has been extensively investigated by means of infrared spectroscopy. Such studies have clearly shown that the frequency separation between the free and the bonded OH peaks ($\Delta\nu$) is a measure of the strength of the hydrogen bond or more specifically of its enthalpy.[42,43]

In the neutral species of 5-hydroxyalkylpyrimidines such as **26**, **29**, and **31** there are two potential hydrogen-bonding basic regions, *i.e.*, the C-4 carbonyl and the C-5,C-6 unsaturated bond. Of these the double bond is the weaker base. However, as hydrogen bonding to a double bond has previously been shown with a number of aliphatic unsaturated[13] and aromatic[13-15] alcohols its importance as an acceptor site should be considered. Because of the extremely low solubility of the pyrimidines **26**, **29**, and **31** (Figure 2) in carbon tetrachloride, it was necessary to carry out the present hydrogen-bonding infrared spectral studies with the corresponding N,N-dimethyl derivatives **27**, **30**, and **32**.[44] This methylation does not prohibit the applicability of the results to the parent compounds, since the $\Delta\nu$ values attributable to the electron-donor

(31) In paper II of this series (ref 3) we reported a facile elimination reaction in which the 2′-methanesulfonyloxy derivative of 5-(2′-hydroxycyclopentyl)uracil was converted to 5-(1′-cyclopentenyl)uracil in hot ethanol.

(32) J. P. Horwitz, J. Chua, M. A. Da Rooge, M. Noel, and I. Klundt, *J. Org. Chem.*, **31**, 205 (1966), and references therein.

(33) In agreement with the relative readiness of carbanion formation: T. J. Wallace, J. E. Hofmann, and A. Schriesheim, *J. Am. Chem. Soc.*, **85**, 2739 (1963).

(34) J. Cunningham, R. Gigg, and C. D. Warren, *Tetrahedron Letters*, 1191 (1964).

(35) J. Feeney, A. Ledwith, and L. Sutcliffe, *J. Chem. Soc.*, 2021 (1962).

(36) R. T. Hopgood, Jr., G. S. Reddy, and J. H. Goldstein, *J. Phys. Chem.*, **67**, 110 (1965).

(37) See Table I and ref 3.

(38) Either of the free alcohols derived from 23 should provide data on the effect of the C′-3 hydroxyl upon the spectrum of the uracil moiety.

(39) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, p 10.

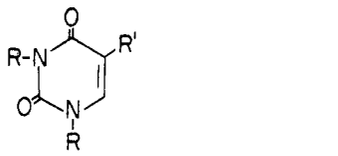
(40) M. C. Dart and H. B. Henbest, *J. Chem. Soc.*, 3563 (1960).

(41) D. Davidson and O. Baudisch, *J. Am. Chem. Soc.*, **48**, 2379 (1926).

(42) R. F. Badger, *J. Chem. Phys.*, **8**, 288 (1940).

(43) M. L. Huggins and G. C. Pimentel, *J. Phys. Chem.*, **60**, 1615 (1956).

(44) The synthesis of **32** was reported in ref 3.



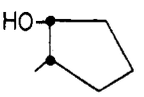
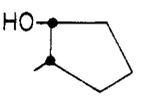
26	R=H	R'=	CH_2OH
27	R=CH_3	R'=	CH_2OH
28	R=CH_3	R'=	CH_2OCH_3
29	R=H	R'=	CH_2CH_2OH
30	R=CH_3	R'=	CH_2CH_2OH
31	R=H	R'=	
32	R=CH_3	R'=	

Figure 2.—Structures of 5-hydroxymethyluracil, 5-hydroxyethyluracil, 5-hydroxycyclopentyluracil, and the corresponding methylated derivatives.

ability of methyl groups were found, from the increased hydrogen-bond basicity upon alkylation of aromatic hydrocarbons,[45] to be small (of the order of *ca.* 10 cm^{-1}).

The infrared spectra of **27**, **30**, and **32** are depicted in Figure 3. It is clear that very dilute solutions ($<3 \times 10^{-3}$ *M*) of all three compounds, in an inert solvent, display two concentration-independent peaks in the OH-stretching region. These data indicate that all three compounds, in carbon tetrachloride, are highly intramolecularly hydrogen bonded. In the case of **30** and **32**, the relative large value (*ca.* 200 cm^{-1}) of $\Delta\nu$ between the free and bonded peaks indicate a hydrogen bond to a strong base, *i.e.*, the C-4 carbonyl.[46]

The small $\Delta\nu$ (60 cm^{-1}) value for **27** indicates a weak hydrogen bond. This can theoretically be attributed to either a weak bond to the relatively strong basic center of the C-4 carbonyl, or alternatively by a bond to a weak acceptor site such as a π-electron system,[46,13] in this case the C-5, C-6 double bond. From the geometry of the OH· · ·O=C bond, where an unstrained five-membered ring can form and the higher acidity of the allylic hydroxyl, one would expect a strong hydrogen bond, whereas a weak one is observed. On the other hand a weak bond to the π-electron system is equally permissible stereochemically, and is a possible explanation of the hydrogen bonding observed.

