

*Anal.* Calcd. for  $C_{13}H_{15}N_3O_2$ : C, 63.7; H, 6.2; N, 17.1. Found: C, 63.8; H, 6.25; N, 17.5.

**2-Carboxamido-4-dimethylamino-6-hydroxy-s-triazine.**—To a stirred mixture of 25 ml. of 1 *N* sodium hydroxide solution and 100 ml. of 3% hydrogen peroxide at 75–80°, 3.85 g. of finely powdered 2-cyano-4-dimethylamino-6-hydroxy-s-triazine was slowly added. After the addition, the mixture was stirred for 2.5 hours, cooled and neutralized with dilute acetic acid. A pale yellow precipitate formed which was collected and dried; yield 2.72 g. (64%), m.p. 272°. Recrystallization from ethanol gave colorless crystals, m.p. 287°.

*Anal.* Calcd. for  $C_8H_9N_5O_2$ : C, 39.3; H, 4.95; N, 38.2. Found: C, 39.0; H, 5.2; N, 38.0.

**2-Methyl-4-dimethylamino-6-acetoxy-s-triazine (XIX).**—A mixture of 11.7 g. of 2-cyano-4-dimethylamino-6-hydroxy-s-triazine, excess acetic anhydride, 0.9 g. of anhydrous sodium acetate and 0.2 g. of W-7 Raney nickel<sup>24</sup> was hydrogenated at 40 p.s.i. for 1 hour at 50°. The mixture was filtered, excess acetic anhydride was removed *in vacuo* and the residual liquid allowed to stand overnight. The colorless crystals which deposited (1.3 g., 66%) were recrystallized from benzene; m.p. 200°.

(24) These reaction conditions have been claimed (ref. 13) to effect a mild reduction of nitriles in good yield without secondary amine formation.

*Anal.* Calcd. for  $C_8H_{12}N_4O$ : C, 49.0; H, 6.2; N, 28.6. Found: C, 48.3; H, 6.0; N, 28.75.

**2-Aminomethyl-4-methylthio-6-acetyl-amino-s-triazine.**—A mixture of 1.00 g. of 2-cyano-4-methylthio-6-acetyl-amino-s-triazine, excess acetic anhydride, 0.6 g. of anhydrous sodium acetate and about 0.2 g. of W-7 Raney nickel was hydrogenated at 45 p.s.i. for 2 hours at 50°. The solution was filtered while warm, the acetic anhydride was removed by distillation, and the residue was dissolved in ethanol. Ether was added to the ethanol solution, causing the deposition of 0.91 g. (89%) of pale yellow solid. Recrystallization from ethanol-ether gave light tan-colored crystals, m.p. 211°.

*Anal.* Calcd. for  $C_7H_{11}N_5OS$ : C, 39.4; H, 5.2. Found: C, 39.4; H, 5.3.

**2-Aminomethyl-4-dimethylamino-6-acetyl-amino-s-triazine.**—A mixture of 1.00 g. of 2-cyano-4-dimethylamino-6-acetyl-amino-s-triazine, excess acetic anhydride, 0.6 g. of anhydrous sodium acetate and about 0.2 g. of W-7 Raney nickel was hydrogenated at 43 p.s.i. for 1 hour at 50°. The catalyst was removed by filtration and the acetic anhydride solution was evaporated to dryness, leaving 0.80 g. (78%) of colorless solid. Recrystallization from ethanol-ether gave white crystals, m.p. 159°.

*Anal.* Calcd. for  $C_8H_{14}N_6O$ : C, 45.7; H, 6.7. Found: C, 45.3; H, 6.7.

CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMI CO., PEARL RIVER, N. Y.]

## 1-(Hydroxycyclopentyl)-thymines and Anhydro Derivatives. Evidence for Zwitterionic Structures for Anhydronucleoside Derivatives of Thymine and Uracil<sup>1a</sup>

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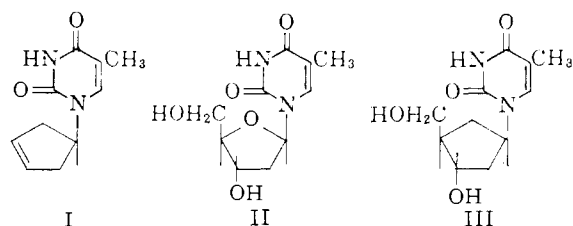
1-(3-Cyclopenten-1-yl)-thymine (I) in strong sulfuric acid unexpectedly isomerized to give a cyclic ether closely related to the anhydronucleosides. Dipole moments and other data strongly suggest that such anhydro compounds are zwitterions such as IVa. Alkaline hydrolysis cleaved the ether linkage of IVa without Walden inversion to give the hydroxycyclopentylthymine XI, while cleavages with trifluoroacetic acid and hydrogen chloride led to hydroxy- and chlorocyclopentylthymines with inverted configurations. The cleavage product with methyl iodide was an iodinated, N-3-methyl derivative VI. In accord with this methylation and other data it is postulated that the inversions of configuration in the acidic cleavages result from the attack of an anion on N-3-protonated intermediates which may be viewed as oxonium ions (*i.e.*, Vb). The olefin I and perbenzoic acid gave a pair of isomeric oxides XIV and XV. Cleavages of the oxide functions with alkali, trifluoroacetic acid, hydrogen, pyridine, hydrogen bromide, methanol, ammonia and hydrogen cyanide led to a variety of hydroxycyclopentylthymines. The respective configurations of the oxides XIV and XV were revealed when it was established that only one of them (XV) could be cyclized to form an anhydro derivative XII. Related cyclizations occurred with halogenated compounds (VII and XVII) in the presence of a hindered amine, and with the olefin I and N-bromoacetamide.

Preceding papers describe syntheses leading to 1-(3-cyclopenten-1-yl)-thymine (I).<sup>1b</sup> This report describes the conversion of I to a variety of hydroxycyclopentylthymines, cyclopentane counterparts of thymidine (II) desired as potential anticancer or mutagenic agents. A stereospecific synthesis of 1-(*trans*-3-hydroxy-*cis*-4-hydroxy-methylcyclopentyl)-thymine (III) is reported separately.<sup>2</sup>

The synthesis of III involved a Prins condensation of the olefin I with formaldehyde in acetic acid. Part of the present report deals with the product of an unexpected reaction which occurred in an early attempt to accomplish this condensation in 83% sulfuric acid. In this case the product was not III, but an isomer of the starting olefin.

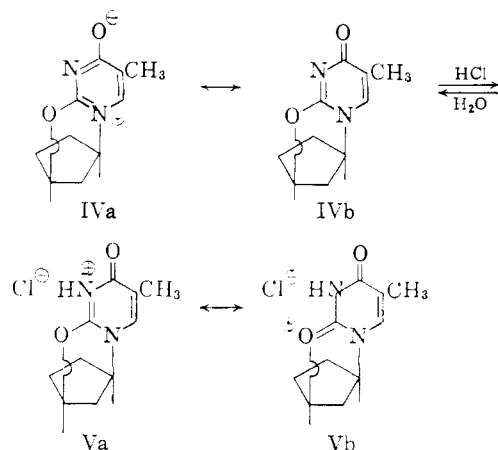
(1) (a) Preliminary communication: K. C. Murdock and R. B. Angier, *Tetrahedron Letters*, 415 (1962); (b) K. C. Murdock and R. B. Angier, *J. Org. Chem.*, papers in press.

(2) K. C. Murdock and R. B. Angier, "Abstracts, 141st Meeting, American Chemical Society, Washington, D. C., March, 1962," p. 22-N; *J. Am. Chem. Soc.*, **84**, 3758 (1962).



It was found that the isomerization also proceeded rapidly and smoothly at room temperature in the absence of the formaldehyde (79% yield). The product showed an altered ultraviolet absorption pattern in which the maximum of the thymine group at 272 m $\mu$  was gone and a pair of new maxima were present at 230 and 258 m $\mu$ . The infrared absorption spectrum was also strikingly different, with new, strong, sharp peaks at 6.02, 6.16 and 6.55  $\mu$ , and without the 3.16 and 14.3  $\mu$  peaks characteristic of the -NH and olefinic groups of the starting material. These spectral properties and

other physical and chemical properties described below indicate that the isomerization product is IV, a counterpart of the pyrimidine anhydronucleosides prepared from nucleoside sulfonates, halides or phosphates by Todd<sup>3</sup> and Fox<sup>4</sup> and their co-workers, and by others.<sup>2,5,6</sup>



Todd and Michelson<sup>3a</sup> initially represented such pyrimidine anhydronucleosides with zwitterionic structures analogous to IVa, but they and other workers have since tacitly rejected dipolar representations in favor of covalent formulas akin to IVb. A choice between the alternative structures IVa and IVb should be clear-cut, since physical properties reflecting the actual type of bonding in IV would not be obscured by effects due to the hydroxyl groups or other substituents usually present in anhydronucleosides. In contrast with I, an isomer with structure IVb should have a lower crystal lattice stability due to the absence of a hydrogen atom suitable for hydrogen bonding, and therefore should be considerably more soluble in non-polar solvents. Actually, just the opposite was true, *i.e.*, the isomerization product showed salt-like solubility behavior, in accord with that to be expected from zwitterionic structures such as IVa.<sup>7a</sup> In chloroform it dissolved to an extent of just 2%, compared to 33% for I (wt./wt. at 23°). Solu-

bility in dimethylformamide was similarly low, and in acetone, ether and benzene it was almost nil. Unlike III, it was freely soluble in water. Data from paper chromatography were confirmatory. Experience with a variety of 1-substituted thymines and other compounds in the system butanone-water, 9:1, has shown that the most polar compounds have the lowest  $R_f$  values.<sup>2,8</sup> The  $R_f$  values obtained concurrently for I and IV were 0.81 and 0.20, respectively. Finally, the dipole moment of IV was found to be 8.2 D., which compares with a calculated value of only 3.8 D. for the covalent structure IVb.<sup>9</sup> Thus the physical properties of IV indicate that it is even more polar than phenylsydnone and related 5-membered heterocycles, compounds with valency requirements allowing them to be represented plausibly *only* with zwitterionic structures.<sup>7b</sup>

It is to be noted that because of the symmetry in the olefin I the cyclization product IV could have been represented with the ethereal oxygen atom extending to either C-3 or C-4 of the cyclopentane ring, representing either of the optical isomers that must be present as a racemic mixture. Similar considerations hold for all of the other compounds pictured in this report.

Hydrolytic cleavage of the "ether" linkage of IV with dilute sodium hydroxide at 100° gave an 84% yield of 1-(*cis*-3-hydroxycyclopentyl)-thymine (XI, Chart I). In contrast to results with anhydronucleosides, this alkaline hydrolysis did not occur at room temperature (*cf.* ref. 3a), nor did IV react in solution with other basic reagents (*cf.* ref. 3c,d,4a,d) under non-aqueous conditions. The reaction systems tested included (a) anhydrous hydrazine, 63 hr. at *ca.* 24°; (b) anhydrous ammonia in methanol, 14 hr. at 100°; (c) liquid ammonia, 14 hr. at 100°; (d) aniline, 14 hr. at 100°; and (e) 0.1 *N* sodium methoxide in methanol, 16 hr. at 67°.

The reactivity of IV toward electrophilic reagents is much greater and is coupled with some interesting inversions of configuration. Tetrahydrofuran is cleaved by acetyl chloride in the presence of zinc chloride to give 4-chlorobutyl acetate.<sup>10</sup> But with IV, acetyl chloride and no added catalyst, 1-(*trans*-3-chlorocyclopentyl)-thymine (VII) was obtained in 81% yield. This chloro derivative was cyclized back to the anhydro compound IV by the action of a hindered amine (diisopropylmethylamine) in dimethylformamide at 100°. This cyclization presumably proceeds *via* an internal nucleophilic displacement requiring the

(8) These  $R_f$  values are listed in the first paragraph of the Experimental section. Inspection of data tabulated by Todd and Michelson (ref. 3a, p. 822) shows that the system 1-butanol-water, 86:14, also gives characteristically low  $R_f$  values for anhydronucleosides.

(9) In a control study the observed and calculated values for the olefin I were in reasonably good agreement, 3.9 and 3.4 D., respectively. For these dipole moment studies we thank Mr. R. J. Best of the Research Division, American Cyanamid Co., Stamford, Conn. Because of solubility limitations the measured figures were obtained from 2% solutions in chloroform. Calculated figures were obtained by summation of dipole group values from the literature. The literature values were from benzene solutions, known to give results 5-20% lower than chloroform solutions.

(10) M. E. Synerholm, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 187.

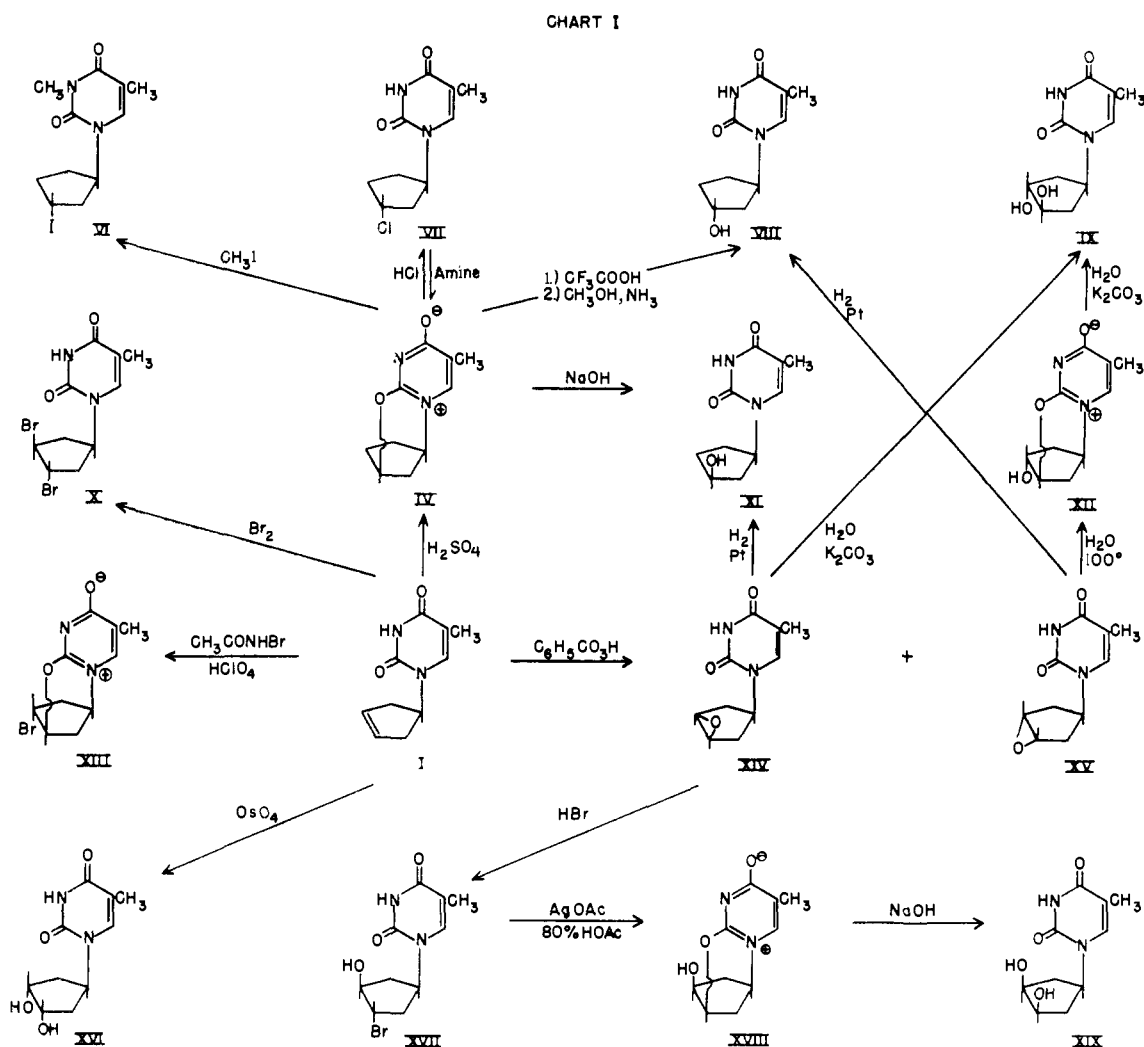
(3) (a) A. M. Michelson and A. R. Todd, *J. Chem. Soc.*, 816 (1955); (b) D. M. Brown, A. Todd and S. Varadarajan, *ibid.*, 2388 (1956); (c) D. M. Brown, A. R. Todd and S. Varadarajan, *ibid.*, 868 (1957); (d) D. M. Brown, D. B. Parihar, A. Todd and S. Varadarajan, *ibid.*, 3028 (1958); (e) D. M. Brown, D. B. Parihar and A. Todd, *ibid.*, 4242 (1958).

(4) (a) J. J. Fox and I. Wempen in *Adv. Carbohydrate Chem.*, **14**, 214 (1959); (b) J. J. Fox, N. Yung and A. Bendich, *J. Am. Chem. Soc.*, **79**, 2775 (1957); (c) J. J. Fox, J. F. Codington, N. C. Yung, L. Kaplan and J. O. Lampen, *ibid.*, **80**, 5155 (1958); (d) J. F. Codington, R. Fecher and J. J. Fox, *ibid.*, **82**, 2794 (1960); (e) R. Fecher, J. F. Codington and J. J. Fox, *ibid.*, **83**, 1889 (1961); (f) N. C. Yung and J. J. Fox, *ibid.*, **83**, 3060 (1961).

(5) (a) E. R. Walwick, W. K. Roberts and C. A. Dekker, *Proc. Chem. Soc.*, 84 (1959); (b) G. Shaw and R. N. Warren, *J. Chem. Soc.*, 50 (1959); J. P. Horwitz and A. J. Tomson, Abstracts of Papers, American Chemical Society Meeting, Chicago, Ill., Sept., 1961, p. 14-O.