It is assumed that the same types of hydrogen bonding occur in the unmethylated pyrimidines **26**, **29**, and **31**. Although the hydrogen bonding observed in carbon tetrachloride does not necessarily occur in polar solvents, it is clear that the factor of OH· · ·π-hydrogen bonding should be considered in interpreting the properties of the 5-hydroxyalkylpyrimidines.

It has been unequivocally shown[47-49] that the mono-

(45) M. Tamres, *J. Am. Chem. Soc.*, **74**, 3375 (1952).
(46) A. W. Baker and A. T. Shulgin, *ibid.*, **80**, 5358 (1958).
(47) K. Nakanishi, N. Sujuki, and F. Yamazaki, *Bull. Chem. Soc. Japan*, **34**, 53 (1961).
(48) K. L. Wierzchowski, E. Litonska, and D. Shugar, *J. Am. Chem. Soc.*, **87**, 4621 (1965).
(49) E. Wittenburg, *Ber.*, **99**, 2391 (1966).

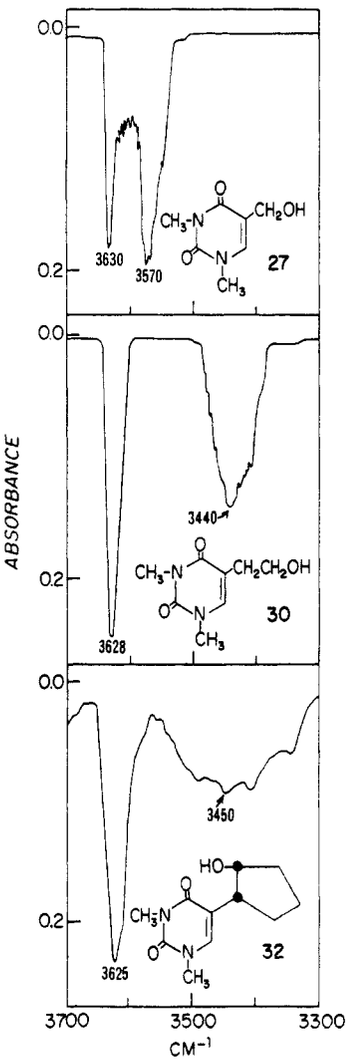


Figure 3.—Infrared hydroxyl absorption of some 5-hydroxyalkyluracils.

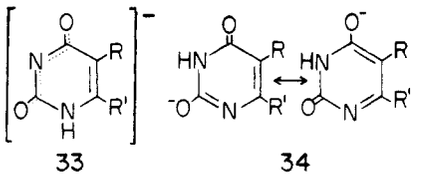


Figure 4.—Tautomeric structures of the uracil monoanion.

anions of uracil and thymine each consist of an equilibrium mixture represented by the tautomeric forms **33** and **34** (Figure 4). The ultraviolet spectrum of each of these corresponds to that of the monoanion of a monomethyl derivative. From comparative studies of the ultraviolet absorption of uracil and thymine derivatives in mixture of dioxane–water (Shugar, *et al.*[48]) have concluded that structure **34** in which the distribution of charge density is more equally dispersed throughout the molecule, is the less polar one.

With regard to the ultraviolet absorption properties of the uracil moiety in the 5-hydroxyalkylpyrimidines, hydrogen bonding to the C-5,C-6 double bond may conceivably interfere with the polarization of the molecule. Any condition that favors a delocalization of the electron density along the system ($O{=}C_4{=}C_5{=}C_6{=}N_1{=}C_2{=}O)^-$ would lead to a shift of equilibrium

of the monoanions toward the **34** form. In comparing the ultraviolet spectra of **26**, **29**, **31**, and **14** at pH 11–12, we observed that the favored (75%) monoanion of **26** is represented by structure **34** while that of all the others is an almost equimolar equilibrium mixture of both forms **33** and **34**. We propose that this difference could be interpreted by postulating an intramolecular hydrogen bond with the pyrimidine double bond in hydroxymethyluracil (**26**). The effect of such a hydrogen bond could be an attraction of charge away from the system $(O{=}C_4{=}N_3{=}C_2{=}O)^-$ with **34** becoming the predominant form.