(6) R. Letters and A. M. Michelson, *J. Chem. Soc.*, 1410 (1961); E. J. Reist, *et al.*, *J. Am. Chem. Soc.*, **83**, 2208 (1961).

(7) (a) In addition to IVa and IVb there are probably a number of other contributing resonance forms. These would include another aromatic Kekulé form and structures with negative charge on N<sub>3</sub> and/or positive charge on the ethereal oxygen atom; (b) W. Baker and W. D. Ollis, *Quart. Rev.*, **11**, 15 (1957).



indicated *trans* relationship<sup>2,3a,11</sup> of the chloro substituent and the thymine group. (A hindered amine was chosen for use as an acid binder so that it would be resistant to alkylation by the chloro compound VII (*cf.* ref. 12)).

As might be expected, the chloro compound VII was also formed by the reaction of the anhydro compound IV with dry hydrogen chloride in hot chloroform. When the hydrogen chloride was introduced, a crystalline material separated which finally dissolved just before the reaction was terminated. It was found that this crystalline intermediate was a strongly acidic, water-soluble substance. When first prepared it gave an ultraviolet absorption spectrum in water which was identical with the spectrum of the starting anhydro compound. On storage the solid salt gradually rearranged until it was identical with the above covalent chloro compound VII. It is probable that the intermediate is a hydrochloride such as Va,

(11) G. E. McCasland, R. K. Clark, Jr., and H. E. Carter, *J. Am. Chem. Soc.*, **71**, 637 (1949); S. Winstein and R. Boschan, *ibid.*, **72**, 4669 (1950); J. Sicher, *et al.*, *Coll. Czech. Chem. Comm.*, **26**, 2418 (1961); compare R. N. Boyd and R. C. Rittner, *J. Am. Chem. Soc.*, **82**, 2032 (1960).

(12) (a) E. L. Carpenter, U. S. Patent 2,453,062, June 4, 1946; (b) S. Hünig and M. Kiessel, *Chem. Ber.*, **91**, 380 (1958).

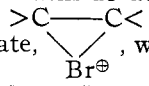
in which a proton is affixed to N-3<sup>13a</sup>; attack by chloride ion to give VII with an inversion of configuration may be explained on the basis of a contributing resonance form such as Vb, in which positive charge on the ether-like oxygen atom enables the thyminyloxy residue to behave as a "leaving group" akin to methanesulfonyloxy or halogen functions.<sup>13b,c</sup>

In support of the view that IV is protonated at N-3 it was found that IV reacted with methyl iodide to give a 3-methyl, iodinated derivative VI. The

(13) (a) Analogously, ultraviolet absorption studies show that in acid 1-methyl-4-pyrimidone (which may really be a zwitterion) is protonated on N-3 rather than on the oxygen atom (D. J. Brown, E. Hoerger and S. F. Mason, *J. Chem. Soc.*, 211 (1955)). (b) A reaction which appears to be related to the rearrangement of this hydrochloride is the pyrolysis of optically active 2-butyl acetimidate hydrochloride. This reaction gave 2-butyl chloride with an inversion of configuration (C. L. Stevens, D. Morrow and J. Lawson, *J. Am. Chem. Soc.*, **77**, 2341 (1955)). F. Cramer and co-workers have demonstrated that alkyl trichloroacetimidates very readily undergo such inversion reactions with various acids (*Chem. Ber.*, **92**, 370 (1959); **91**, 1555 (1958)). (c) After the present investigation was finished there appeared a communication establishing an inversion of configuration in the reaction of 2,2-anhydro-1-(β-D-ribofuranosyl)-uracil with hydrogen fluoride, a reaction analogous to the synthesis of VIIIa. Similar reactions with hydrogen chloride and hydrogen bromide were also reported and presumably these also occur with inversion [J. F. Codrington, I. Doerr, D. Van Praag, A. Bendich and J. J. Fox, *J. Am. Chem. Soc.*, **83**, 5030 (1961)].

positional assignment of the methyl group to N-3 rather than to an oxygen atom was made on the basis of spectral evidence. A maximum at 271  $m\mu$  was typical of 1-substituted thymines except that it was virtually unchanged by alkali, indicating that the compound could not form an enolate salt. The infrared spectrum was also typical except for the expected absence of an  $-NH$  peak at 3.15  $\mu$ . In the above methylation reaction it is interesting to note that an apparently ionic reactant gave a covalent product, just the reverse of the usual pattern in the reaction of methyl iodide with pyridines or tertiary aliphatic amines.

The anhydro compound IV was relatively more basic than the olefin I. In a potentiometric titration in acetic acid solution Compound I was neutral toward perchloric acid while IV could be titrated quantitatively. Nevertheless, IV was apparently protonated only under very strongly acidic conditions; an altered ultraviolet absorption spectrum was obtained with concentrated sulfuric acid (maxima at 227 and 277  $m\mu$ ), but with 13.5  $N$  sulfuric acid the spectrum was almost the same as it was with water. Correspondingly, the results from acidic hydrolyses of IV were found to be dependent on the degree of acidity of the medium. With 0.1  $N$  sulfuric acid a mixture of products was formed. A cleavage product with an inverted configuration, the *trans*-alcohol VIII, was finally isolated in only 11% yield. Reported hydrolyses of anhydronucleoside derivatives in dilute acid have given both inversions<sup>3e,4b,d</sup> and retentions of configuration.<sup>3b,e,4c,d,e</sup> In one case it was shown that both types of reaction occurred concurrently.<sup>3e</sup> This suggests that both protonated and unprotonated species can exist together and then suffer hydrolyses by different mechanisms. In an attempt to exclude non-protonated species, IV was heated for an hour in a strong acid, trifluoroacetic acid (b.p. 72°). Excess acid was removed by evaporation and the presumed trifluoroacetate intermediate was subjected to methanolysis with methanolic ammonia during one hour at room temperature. Removal of volatile material then gave the *trans*-alcohol VIII in high purity (76% yield).

Bromine reacts readily with the 5,6-double bond of 2,4-dioxypyrimidines,<sup>14</sup> but it was found that the olefin I could be brominated selectively to give the *cis,trans*-dibromo derivative X. With *N*-bromoacetamide used as a source of hypobromous acid<sup>15</sup> the adduct with the olefin I was not a bromohydrin (*i.e.*, XVII), but a brominated anhydro compound, probably XIII. The presence of a cyclized, anhydro structure was apparent from analyses and spectral comparisons. Cyclization *via* an internal backside attack on a bromonium ion<sup>16</sup> intermediate, , would leave the bromine atom *trans* as in XIII.<sup>17</sup>

(14) See S. Y Wang, *J. Org. Chem.*, **24**, 11 (1959), for examples and leading references.

(15) J. Fried and E. F. Sabo, *J. Am. Chem. Soc.*, **79**, 1130 (1957).

(16) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 147.

(17) (a) Similar stereochemistry has been established for halocyclization reactions of  $\beta,\gamma$ - and  $\gamma,\delta$ -olefinic acids (ref. 17b) and steroidal

The cyclopentene oxides XIV and XV were desired as likely intermediates<sup>18</sup> for the synthesis of a variety of hydroxycyclopentylthymines. Reaction of the olefin I with perbenzoic acid gave a pair of isomeric oxides; the yields of the higher-melting and lower-melting isomers were 53 and 26%, respectively. A small amount of a third compound was also obtained, with a composition and spectral properties corresponding to the addition of a molecule of perbenzoic acid to the 5,6-double bond in the pyrimidine ring of one of the above oxides. In reactions with basic and acidic reagents intended to differentiate the oxide isomers it was found that only the lower-melting isomer cyclized to form a hydroxy anhydro compound XII, establishing that this was the *trans,trans*-oxide XV. Both the hydroxy anhydro compound XII and the *cis,cis*-oxide XIV gave the *cis,trans*-diol IX when the basic hydrolyses were more prolonged. The cyclization of the *trans,trans*-oxide XV to XII occurred with great ease. It proceeded readily even in hot water (*cf.* ref. 19).

A trifluoroacetic acid-methanolic ammonia sequence similar to that applied to the anhydro compound IV was also used with the *cis,cis*-oxide XIV, providing a convenient, alternative synthesis of the *cis,trans*-diol IX.