From infrared spectra it has been shown that weak intramolecular hydrogen bonding occurs in **27**, and a stronger type in **30** and **32**. Variations in the strength of bonding to a single site, such as the C-4 carbonyl, do not correlate with the ultraviolet changes observed since a stronger hydrogen bond in **27** would predict a higher $A_{280}:A_{260}$ ratio, whereas a lower is observed. An alternative hydrogen-bonding site in the 5-hydroxymethyluracil, such as the π electrons, correlates with the observed ultraviolet and infrared differences.

Experimental Section

Melting Points.—All melting points were determined with a Mel-Temp apparatus calibrated to 235° and are uncorrected above that temperature.

Paper Chromatography.—Ascending technique on Whatman No. 1 paper was used with the solvents (A) *n*-BuOH–HOAc–H_2O (60:15:25), (B) *n*-BuOH–H_2O (85:15), and (C) *i*-PrOH–H_2O–NH_4OH (70:20:10).

Nmr spectra were measured with a Varian A-60 spectrometer. DMSO with tetramethylsilane as the internal standard was used as a solvent unless it is indicated otherwise.

Infrared spectra were recorded with a Perkin-Elmer Model 221 spectrophotometer. Solutions of the compounds in Spectrograde carbon tetrachloride freshly distilled over P_2O_5 were used. The concentrations were less than 0.003 *M*.

(*trans*-2,3-Dihydroxycyclopentyl)acetic Acid *γ*-*cis*-Lactone (3).—To a well-stirred mixture of 12.6 g (1×10^{-1} mole) of 2-cyclopentenyl-1-acetic acid and 84.6 ml of formic acid (97–100%) was added 11.8 g of 30% hydrogen peroxide solution dropwise (within *ca.* 3 min) while the temperature was kept at *ca.* 20–23°. Within 10 min a spontaneous exothermic reaction occurred (temperature rising to *ca.* 35°). After it had subsided, the mixture was maintained at 40° for 3 hr and then at room temperature overnight. The excess peroxide was carefully decomposed completely by stirring with palladium catalyst (5% on carbon) and the mixture was filtered and concentrated *in vacuo*. The remaining oil was refluxed with 100 ml of water for about 5 hr after which the solution was reconcentrated and the residue was distilled. The fraction boiling at 89–95° (75×10^{-3} mm) was collected (12.6 g, 88.5%). Several batches of the crude material were combined and redistilled. The pure product was collected at 112–123° (85×10^{-3} mm), $n^{25}D$ 1.4957.

Anal. Calcd for $C_7H_{10}O_3$: C, 59.12; H, 7.08. Found: C, 59.06; H, 7.17.

(*trans*-2-Hydroxy-3-methoxycyclopentyl)acetic Acid *γ*-*cis*-Lactone (5).—To a refluxing solution of 14.2 g (1×10^{-1} mole) of **3** in 31.2 ml (5×10^{-1} mole) of methyl iodide, 28.9 g (1.25×10^{-1} mole) of silver oxide was added in ten equal portions at 0.5-hr intervals. Heating and refluxing was continued for several hours after the final addition. The mixture was then cooled and filtered; the solids were extracted thoroughly by boiling with chloroform. The combined filtrates were dried and concentrated *in vacuo*. The residue was remethylated once more under the same conditions except that 14.5 g of silver oxide was used. The final residue was fractionated. The product was collected at 67–68° (100×10^{-3} mm), yield 13.98 g (89.5%), $n^{20}D$ 1.4737.

Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74; CH_3O, 19.87. Found: C, 61.62; H, 7.75; CH_3O, 20.22.

(*trans*-2-Hydroxy-3-triphenylmethoxycyclopentyl)acetic Acid *γ*-*cis*-Lactone (4).—To a solution of 650 mg (4.57×10^{-3} mole) of **3** in 10 ml of dry pyridine was added 1.4 g (4.95×10^{-3} mole) of chlorotriphenylmethane. The yellow mixture was stirred overnight and then left at room temperature for 12 days. The pyridine was removed *in vacuo*, the residue was washed with ethanol, and the solvents were again evaporated similarly. The residue was triturated with chilled water. The aqueous layer was poured off and the trituration was repeated. The remaining solid was dried and then extracted well first with ether and then with benzene. The combined extracts were concentrated *in vacuo* to give a yellow solid which upon recrystallization from ether gave tannish crystals: yield 76 mg (9%), mp 149–153°.

Anal. Calcd for $C_{26}H_{24}O_3$: C, 81.22; H, 6.29. Found: C, 81.09; H, 6.14.

α-Hydroxymethylene-(*trans*-2-hydroxy-3-methoxycyclopentyl)acetic Acid *γ*-*cis*-Lactone, Sodium (6).—To a cooled stirred suspension of 540 mg (1×10^{-2} mole) of sodium methylate in 30 ml of dry ether, a mixture of 1.56 g (1×10^{-2} mole) of the lactone **5** and 1.2 g (2×10^{-2} mole) of methyl formate was added dropwise. In *ca.* 15 min a cream-colored solid began separating. The mixture was stirred in the cold overnight and then filtered. The solid was washed well with ether and dried: yield 1.72 g.

α-Hydroxymethylene-(*trans*-2-hydroxy-3-methoxycyclopentyl)acetic Acid *γ*-*cis*-Lactone (7).—Compound **6** (824 mg, 4×10^{-3} mole) was dissolved in 4–5 ml of cold water and the solution was acidified with a few drops of concentrated hydrochloric acid. Crystalline material separated at this stage. The mixture was continuously extracted with ether. The ether extract was dried with Na_2SO_4 and concentrated to a small volume. Petroleum ether (bp 30–60°) was added to induce turbidity and the mixture was chilled. The product was filtered, washed with petroleum ether, and dried: yield 560 mg (67%), mp 106–107°. It was recrystallized once more from the same system without a change in the melting point.

Anal. Calcd for $C_9H_{12}O_4$: C, 58.68; H, 6.57. Found: C, 58.65; H, 6.56.

2,4-Dinitrophenylhydrazone.—A small sample of **6** dissolved in a few drops of water was added to a solution of 2,4-dinitrophenylhydrazine in 2 *N* hydrochloric acid. The yellow derivative separated promptly. After standing in the cold for a few hours, it was filtered, washed well with water, and dried *in vacuo*. It was recrystallized twice from ethanol–water yielding small yellow crystals that melted at 124–127°.

Anal. Calcd for $C_{15}H_{16}N_4O_7$: N, 15.38. Found: N, 15.46.

α-Carbamyliminomethylene-(*trans*-2-hydroxy-3-methoxycyclopentyl)acetic Acid *γ*-*cis*-Lactone (8), α-N-Methylcarbamyliminomethylene-(*trans*-2-hydroxy-3-methoxycyclopentyl)acetic Acid *γ*-*cis*-Lactone (9), and α-Thiocarbamyliminomethylene-(*trans*-2-hydroxy-3-methoxycyclopentyl)acetic Acid *γ*-*cis*-Lactone (10).—The sodium derivative **6** (1 equiv) was added in small portions to a cold solution of the corresponding urea (2 equiv) in 3 *N* hydrochloric acid. The resulting mixture was stirred at room temperature overnight. The precipitated product was collected, washed well with water, and dried *in vacuo*.

Compound 8 yielded 77.5% and was recrystallized from methanol in elongated plates that melted at 243–244°.

Anal. Calcd for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.24; N, 12.38. Found: C, 52.79; H, 6.03; N, 12.31.

Compound 9 yielded 76% and was recrystallized from methanol in small plates that melted at 210–212°.

Anal. Calcd for $C_{11}H_{16}N_2O_4$: C, 54.99; H, 6.71; N, 11.66. Found: C, 55.59; H, 6.83; N, 11.46.

Compound 10 yielded 74.5% and was recrystallized from methanol in small rosettes that melted at 222–223.5°.

Anal. Calcd for $C_{10}H_{14}N_2O_3S$: N, 11.56; S, 13.23. Found: N, 11.36; S, 13.11.

2,4-Dihydroxy-5-(*trans*-2′-hydroxy-3′-methoxycyclopentyl)-pyrimidine (11), 2,4-Dihydroxy-5-(*trans*-2′-hydroxy-3′-methoxycyclopentyl)-3-methylpyrimidine (12), and 4-Hydroxy-5-(*trans*-2′-hydroxy-3′-methoxycyclopentyl)-2-mercaptopyrimidine (13).—Compound **8**, **9**, or **10** was refluxed with a solution of 2 equiv of sodium in dry ethanol for about 6 hr. The sodium salt of **11** precipitated during the course of the reaction, while the corresponding derivatives of **12** and **13** remained in solution. The solvent was removed *in vacuo* and the white solid residue was dissolved in a small volume of cold water. In the case of **11** and **13** the crude product precipitated from this water solu-

tion after acidification with glacial acetic acid. The mixture was chilled, filtered, washed with water, and dried *in vacuo*. The aqueous solution of the sodium salt of **12** was neutralized with Amberlite IRC-50 (20–50 mesh, H^+) and then taken to dryness *in vacuo*.