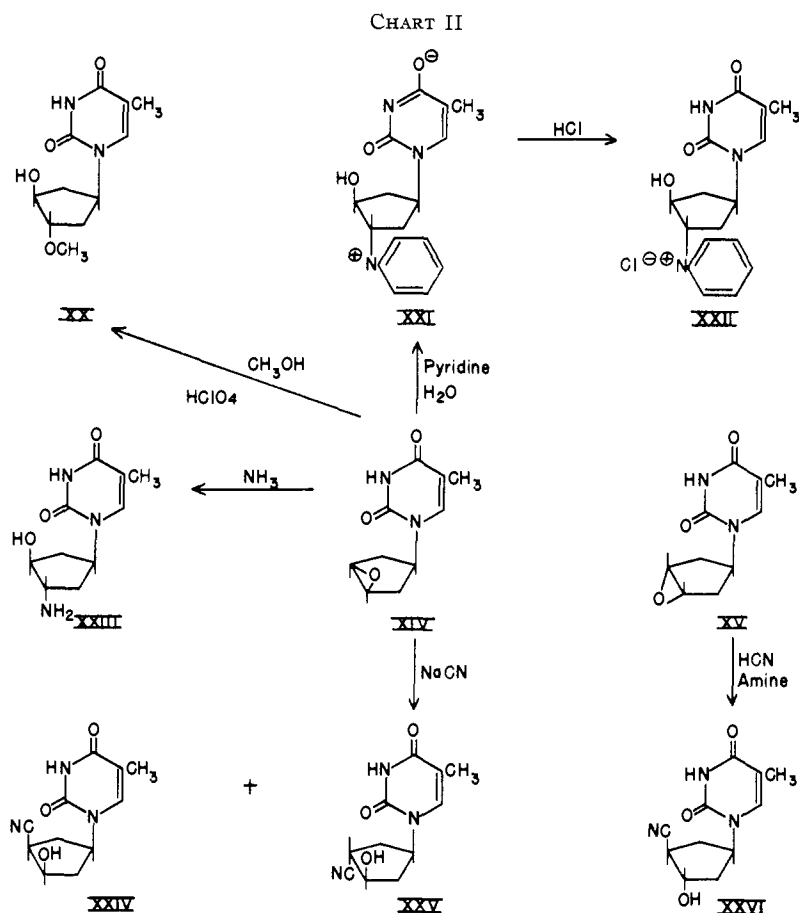
Catalytic reduction of the *cis,cis*- and *trans,trans*-oxides XIV and XV gave the *cis*- and *trans*-alcohols XI and VIII, respectively, confirming the configurational assignments made earlier for these four compounds.

A synthesis of the *cis,cis*-diol XIX proceeded *via* the *trans*-bromo-*cis*-hydroxy derivative XVII, which was made by the reaction of the *cis,cis*-oxide XIV with hydrogen bromide in acetic acid. The yield of XVII was good when the reaction was brief and care was taken to avoid heat during the work-up. Otherwise the major product was the acetate of XVII. Cyclization of XVII to the *cis*-hydroxy anhydro compound XVIII was complete after 72 hours at 100° in dimethylformamide containing diisopropylmethylamine. Some degrada-

olefinic alcohols (ref. 17c); (b) J. Klein, *J. Am. Chem. Soc.*, **81**, 3611 (1959); E. E. van Tamelen and M. Shamma, *ibid.*, **76**, 2315 (1954); R. T. Arnold and K. L. Lindsay, *ibid.*, **75**, 1048 (1953); M. de Moura Campos, *Chem. Ber.*, **93**, 1075 (1960); W. B. Lawson and B. Witkop, *J. Org. Chem.*, **26**, 247 (1961); (c) F. W. Bollinger and N. L. Wendler, *Chemistry & Industry*, 441 (1960); R. D. Hoffsommer, D. Taub and N. L. Wendler, *ibid.*, 251 (1961).

(18) For summaries of the cleavage reactions of olefin oxides and the *trans* stereochemistry known to result from these cleavages see: (a) S. Winstein and R. B. Henderson, "Heterocyclic Compounds," Vol. I, R. B. Elderfield, ed., John Wiley and Sons, Inc., New York, N. Y., 1950, p. 1; (b) R. E. Parker and N. S. Isaacs, *Chem. Revs.*, **59**, 737 (1959); (c) F. H. Newth, *Quart. Revs.*, **13**, 30 (1959); (d) A. D. Cross, *ibid.*, **14**, 317 (1960).

(19) (a) The ease of cyclization of XV and other oxido "acids" with suitable spatial relationships appears to correlate with the acidity of the acid group. Thus certain oxido carboxylic acids cyclized before they could be isolated (ref. 19b). Oxido phenols cyclized on standing or during distillation (ref. 19c) and an oxido alcohol cyclized in the presence of acid or base (ref. 18d, p. 335, ref. 19d). The acidity of XV must be close to that of thymidine (II) which has a  $pK_a$  of 9.8 (ref. 19d); (b) G. Berti, *J. Org. Chem.*, **24**, 934 (1959); (c) S. A. Harrison and D. Aelony, Abstracts of Papers, Am. Chem. Soc., Atlantic City, N. J., Sept., 1959, p. 67-P; W. W. Tinsley, *J. Org. Chem.*, **24**, 1197 (1959); (d) H. Henbest and B. Nichols, *J. Chem. Soc.*, 221 (1959); (e) K. Nakanishi, N. Sazuki and F. Yamazaki, *Bull. Chem. Soc. Japan*, **34**, 53 (1961).



tion occurred, since thymine was also isolated. In accord with other experience this cyclization was much more rapid at 100° in 80% acetic acid<sup>2</sup> which contained silver acetate; the yield was thereby increased from 10% to 45% and the reaction time was reduced to 10 minutes. Subsequent basic hydrolysis of XVIII gave the *cis,cis*-diol XIX in 79% yield.

The olefin I and osmium tetroxide gave a third diol which was different from either XIX or IX. Therefore this product should be the remaining possible 3',4'-diol, the *trans,trans* isomer XVI, a formulation which is also in agreement with the usual stereochemistry known to result from the action of osmium tetroxide on alicyclic olefins. It is interesting to note the relative stability of the 5,6-double bond of the thymynyl group during this reaction, as well as in the preceding reactions with N-bromoacetamide, perbenzoic acid and hydrogen on platinum.

The *cis,cis*-oxide reacted smoothly with methanol with perchloric acid as a catalyst to give the, *trans*-methoxy-*cis*-hydroxy adduct XX (Chart II). Under the same reaction conditions the product from the *trans,trans*-oxide XV was the *trans*-hydroxy anhydro compound XII. The *cis,cis*-oxide XIV and ammonia in methanol or water gave the *trans*-amino-*cis*-hydroxy adduct XXIII in good yield.

The *cis,cis*-oxide reacted with aqueous pyridine to give a 76% yield of a water-soluble, moderately

basic compound believed to be a hydroxy pyridinium zwitterion XXI. It formed salts with both hydrochloric and acetic acids (*i.e.*, XXII). The formation of these salts was accompanied by marked changes in infrared spectra, restoring the usual pattern shown by 1-substituted thymines.<sup>20</sup>

An early route to the cyclopentane isostere III of thymidine (II) was to have proceeded *via* the *trans,trans*-oxide XV and a *trans*-hydroxy-*cis*-cyano derivative XXVI. The literature gave little information about the reaction of cyanide ion with oxides other than highly reactive compounds such as ethylene oxide<sup>12a,21</sup> and epichlorohydrin.<sup>22</sup> Styrene oxide and anhydrous hydrogen cyanide in a sealed tube at an unstated temperature reportedly gave a rearranged product, the cyanohydrin of phenylacetaldehyde.<sup>23</sup> In a model reaction at 100° with aqueous sodium cyanide and the more plentiful *cis,cis*-oxide XIV we obtained a pair of isomeric cyano alcohols. A possible explanation for the formation of these isomers was implicit in a subsequent report by Bowers and co-workers.<sup>24</sup> They found that a steroidal 5 $\alpha$ ,6 $\alpha$ -oxide reacted with potassium cyanide in ethylene glycol at 90° to give two isomeric cyano alcohols. The minor isomer was assigned a 5 $\alpha$ -hydroxy-6 $\beta$ -cyano structure. Further reaction under the same alkaline conditions converted this compound to the other isomer, which was more levorotatory and was thus assigned a 5 $\alpha$ -hydroxy-6 $\alpha$ -cyano configuration.

Our objectives thus called for a less alkaline reaction system, one which would not epimerize a cyano group. A system of low alkalinity was described by Carpenter.<sup>12a</sup> He found that ethylene oxide and a 2% excess of aqueous hydrogen cyanide (*pK* 9.1) with water and a catalytic amount of a sterically hindered amine gave a 95% yield of hydracrylonitrile after one hour at 60–65°. We modified this system toward even lower alkalinity with a 150% excess of hydrogen cyanide, using 50% aqueous tetrahydrofuran as the solvent. Reaction with the *cis,cis*-oxide XIV was slow and much dark,

(20) (a) Condensations of pyridine with oxides under non-acidic conditions do not appear to be well known. From the pyridine-catalyzed reaction of nitroalkanes with ethylene oxide and with styrene oxide corresponding  $\beta$ -hydroxyethylpyridinium derivatives were isolated as by-products (ref. 20b). Ethylene oxide or epichlorohydrin reacted with pyridine or the picolines to give highly polar dyes of uncertain structure (ref. 20c); (b) M. J. Astle and F. J. Donat, *J. Org. Chem.*, **25**, 507 (1960); (c) H. Lohmann, *J. prakt. Chem.*, **153**, 57 (1939).

(21) A. P. Terent'ev and E. V. Vinogradova, *C. A.*, **40**, 7157 (1946); H. S. Davis and B. C. Redmon, U. S. Patent 2,390,519, Dec. 11, 1945; R. Robinson, *Gazz. chim. ital.*, **89**, 270 (1959).