Compound 11 yielded 89% and after recrystallization from boiling methanol gave white crystals melting at 263–264°.

Anal. Calcd for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.24; N, 12.38. Found: C, 53.20; H, 6.35; N, 12.44.

Compound 12 yielded 61.5% and was recrystallized from methanol to give white rosettes, melting at 192–193°.

Anal. Calcd for $C_{11}H_{16}N_2O_4$: C, 54.99; H, 6.71; N, 11.66. Found: C, 55.02; H, 6.80; N, 11.62.

Compound 13 yielded 90% and recrystallization from methanol gave small white needles, melting at 252–254°.

Anal. Calcd for $C_{10}H_{14}N_2O_3S$: N, 11.56; S, 13.23. Found: N, 11.50; S, 13.28.

2,4-Dihydroxy-5-(*trans*-2′,3′-dihydroxycyclopentyl)pyrimidine (14), and 2,4-Dihydroxy-5-(*trans*-2′,3′-dihydroxycyclopentyl)-3-methylpyrimidine (15).—A suspension of 2.73 g (12×10^{-3} mole) of **11** in *ca.* 10 ml of H_2O or a solution of 400 mg (1.65×10^{-3} mole) of **12** in 4 ml of H_2O in a combustion tube was saturated with HBr at −20°. The tube was sealed and stored in the cold for 4 days. The solution was aerated for several hours and neutralized by passing through a column of Amberlite IR-45 (20–50 mesh, OH^-). The column was washed repeatedly until the ultraviolet absorption of the eluent was negligible. The combined eluents were taken to dryness *in vacuo*.

Compound 14.—The residue was dissolved in *ca.* 100 ml of boiling water, and the solution was filtered and concentrated to one-half of the volume *in vacuo*. Chilling gave 2.19 g (86%) of white needles melting at 296–298°.

Anal. Calcd for $C_9H_{12}N_2O_4$: C, 50.94; H, 5.70; N, 13.20. Found: C, 51.04; H, 5.63; N, 13.19.

Compound 15.—The residue was dissolved in hot methanol, and the solution was charcoaled (Norit), filtered, concentrated *in vacuo*, and cooled to give small white rosettes: yield 260 mg (69%), mp 232–237°.

Anal. Calcd for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.24; N, 12.38. Found: C, 53.03; H, 6.23; N, 12.41.

2,4-Dihydroxy-5-(*trans*-2′,3′-diacetoxycyclopentyl)pyrimidine (16).—Compound **14** (2.63 g, 12.4×10^{-3} mole) was suspended in 100 ml of dry pyridine and 24.4 ml (258×10^{-3} mole) of acetic anhydride was added with stirring. The mixture was stirred at room temperature overnight. After addition of some cold water, the solvents were evaporated *in vacuo*. The residue was treated with 10 ml of water and cooled for several hours. The crude product was then filtered, washed with a small volume of cold water, and dried *in vacuo* over P_2O_5 and KOH: yield 3.54 g (96%). Recrystallization from methanol gave white needles melting at 256–257°.

Anal. Calcd for $C_{13}H_{16}N_2O_6$: C, 52.70; H, 5.44; N, 9.46. Found: C, 52.55; H, 5.43; N, 9.49.

2-Hydroxy-5-(*trans*-2′,3′-diacetoxycyclopentyl)-4-mercaptopyrimidine (17).—Compound **16** (1.40 g, 4.73×10^{-3} mole) was dissolved in 50 ml of dry pyridine and 576 mg (2.6×10^{-3} mole) of P_2S_5 was added. The yellow solution was refluxed for 8 hr. The solution was evaporated to a yellow oil which upon addition of a small volume of water solidified. After cooling for several hours, the crude materal was filtered, washed with water, and dried *in vacuo*. It contained a small amount of starting material. Two recrystallizations, once from water and once from methanol–water, gave the pure product as small yellow crystals melting at 238–239°: yield 600 mg (41%).

Anal. Calcd for $C_{13}H_{16}N_2O_5S$: N, 8.97; S, 10.27. Found: N, 9.06; S, 10.34.

2-Hydroxy-5-(*trans*-2′,3′-dihydroxycyclopentyl)-4-methylmercaptopyrimidine (18).—The thione **17** (220 mg, 7.1×10^{-4} mole) was dissolved in 2.35 ml (2.34×10^{-3} mole) of 1 *N* NaOH, 0.05 ml (113.5 mg, 8×10^{-4} mole) of methyl iodide was added, and the mixture was shaken in a sealed tube overnight. The precipitate was collected, washed with cold water, and dried. The combined filtrates were taken to dryness *in vacuo*, and the residue was triturated with 1 ml of cold water and filtered. An additional small amount of product was thus recovered raising the total yield to 115 mg (67.5%). After recrystallization from water–methanol, the product was washed with acetone and dried *in vacuo:* mp 256–257°.

Anal. Calcd for $C_{10}H_{14}N_2O_3S$: N, 11.56; S, 13.23. Found: N, 11.45; S, 13.24.

4-Amino-2-hydroxy-5-(*trans*-2′,3′-dihydroxycyclopentyl)pyrimidine (19).—A solution of 242 mg (1×10^{-3} mole) of methylmercaptopyrimidine (**18**) in *ca.* 10 ml of dry methanol saturated with ammonia at −10° was heated in a sealed tube at 110° for about 18 hr. After cooling the solvent was evaporated and the residue was recrystallized from wet methanol to yield 200 mg (95%) of product. This started decomposing above 235° and melted at 270°. One more recrystallization from wet methanol did not alter the above melting point.

Anal. Calcd for $C_9H_{13}N_3O_3 \cdot 0.5H_2O$: C, 49.08; H, 6.40; N, 19.08. Found: C, 49.05; H, 6.53; N, 18.63.

2,4-Dihydroxy-5-(*trans*-2′-methanesulfonyloxy-3′-methoxycyclopentyl)pyrimidine (20).—To a cooled suspension of 1.56 g (7.1×10^{-3} mole) of **11** in *ca.* 40 ml of dry pyridine 4.7 ml (61.8×10^{-3} mole) of methanesulfonyl chloride was added with stirring. The mixture was stirred in the cold overnight. Then a few drops of water was added and after an additional 0.5 hr of cooling the solvent was removed *in vacuo* at below 35°. The residue was treated with ethanol and the solvent was again evaporated *in vacuo*. This was repeated several times until the pyridine had been removed as completely as possible. The residue was triturated with *ca.* 70 ml of cold water and the mixture was chilled for several hours and then filtered. The crude product was recrystallized from a large volume of ethanol: yield 1.47 g (67%), mp 174°.

Anal. Calcd for $C_{11}H_{16}N_2O_6S$: N, 9.21; S, 10.54. Found: N, 9.14; S, 10.54.

2,4-Dihydroxy-5-(3-′-methoxy-2′-cyclopentenyl)pyrimidine (22).—A mixture of 608 mg (2×00^{-1} mole) of **20**, 448 mg (4×10^{-3} mole) of *t*-BuOK, and 5 ml of DMSO (freshly distilled over calcium hydride) was stirred at room temperature for 1 week. The mixture was then diluted with an equal volume of chilled water and neutralized to pH 6.5–7.0 with glacial acetic acid. The precipitate that separated was immediately collected by centrifugation. It was washed a few times with cold water, and then with acetone: yield 250 mg (60%). It was recrystallized from a concentrated aqueous ammoniacal solution. It decomposed slowly above 250° without melting.

Anal. Calcd for $C_{10}H_{12}N_2O_3$: C, 57.69; H, 5.81; N, 13.45. Found: C, 57.61; H, 5.86; N, 13.22.

Hydrogenation of 22.—A small sample of **22** was dissolved in *ca.* 2 ml of water with the help of 1 or 2 drops of concentrated ammonia solution. After addition of several crystals of sodium nitrite and Adams catalyst, the mixture was hydrogenated at atmospheric pressure for 20 hr. The reduction of the catalyst proceeded slowly. After filtration the solution was tested by paper chromatography. The system Na_2HPO_4–isoamyl alcohol[50] in addition to the systems A–C described above was used. In all systems no starting material could be detected. The reduction mixture gave one ultraviolet-absorbing spot different from that of **24**, indicating that under the conditions employed no hydrogenolysis of the allylic ether function occurred. The ultraviolet absorption and shift in alkaline solution of the water eluent of this spot were similar to those of uracil. It is presumed that the reduction product of **22** is **23**.