(22) C. C. J. Culvenor, W. Davies and F. G. Haley, *J. Chem. Soc.*, 3123 (1950).

(23) E. Fourneau and M. Tiffeneau, *Compt. rend.*, **146**, 697 (1908).

(24) A. Bowers, E. Denot, M. B. Sanchez, L. M. Sanchez-Hidalgo and H. J. Ringold, *J. Am. Chem. Soc.*, **81**, 5233 (1959).

insoluble material was formed. This probably was a mixture of the polymers of hydrogen cyanide, known to be formed readily under weakly alkaline conditions.<sup>25a</sup> After a reaction time of 22 hours and a partition chromatography,<sup>23</sup> there was isolated a single cyano alcohol, identical with the minor product from the earlier synthesis which used sodium cyanide. Thus this compound is thought to be the unpimerized *trans*-cyano-*cis*-hydroxy compound XXV. By analogy with the above-mentioned work of Bowers, *et al.*,<sup>24</sup> it is probable that the major product from the earlier synthesis is the *cis*-cyano-*cis*-hydroxy epimer XXIV.<sup>26</sup>

With the *trans,trans*-oxide XV and a reaction time of 15 hours the hydrogen cyanide-hindered amine procedure gave the *trans*-hydroxy-*cis*-cyano adduct XXVI in 19% yield. Unchanged *trans,trans*-oxide also was isolated (20%), along with the *trans*-hydroxy anhydro compound XII (16%) and dark, insoluble material similar to that obtained in the earlier reaction with the *cis,cis*-oxide. Attempts to convert the nitrile group of XXVI to a carbethoxyl or carboxyl function and then to the hydroxymethyl group of III were not promising and were abandoned after the successful synthesis of III by another route.<sup>2</sup>

### Experimental<sup>27</sup>

Melting points are corrected. Evaporations were conducted under reduced pressure. The ethanol used was "absolute." Solids were pressed with potassium bromide for infrared spectral determinations. The solvent systems generally used for paper chromatography were 1-butanol-5 *N* acetic acid (7:3) and butanone-water (9:1). The latter system gave compact spots with the following  $R_f$  values when the paper was pre-equilibrated overnight with the vapors from the solvent, then developed (Whatman No. 1 paper, descending method) for just 40 minutes (substituents on the cyclopentane ring of the indicated compounds are in parentheses): (1) anhydro compounds: IV, 0.20; XII (*trans*-OH), 0.11; XVIII (*cis*-OH), 0.07. (2) Cyclopentyl- and cyclopentylthymines: I, 0.81; VII (*trans*-Cl) 0.86; VIII (*trans*-OH), 0.51; XI (*cis*-OH), 0.60; IX (*cis,trans*-diol), 0.33; XVI (*trans,trans*-diol), 0.24; XIX, (*cis,cis*-diol), 0.30. Compounds on developed chromatograms were detected as dark spots when viewed under an ultraviolet lamp equipped with a filter giving maximum transmission at 254  $\mu$ .

Diisopropylmethylamine was prepared by the Eschweiler-Clark method.<sup>28</sup> From 64.4 g. of 98% formic acid, 40.5 g. of diisopropylamine and 48.7 g. of 37% aqueous formaldehyde there was obtained 39.9 g. (87%) of product, b.p. 111-113°,  $n_D^{25}$  1.4090 (lit.<sup>29</sup> b.p. 109-112°, for material obtained as a by-product from the reaction of methylamine with isopropyl bromide).

*Anal.* Calcd. for  $C_7H_{17}N$ : C, 72.97; H, 14.87; N, 12.16. Found: C, 72.54; H, 14.68; N, 11.87.

**2,3'-Anhydro-1-(*cis*-3-hydroxycyclopentyl)-thymine (IV).**—A. Partly frozen 83% (wt./wt.) sulfuric acid (15 ml.) was agitated during the gradual addition of 4.00 g. of 1-(3-cyclopenten-1-yl)-thymine (I).<sup>1b</sup> The mixture was stirred

(25) (a) T. Völker, *Angew. Chem.*, **72**, 379 (1960). (b) For partition chromatographic work we are indebted to Mr. C. Pidacks and his group. For their general procedure see H. M. Kissman, C. Pidacks and B. R. Baker, *J. Am. Chem. Soc.*, **77**, 18 (1955).

(26) An epimerization during the saponification of a bridged-ring cyclopentane carboxylic ester was studied in some detail by J. Meinwald and P. G. Gassman, *ibid.*, **82**, 5445 (1960).

(27) We thank M. L. Brancone and W. Fulmor and their groups for microanalytical and spectral data.

(28) This synthesis was adapted from the general amine methylation procedure of H. T. Clark, H. B. Gillespie and S. Z. Weissshaus, *J. Am. Chem. Soc.*, **55**, 4571 (1933).

(29) F. Klages, G. Nöber, F. Kircher and M. Bock, *Ann.*, **547**, 1 (1941).

without further cooling until (4 hr.) the solid had all dissolved. After another hour at ca. 22° the solution was stirred and kept at  $\leq 20^\circ$  with a methanol-solid carbon dioxide bath during neutralization to pH 7 by the dropwise addition of 36 ml. of concentrated aqueous ammonia. The resulting slurry was readily extracted in a separatory funnel with 5  $\times$  45 ml. of chloroform. The extracts were dried ( $MgSO_4$ ), evaporated, and the solid residue was recrystallized from butanone, boiling down from 450 ml. to about 150 ml. to give 3.17 g. (79%) of product, m.p. 236-237°;  $\lambda_{max}^{H_2O}$ ,  $m\mu$  ( $\epsilon$ ) 230 (6,950), 258 (7,790), 274(sh) (3,400);  $\lambda_{max}^{0.1 N NaOH}$ ,  $m\mu$  ( $\epsilon$ ) 232 (6,450), 258 (7,880), 274(sh) (3,400);  $\lambda_{max}^{0.1 HCl}$ ,  $m\mu$  ( $\epsilon$ ) 230 (6,140), 258 (7,380), 280(sh) (2,300);  $\lambda_{max}^{12.5 N H_2SO_4}$ ,  $m\mu$  ( $\epsilon$ ) 231 (5,260), 260 (6,240), 280(sh) (2,300);  $\lambda_{max}^{93\% H_2SO_4}$ ,  $m\mu$  ( $\epsilon$ ) 227 (5,290), 277 (7,620);  $\lambda_{max}^{KBr}$  6.02, 6.16, 6.36(w) and 6.55  $\mu$ , with none of the 3.15  $\mu$  band ( $-NH$ ) of the starting material I. The product was easily soluble in water or methanol. It could be recrystallized from dimethylformamide, pyridine or acetonitrile. In chloroform the solubility was ca. 1 g./45 ml. at 25°, but in other, non-hydroxylated solvents it was almost insoluble.

*Anal.* Calcd. for  $C_{10}H_{12}N_2O_2$  (192): C, 62.48; H, 6.29; N, 14.58. Found: C, 62.60; H, 6.43; N, 14.69.

A potentiometric titration in acetic acid against 0.1 *N* perchloric acid in acetic acid gave an equivalent weight of 202. When titrated potentiometrically in aqueous solution against *N* hydrochloric acid the compound showed no acid-binding power.

With 96% sulfuric acid the yield in an earlier reaction was 57%. (The acid was not cooled and some warming occurred when the olefin was added.) In a spectrophotometric study with 96% sulfuric acid at 25° the reaction appeared to be almost over after 1 min.:  $\lambda_{max}$  226  $m\mu$  ( $\epsilon$  4,310), 277  $m\mu$  ( $\epsilon$  6,210). After reaction times of 5 and 10 min. the spectra were identical:  $\lambda_{max}$  226  $m\mu$  ( $\epsilon$  4,700), 277  $m\mu$  ( $\epsilon$  6,390).

B. A solution of 0.060 g. of 1-(*trans*-3-chlorocyclopentyl)-thymine (VII) in 3 ml. of a 0.3 *N* solution of diisopropylmethylamine in dry dimethylformamide was heated at 100° for 72 hr. The solution was evaporated to dryness. The partly crystalline residue was warmed with 0.3 ml. of butanone, the mixture allowed to cool and the solid (0.021 g.) collected by filtration. A few, large ivory-colored crystals were present. (In an unheated, aqueous solution these gave a precipitate with silver nitrate which was insoluble in nitric acid.) The rest of the solid was white and granular, m.p. 231-235°; it gave an infrared spectrum identical with that of the product from method A.

**Hydrochloride (V) of 2,3'-Anhydro-1-(*cis*-3-hydroxycyclopentyl)-thymine.**—A solution of 0.0092 g. of 2,3'-anhydro-1-(*cis*-3-hydroxycyclopentyl)-thymine (IV) in 0.5 ml. of chloroform was saturated with dry hydrogen chloride. A crystalline solid separated. The mixture was immediately evaporated to dryness and the residue dissolved in 500 ml. of water. This solution exhibited an ultraviolet absorption spectrum identical with that of the starting material IV. For analyses the above reaction was repeated with 0.050 g. of IV dissolved in 2 ml. of chloroform. The resulting solid was collected by filtration and washed with chloroform. The hygroscopic product was very soluble in water, giving a solution with pH  $\leq 1.5$ . After drying for 3 days over phosphorus pentoxide there remained 0.058 g. of product.

*Anal.* Calcd. for  $C_{10}H_{12}N_2O_2 \cdot 1.59HCl$ : Cl, 22.5. Found: Cl, 22.5.

This material was now not entirely soluble in water and the ultraviolet absorption spectrum was somewhat changed. Another sample of this hydrochloride was stored for 5 months, when it was found to be almost insoluble in water. The ultraviolet and infrared spectra were then identical with those of 1-(*trans*-3-chlorocyclopentyl)-thymine (VII).

*Anal.* Calcd. for  $C_{10}H_{13}ClN_2O_2$ : C, 52.52; H, 5.73; Cl, 15.50. Found: C, 52.79; H, 6.06; Cl, 15.37.

**1-(*trans*-3-Iodocyclopentyl)-3-methylthymine (VI).**—A. A sealed tube containing 0.192 g. of 2,3'-anhydro-1-(*cis*-3-hydroxycyclopentyl)-thymine (IV) and 5 ml. of methyl iodide was heated at 100° for 1 hr. The resulting solution was evaporated to dryness, the residue allowed to crystallize, washed with cold methanol and recrystallized from methanol; yield 0.129 g. (39%), m.p. 170-171° dec.;  $\lambda_{max}^{CH_3OH}$  271  $m\mu$  ( $\epsilon$  12,300), min. 240  $m\mu$  ( $\epsilon$  3,610);  $\lambda_{max}^{1.1 N NaOH}$  273  $m\mu$  ( $\epsilon$  12,100), min. 240  $m\mu$  ( $\epsilon$  3,780).

*Anal.* Calcd. for  $C_{11}H_{15}IN_2O_2$ : C, 39.54; H, 4.52; I, 37.98; N, 8.38. Found: C, 39.84; H, 4.75; I, 37.71; N, 8.28.

B. A suspension of 0.0016 g. of the anhydro compound IV in 0.1 ml. of methyl iodide at about 24° was agitated occasionally for 24 hr., when the solid had all dissolved. The solution was evaporated to dryness and the residue washed with a drop of methanol. The product, 0.0011 g. of pale yellow crystals, gave an infrared absorption spectrum slightly less sharp than that from the product of method A, but otherwise identical.

1-(*trans*-3-Chlorocyclopentyl)-thymine (VII).—A. A suspension of 0.384 g. of the 2,3'-anhydro-1-(*cis*-3-hydroxycyclopentyl)-thymine (IV) in 25 ml. of acetyl chloride was protected from moisture with a drying tube filled with anhydrous calcium sulfate, heated under reflux until the solid had all dissolved (110 min.), and then heated for another 10 min. Evaporation to dryness left a semi-solid residue which was agitated with 10 ml. of hot carbon tetrachloride. The hot solution was filtered from 0.050 g. of solid, m.p. 163–168°. Crystallization from benzene returned 0.038 g. of product, m.p. 168–170°. The residue remaining after evaporation of the carbon tetrachloride filtrate became largely crystalline after 4 days. Agitation with carbon tetrachloride and collection by filtration gave 0.321 g. of crystals (78% total yield), m.p. 169–171°, unchanged after recrystallization from benzene;  $\lambda_{\text{max}}^{\text{CH}_3\text{OH}}$  271  $\mu$  ( $\epsilon$  9,700), min. 237  $\mu$  ( $\epsilon$  2,290);  $\lambda_{\text{max}}^{\text{0.1N NaOH}}$  271  $\mu$  ( $\epsilon$  6,500), min. 247  $\mu$  ( $\epsilon$  4,350). The infrared spectra of this material and the original 0.050 g. of product were identical.

*Anal.* Calcd. for  $C_{10}H_{13}ClN_2O_2$ : C, 52.52; H, 5.73; Cl, 15.50; N, 12.26. Found: C, 52.56; H, 5.67; Cl, 15.30; N, 12.57.

B. A solution of 0.0012 g. of 2,3'-anhydro-1-(*cis*-3-hydroxycyclopentyl)-thymine (IV) in 0.1 ml. of chloroform in a small test-tube was saturated with dry hydrogen chloride. Crystals separated as the gas was bubbled in. The test-tube was corked tightly and heated in an oven at 67° for 2.5 hr., when the last of the crystals had dissolved. The solution was evaporated to dryness, chloroform was added and the evaporation repeated to remove residual hydrogen chloride. A solution of the residue was evaporated with 0.200 g. of potassium bromide. A disk pressed from the resulting residue gave an infrared spectrum identical with that of the product from method A.

1-(*trans*-3-Hydroxycyclopentyl)-thymine (VIII).—A. A solution of 0.208 g. of 2,3'-anhydro-1-(*cis*-3-hydroxycyclopentyl)-thymine (IV) in 5.0 ml. of 0.1 *N* sulfuric acid was heated with a steam-bath for 1.0 hr., cooled, neutralized with 2 *N* sodium hydroxide and evaporated to dryness. Repeated extraction of the residue with chloroform, evaporation of the extracts, and crystallization of the residue from 0.4 ml. of water gave 0.024 g. (11%) of dense crystals, m.p. 219–220°;  $\lambda_{\text{max}}^{\text{CH}_3\text{OH}}$  272  $\mu$  ( $\epsilon$  9,720);  $\lambda_{\text{max}}^{\text{KBr}}$  2.92 ( $-\text{OH}$ ) and 3.17  $\mu$  ( $-\text{NH}$ ).

*Anal.* Calcd. for  $C_{10}H_{14}N_2O_3$ : C, 57.13; H, 6.71; N, 13.33. Found: C, 56.86; H, 6.83; N, 13.61.

Subsequent extraction of the remainder of the first residue with 3  $\times$  5 ml. of ethanol and evaporation of the extracts gave another 0.162 g. of product, m.p. 193–195°. Recrystallization from water and then from acetonitrile raised the m.p. to 204–207°, or m.p. 212–217° after admixture with the analytical sample.

B. A solution of 0.192 g. of 2,3'-anhydro-1-(*cis*-3-hydroxycyclopentyl)-thymine (IV) in 3 ml. of trifluoroacetic acid was protected with a drying tube, heated under reflux for 1 hr., evaporated to dryness, then evaporated to dryness with 3  $\times$  3 ml. of ethanol to remove traces of acid. A solution of the residue in 3 ml. of methanol saturated with gaseous ammonia was allowed to stand at ca. 23° for 1 hr., then evaporated to dryness. The residue was washed with ethanol, leaving 0.159 g. (76%) of crystals, m.p. 219–221°, undepressed after admixture with the product of method A. The infrared absorption spectra of the two products were identical.

C. A suspension of 0.208 g. of 1-(*trans*-3,*trans*-4-oxidocyclopentyl)-thymine (XV)<sup>30</sup> in 40 ml. of ethanol was hydrogenated at atmospheric pressure for 14 hours at room

temperature with 0.050 g. of platinum oxide catalyst. Removal of the catalyst by filtration, evaporation of the filtrate and crystallization of the residue from ethanol gave 0.175 g. (83%) of product, m.p. 212–217°. Two more recrystallizations raised the m.p. to 214–218° or 217–220° after admixture with the product of method A. The infrared spectra of the two samples were identical.

1-(*cis*-3,*trans*-4-Dihydroxycyclopentyl)-thymine (IX).—A. A mixture of 1.040 g. of 1-(*cis*-3,*cis*-4-oxidocyclopentyl)-thymine (XIV) and 40 ml. of 2 *M* aqueous potassium carbonate was heated on a steam-bath and agitated intermittently. After 0.2 hr. the solid had dissolved. Heating was continued for 1.2 hr., the solution was cooled, then adjusted to pH 6 by adding concentrated sulfuric acid dropwise with cooling. The resulting slurry was evaporated to dryness. The residue was extracted with 20 ml. of unheated 1-propanol, then washed with 3  $\times$  5 ml. of 1-propanol. Evaporation of the extract and washes, crystallization of the residue from 1-propanol and recrystallization from ethanol gave 0.536 g. (47%) of crystals, m.p. 207–213°, or m.p. 215° after recrystallization from water;  $\lambda_{\text{max}}^{\text{CH}_3\text{OH}}$  272  $\mu$  ( $\epsilon$  10,120),  $\lambda_{\text{max}}^{\text{KBr}}$  2.95  $\mu$ .

*Anal.* Calcd. for  $C_{10}H_{14}N_2O_4$ : C, 53.09; H, 6.24; N, 12.38. Found: C, 52.97; H, 6.57; N, 12.51.

B. A solution of 0.060 g. of 2,3'-anhydro-1-(*cis*-3,*trans*-4-dihydroxycyclopentyl)-thymine (XII) in 2.5 ml. of 2 *M* aqueous potassium carbonate was heated on a steam-bath for 1.8 hr. A work-up as in method A followed by crystallization from 1-propanol gave 0.041 g. (63%) of product, m.p. 209–212°. Material recrystallized from water had a m.p. of 215–216°, unchanged after admixture with the product of method A. The infrared spectra of the two samples were identical.