2,4-Dihydroxy-5-cyclopentylpyrimidine (24).—2,4-Dihydroxy-5-(1′-cyclopentenyl)pyrimidine (180 mg, 1×10^{-3} mole)[3] dissolved in 20 ml of 10% sodium hydroxide was reduced overnight at atmospheric pressure in the presence of Raney nickel catalyst. The mixture was filtered, the catalyst was washed well with boiling water, and the combined filtrates were cooled in an ice bath and acidified with glacial acetic acid. White solid separated at this stage. After cooling, it was filtered, washed with cold water, and dried: yield 150 mg (83%). It was recrystallized from *ca.* 100 ml of a saturated aqueous solution of ammonia as small white needles melting at 327°.

Anal. Calcd for $C_9H_{12}N_2O_2$: C, 59.98; H, 6.71; N, 15.55. Found: C, 59.89; H, 6.80; N, 15.40.

5-Hydroxymethyl-1,3-dimethyluracil (27) and 5-hydroxyethyl-1,3-dimethyluracil (30).—Hydroxymethyluracil (852.6 mg, 6×10^{-3} mole) was dissolved in 14.4 ml (14.4×10^{-3} mole) of 1 *N* sodium hydroxide and to this solution 1.36 ml (14.4×10^{-3} mole) of dimethyl sulfate was added. For **30** the corresponding quantities were 780.7 mg (5×10^{-3} mole) of 5-hydroxyethyluracil, 12 ml (12×10^{-3} mole), 1 *N* sodium hydroxide, and 1.14 ml (12×10^{-3} mole) of dimethyl sulfate. In either case, the reaction mixture was heated to boiling when one phase resulted.

(50) G. R. Wyatt, "The Nucleic Acids," Vol. 1, E. Chargaff and J. D. Davidson, Ed., Academic Press Inc., New York, N. Y., 1955, p 243.

After cooling in an ice bath, it was extracted ten times each with an equal volume of chloroform. The combined chloroform extracts were dried over Na_2SO_4 and evaporated *in vacuo* leaving a solid residue.

Compound 27.—The crude product was dissolved in *ca.* 10 ml of methanol; the solution was treated with Norit, and then filtered. After addition of an equal volume of ether and chilling, it gave short white needles: yield 290 mg (28.5%), mp 138–142°.

Anal. Calcd for $C_7H_{10}N_2O_3$: C, 49.40; H, 5.92; N, 16.46. Found: C, 49.68; H, 6.13; N, 16.32.

Compound 30.—The yield of crude product was 500 mg (54.5%). It was recrystallized similarly from methanol–ether as white needles melting at 140–142°.

Anal. Calcd for $C_8H_{12}N_2O_3$: C, 52.16; H, 6.57; N, 15.21. Found: C, 52.23; H, 6.57; N, 15.22.

5-Methoxymethyl-1,3-dimethyluracil (28).—Chromatographic examination of the aqueous phase after extraction of **27** with chloroform indicated the presence of partially methylated products.

In all three systems A–C it gave four well-separated ultraviolet-absorbing spots. The corresponding R_f values were the following: in A 0.70, 0.60, 0.49, 0.39; in B 0.56, 0.48, 0.32, 0.24; and in C 0.76, 0.64, 0.50, 0.36. In all cases the fastest and slowest moving spot corresponded to the product (**27**) and starting material (**26**), respectively. From the chromatogram developed in system A, the spots with R_f's 0.60 and 0.49 were eluted with water and the ultraviolet absorption of the solutions was examined. The spectrum of the extract of the spot with R_f 0.60 resembled that of 3-methyluracil while that of the extract of the spot with R_f 0.49 was similar to that of 1-methyluracil.

After the solvent was evaporated *in vacuo*, the residue was dried and extracted repeatedly with hot methanol until no more ultraviolet-absorbing material remained. The combined alcoholic extracts were taken to dryness and the crystalline residue was remethylated following the procedure described above for **27** and **30**. The solid thus recovered from the chloroform extract was recrystallized twice from methanol–ethyl ether to give 270 mg of short white needles, which on slow heating gave a "wet" solid at 125° that melted at 273–275°.

Anal. Calcd for $C_8H_{12}N_2O_3$: C, 52.16; H, 6.57; N, 15.21. Found: C, 52.19; H, 6.45; H, 15.46.