C. A solution of 0.050 g. of 1-(*cis*-3,*cis*-4-oxidocyclopentyl)-thymine (XIV) in 1 ml. of trifluoroacetic acid was allowed to stand at 25° for 1 hr., evaporated to dryness, then evaporated to dryness with 3  $\times$  1 ml. of ethanol. A solution of the residue in 1 ml. of methanol saturated with ammonia was allowed to stand at 25° for 1 hr., evaporated to dryness, then evaporated to dryness with 3  $\times$  1 ml. of ethanol. A solution of the residual gum in 0.4 ml. of ethanol gradually deposited 0.032 g. (59%) of crystals, m.p. 211–214°. The product gave an infrared spectrum identical with that of the product from method A.

1-(*trans*-3,*cis*-4-Dibromocyclopentyl)-thymine (X).—An ice-cold solution of 0.192 g. (1.0 mmole) of 1-(3-cyclopenten-1-yl)-thymine (I)<sup>b</sup> in 5 ml. of methylene chloride was stirred during the addition of a solution of 0.159 g. (1.0 mmole) of bromine in 5 ml. of methylene chloride. A solid immediately began to separate. After 20 min. without further cooling the solid was collected, washed with methylene chloride and crystallized from ethanol to give 0.152 g. of crystals, m.p. 229–231° dec. Evaporation of the methylene chloride mother liquor and washes and crystallization of the residue from ethanol and then from 2-methoxyethanol gave another 0.020 g. of product (49% total yield), m.p. 229–231° dec.,  $\lambda_{\text{max}}^{\text{CH}_3\text{OH}}$  269  $\mu$  ( $\epsilon$  11,400).

*Anal.* Calcd. for  $C_{10}H_{12}Br_2N_2O_2$ : C, 34.12; H, 3.41; Br, 45.40. Found: C, 34.34; H, 3.73; Br, 45.41.

1-(*cis*-3-Hydroxycyclopentyl)-thymine (XI).—A. To the solution from 0.346 g. (6.1 mmoles) of aluminum chloride, 0.567 g. (15.0 mmoles) of sodium borohydride and 25 ml. of dry bis-(2-methoxyethyl) ether was added 0.625 g. (3.0 mmoles) of 1-(*cis*-3,*cis*-4-oxidocyclopentyl)-thymine (XIV). The mixture was protected from moisture with a calcium chloride tube, stirred vigorously for 2.0 hr. at 25–30°, poured on ca. 20 g. of ice, and acidified to ca. pH 2 with 1.0 ml. of concentrated sulfuric acid. Filtration gave 0.091 g. of crystals, m.p. 256–259° or m.p. 258–264° after admixture with the starting oxide. The filtrate was evaporated to give a slush which was extracted with 6  $\times$  100 ml. of hot chloroform. Evaporation of the extracts left 0.498 g. of a glass which could not be induced to crystallize;  $\lambda_{\text{max}}^{\text{CH}_3\text{OH}}$  271  $\mu$  ( $\epsilon$  9,300, assuming mol. wt. 210). The glass was subjected to partition chromatography<sup>25b</sup> on Celite,<sup>31</sup> using the system ethyl acetate-heptane-water (4:1:1). Material eluted in the fourth and fifth hold-back-volumes was washed with ether, then crystallized from butanone; yield 0.073 g. (12%), m.p. 189–190°,  $\lambda_{\text{max}}^{\text{CH}_3\text{OH}}$  271  $\mu$  ( $\epsilon$  9,890),  $\lambda_{\text{max}}^{\text{0.1N NaOH}}$

(30) This batch of *trans,trans*-oxide probably contained  $\geq 1\%$  of the isomeric *cis,cis*-oxide, as indicated by the isolation of the latter in the synthesis of XXVI.

(31) Celite is acid-washed, diatomaceous earth sold by the Johns-Manville Corp.

273  $\mu\mu$  ( $\epsilon$  10,100),  $\lambda_{\max}^{0.1N NaOH}$  270  $\mu\mu$  ( $\epsilon$  7,730);  $\lambda_{\max}^{KBr}$  2.82  $\mu$  (-OH).

*Anal.* Calcd. for  $C_{10}H_{14}N_2O_3$ : C, 57.13; H, 6.71; N, 13.33. Found: C, 56.72; H, 6.70; N, 13.27.

B. A solution of 0.600 g. of 2,3'-anhydro-1-(*cis*-3-hydroxycyclopentyl)-thymine (IV) in 6.0 ml. of *N* sodium hydroxide was heated on a steam-bath for 14 hr., acidified to pH 5 with concentrated hydrochloric acid, then evaporated to dryness. The residual solid was extracted for ca. 15 min. with 40 ml. of refluxing butanone. The filtered, concentrated extract deposited 0.553 g. (84%) of granular crystals, m.p. 186–188° or m.p. 186–188° after admixture with the product of method A.

When a solution of 0.194 g. of the anhydro compound IV in 2.0 ml. of 0.1 *N* sodium hydroxide was allowed to stand at ca. 25° for 8 days, paper chromatography showed only starting material. After 60 hr. at 100° starting material still appeared to be the major component although a considerable amount of the hydrolysis product was also present.

C. A suspension of 0.208 g. of finely divided 1-(*cis*-3,*cis*-4-oxidocyclopentyl)-thymine (XIV) in 40 ml. of absolute ethanol was hydrogenated for 9 hr. at a pressure of 1 atmosphere over 0.050 g. of Adams platinum oxide catalyst. The solution was filtered, evaporated to dryness and the residue washed with butanone to give 0.174 g. (83%) of product, m.p. 178–183°. Recrystallization from butanone returned 0.134 g. of prisms, m.p. 182–185° or m.p. 184–187° after admixture with the product of method A. The infrared absorption spectra of the two samples were identical.

**2,3'-Anhydro-1-(*cis*-3,*trans*-4-dihydroxycyclopentyl)-thymine (XII).**—A. A solution of 0.150 g. of 1-(*trans*-3,*trans*-4-oxidocyclopentyl)-thymine (XV) in 10 ml. of water was heated on a steam-bath for 7 hr., then evaporated to dryness. Crystallization of the residue from dimethylformamide returned 0.110 g. (73%) of leaflets, m.p. 246–248° or m.p. 248–250° after recrystallization;  $\lambda_{\max}^{CH_3OH}$  232  $\mu\mu$  ( $\epsilon$  7,890), 255  $\mu\mu$  ( $\epsilon$  7,270);  $\lambda_{\max}^{KBr}$  3.02, 6.05, 6.28, 6.34, 6.59 and 6.70  $\mu$ , but with no significant absorption at 3.15  $\mu$  (-CONH-CO-). The product was very soluble in water.

*Anal.* Calcd. for  $C_{10}H_{12}N_2O_3$ : C, 57.68; H, 5.81; N, 13.46. Found: C, 57.33; H, 5.81; N, 13.82.

In preliminary reactions followed by paper chromatography the above isomerization in water appeared to be complete after 3 hr. In 2 *M* potassium carbonate solution it was complete in 3 min. at 100°, but after 1 hr. at 100° a subsequent reaction had formed the *cis*-3,*trans*-4-diol IX as the predominant product. Parallel studies with the *cis*-3,*cis*-4-oxide XIV gave no suggestion of isomerization to an anhydro compound.

B. A stirred suspension of 0.208 g. of 1-(*trans*-3,*trans*-4-oxidocyclopentyl)-thymine (XV) in 15 ml. of methanol soon gave a clear solution after the addition of 0.10 ml. of 72% perchloric acid. After 14.5 hr. the mixture was adjusted to pH ca. 6 with 0.4 ml. of 2 *M* aqueous potassium carbonate. Evaporation to dryness, extraction of the residue with 4  $\times$  4 ml. of chloroform and evaporation of the extracts left only 0.028 g. of a glassy residue.

The chloroform-insoluble material was extracted portionwise with a total of 5 ml. of methanol. Evaporation of the extracts left 0.140 g. of a white solid, m.p. 205–235° dec. An infrared spectrum showed it to be crude, but otherwise the same as the product of method A, above. Material crystallized twice from dimethylformamide melted at 247–250°, before or after admixture with the product of method A.

**2,3'-Anhydro-1-(*trans*-4-bromo-*cis*-3-hydroxycyclopentyl)-thymine (XIII).**—A solution of 0.192 g. (1.0 mmole) of 1-(3-cyclopenten-1-yl)-thymine (I)<sup>1b</sup> in 2 ml. of purified dioxane was combined with 0.3 ml. of 0.5 *N* aqueous perchloric acid, then placed in a dark room. *N*-Bromoacetamide (0.138 g., 1.0 mmole) was added in two portions at 10-min. intervals. After another 20 min. the solution gave no response with moistened starch-iodide paper. The solution was adjusted to pH 7 with 0.70 ml. of 2 *N* sodium hydroxide plus the requisite amount of 5% sodium bicarbonate solution. Evaporation to dryness at  $\leq 35^\circ$  left a residual sirup which was extracted with 10 ml. of hot carbon tetrachloride. The remaining sirup was dissolved in 10 ml. of acetone; this solution was filtered from 0.007 g. of an almost infusible solid, then concentrated to a volume of about 2 ml. The crystals which gradually separated (0.074 g., 27%, m.p. 165–166°) had a m.p. of 169–170° after recrystallization from

acetonitrile;  $\lambda_{\max}^{CH_3OH}$  232  $\mu\mu$  ( $\epsilon$  9,100), 255  $\mu\mu$  ( $\epsilon$  8,140);  $\lambda_{\max}^{KBr}$  5.97, 6.10, 6.50 and 6.70  $\mu$ .