Registry No.—**3a**, 14181-27-2; **3b**, 14181-50-1; **4**, 14181-28-3; **5**, 14181-29-4; **6**, 14271-28-4; **7**, 14181-30-7; **7** (2,4-dinitrophenylhydrozone), 14181-31-8; **8**, 14181-32-9; **9**, 14181-33-0; **10**, 14181-34-1; **11**, 14181-35-2; **12**, 14181-36-3; **13**, 14181-37-4; **14**, 14181-38-5; **15**, 14181-39-6; **16**, 14181-40-9; **17**, 14181-41-0; **18**, 14181-42-1; **19**, 14181-43-2; **20**, 14181-44-3; **22**, 14181-45-4; **24**, 14271-29-5; **27**, 14181-46-5; **28**, 14181-47-6; **30**, 14181-48-7; **32**, 10082-51-6.

Acknowledgment.—The authors are indebted to Dr. George Bosworth Brown for his encouragement and continued interest, Dr. Robert Cushley for many discussions regarding the interpretation of the nmr spectra, and Mr. Marvin Olsen for recording these spectra.

Schmidt Reaction of Hydroxyquinones

HAROLD W. MOORE AND H. RAYMOND SHELDEN

Department of Chemistry, University of California at Irvine, Irvine, California

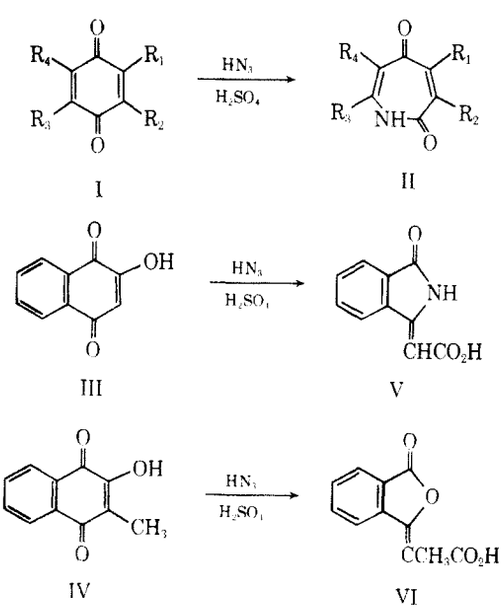
Received April 28, 1967

The reactions of 2-hydroxy-1,4-naphthoquinone and 2-hydroxy-3-methyl-1,4-naphthoquinone with hydrazoic acid were investigated. Both quinones reacted, giving ring contracted products; the former gave 3-oxo-$\Delta^{1\alpha}$-isoindolineacetic acid (V) and the latter gave phthalidine-2-propinoic acid (VI). Mechanisms for these transformations are presented in the text.

In earlier publications it was shown that various alkyl-substituted 1,4-benzoquinones and 1,4-naphthoquinones react with hydrazoic acid in concentrated sulfuric acid to give azepinediones (II).[1–4] Reported here are the results of an investigation of the Schmidt reaction on 2-hydroxy-1,4-naphthoquinone (III) and 2-hydroxy-3-methyl-1,4-naphthoquinone (IV). This study was initiated with the idea of preparing hydroxy-substituted azepinediones which would be attractive synthetic intermediates to the illusive azatropolone ring system. However, instead of the expected ring expansion, ring contraction was realized giving 3-oxo-$\Delta^{1\alpha}$-isoindolineacetic acid (V) from 2-hydroxy-1,4-naphthoquinone (III) and the γ-lactone (VI), phthalidine-2-propionic acid, from 2-hydroxy-3-methyl-1,4-naphthoquinone (IV) (see Scheme I).

Compound V and its decarboxylation product, 2-methylenephthalimidine, have previously been synthesized by a more complex method and were shown to be important synthetic intermediates in the preparation of tetrabenzoporphins.[5–8] The conversion of

SCHEME I



(1) D. Misiti, H. W. Moore, and K. Folkers, *Tetrahedron Letters*, No. 16, 1071 (1965).

(2) D. Misiti, H. W. Moore, and K. Folkers, *Tetrahedron*, **22**, 1201 (1966).

(3) R. W. Richards and R. M. Smith, *Tetrahedron Letters*, No. 22, 2361 (1966).

(4) G. R. Bedford, G. Jones, and B. R. Webster, *ibid.*, No. 22, 2367 (1966).

(5) C. E. Dent, *J. Chem. Soc.*, 1 (1938).

(6) R. P. Linstead and G. A. Rowe, *ibid.*, 1070 (1940).

(7) P. A. Barrett, R. P. Linstead, J. J. Leavett, and G. A. Rowe, *ibid.*, 1076 (1940).

(8) P. A. Barrett, R. P. Linstead, F. G. Rundall, and G. A. P. Tuey, *ibid.*, 1079 (1940).