*Anal.* Calcd. for  $C_{10}H_{11}BrN_2O_2$ : C, 44.30; H, 4.09; Br, 29.47; N, 10.33. Found: C, 44.19; H, 4.54; Br, 29.36; N, 10.52.

**1-(*cis*-3,*cis*-4-Oxidocyclopentyl)-thymine (XIV), 1-(*trans*-3,*trans*-4-Oxidocyclopentyl)-thymine (XV) and 6(or 5)-Benzoyloxy-5(or 6)-hydroxy-1-(3,4-oxidocyclopentyl)-5,6-dihydrothymine.**—To a cold solution of 19.22 g. (0.1 mole) of 1-(3-cyclopenten-1-yl)-thymine (I)<sup>1b</sup> in 300 ml. of methylene chloride was added 227 ml. of a cold, 0.441 *M* solution of perbenzoic acid in benzene. A slight evolution of heat was counteracted with a pan of cold water. Iodimetric titrations showed the consumption of 85% of the peracid after 8 hr. and 98% after 48 hr. at ca. 21°. The mixture was evaporated to dryness at 40° and the residue was stirred for 1 hr. with 500 ml. of tetrahydrofuran. The insoluble material was collected by filtration (13.6 g.) and crystallized from 270 ml. of 2-methoxyethanol to give 10.6 g. (fraction A) of the *cis,cis*-oxide XIV, m.p. 258–264° dec. or m.p. 264–268° dec. after recrystallization,  $\lambda_{\max}^{CH_3OH}$  270  $\mu\mu$  ( $\epsilon$  10,000).

*Anal.* Calcd. for  $C_{10}H_{12}N_2O_3$ : C, 57.68; H, 5.81; N, 13.46. Found: C, 57.86; H, 6.02; N, 13.55.

The tetrahydrofuran filtrate was evaporated to dryness at  $\leq 35^\circ$ , and the benzoic acid in the residue was removed by extraction with a total of 80 ml. of unheated ethanol, leaving 4.37 g. of crude *trans,trans*-oxide, m.p. 200–206° (fraction B). The 2-methoxyethanol mother liquor of fraction A was evaporated to dryness with a minimum of heat and the residue was heated briefly with 80 ml. of ethanol. Filtration removed 0.520 g. of crude *cis,cis*-oxide, m.p. 252–254° (fraction C). On cooling, the filtrate deposited solids which only gradually assumed well-defined forms (relatively dense, transparent, prisms of the *trans,trans*-oxide and white, finely divided solid, which contained *cis,cis*-oxide). After 3 days the mother liquor was decanted, the solids were suspended in carbon tetrachloride, and heptane was added until the dense crystals sank. Slight agitation and decantation allowed the "*cis,cis*-oxide" (0.639 g., m.p. 196–211°, fraction D) to be separated from the *trans,trans*-oxide (1.030 g., m.p. 203–207°, fraction E). Fraction D was extracted with 26 ml. of hot ethanol, decanting from 0.084 g. of tan powder, m.p. 251–255°, fraction F. This extract was combined with 200 ml. of ethanol and used to recrystallize fractions B and C, returning 5.1 g.<sup>30</sup> (24%) of *trans,trans*-oxide XV, m.p. 212–214°, or m.p. 214–216° after recrystallization,  $\lambda_{\max}^{CH_3OH}$  270  $\mu\mu$  ( $\epsilon$  10,480).

*Anal.* Found: C, 57.62; H, 6.01; N, 13.43.

Occasionally the *trans,trans*-oxide separated from ethanol as needles, and once both needles and prisms were deposited together. These could be separated mechanically and were found to have different infrared absorption maxima; distinguishing peaks in the needles were at 5.95 (broad), 6.98, 8.22, 11.12, 11.3 (broad) and 13.54  $\mu$ , and in the prisms at 5.87, 6.02, 7.30 and 10.68  $\mu$ . When a potassium bromide pressed disk prepared from the needles was ground in a mortar and then repressed, it gave the absorption spectrum characteristic of the prisms. The needles had a m.p. of 211–213.5° or m.p. 210–212° after admixture with prisms (m.p. 213–214°). Recrystallization of the needles from ethanol gave the prisms.

Recrystallization of fractions C and F from 2-methoxyethanol gave another 0.416 g. of *cis,cis*-oxide, m.p. 261–265°: total = 11.0 g. (53%) of *cis,cis*-oxide.

After 6 hr. the ethanolic mother liquor of fraction B had deposited a crude solid (0.270 g., m.p. 165–187°) from which it was separated by decantation. After another 22 hr. this liquor had deposited 0.292 g. of a dihydrothymine derivative, m.p. 168–169° or m.p. 170° after recrystallization from ethanol;  $\lambda_{\max}^{CH_3OH}$  231  $\mu\mu$  ( $\epsilon$  14,000), 274  $\mu\mu$  ( $\epsilon$  760) [vs.  $\lambda_{\max}^{CH_3OH}$  230  $\mu\mu$  ( $\epsilon$  12,700), 272  $\mu\mu$  ( $\epsilon$  980) for methyl benzoate];  $\lambda_{\max}^{KBr}$  2.91  $\mu$  (-OH), 3.15  $\mu$  (-NH), 5.82 and 8.00  $\mu$  (-OCOC<sub>6</sub>H<sub>5</sub>) and 5.91  $\mu$  (-CONH-). A solution of this compound in acetic acid did not decolorize bromine, indicating that a cyclopentenyl group was no longer present.

*Anal.* Calcd. for  $C_{17}H_{18}N_2O_6$ : C, 58.95; H, 5.24; N, 8.09. Found: C, 58.59; H, 5.64; N, 8.06.

Epoxidations were also accomplished with trifluoroperacetic acid<sup>32</sup> and monopero-phthalic acid, but the yields of

(32) W. D. Emmous and A. S. Pagano, *J. Am. Chem. Soc.*, **77**, 89 (1955).



*trans,trans*-oxide were not as high as in the present experiment.

**1-(*trans*-3,*trans*-4-Dihydroxycyclopentyl)-thymine (XVI).**—A solution of 0.485 g. (1.91 mmoles) of osmium tetroxide in 7 ml. of benzene was added dropwise with agitation and gentle cooling to a solution of 0.288 g. (1.5 mmoles) of 1-(3-cyclopenten-1-yl)-thymine (I)<sup>1b</sup> and 0.25 ml. of dry pyridine in 10 ml. of dry dimethylformamide. There was a slight evolution of heat and an immediate brown coloration. [In preliminary control tests osmium tetroxide in benzene gave no color with either dimethylformamide or a solution of 1-(*cis*-3,*cis*-4-oxidocyclopentyl)-thymine (XIV) in dimethylformamide.] The stoppered reaction solution was allowed to stand 1 hr. at *ca.* 26°. It was then saturated with hydrogen sulfide and filtering from the resulting black solid. Evaporation of the filtrate and crystallization of the residue from 1.5 ml. of water, finally at 5°, gave 0.126 g. (37%) of crystals, m.p. 236–241°. Twice-recrystallized material was straw-colored, m.p. 241–246°, unchanged after another recrystallization;  $\lambda_{\text{max}}^{\text{CH}_3\text{OH}}$  272 m $\mu$  ( $\epsilon$  10,060),  $\lambda_{\text{max}}^{\text{KBr}}$  2.90 (shoulder) and 3.00  $\mu$ . The infrared absorption spectrum was sharply defined and well-differentiated from that of either of the isomeric diols IX or XIX.

*Anal.* Calcd. for C<sub>10</sub>H<sub>14</sub>N<sub>2</sub>O<sub>4</sub>: C, 53.09; H, 6.24; N, 12.38. Found: C, 52.77; H, 6.43; N, 12.38.

**1-(*trans*-3-Bromo-*cis*-4-hydroxycyclopentyl)-thymine (XVII) and 1-(*trans*-3-Bromo-*cis*-4-acetoxycyclopentyl)-thymine.**—A suspension of 0.208 g. of 1-(*cis*-3,*cis*-4-oxidocyclopentyl)-thymine (XIV) in 2 ml. of methylene chloride was stirred magnetically and chilled with an ice-bath during the gradual addition of 2.0 ml. of a 30% solution of hydrogen bromide in acetic acid. After 10 min. the cooling bath was removed and stirring was allowed to continue for 1 hr. at room temperature. The solid was collected by filtration and washed with methylene chloride. It initially exuded a strong odor of hydrogen bromide, but after standing in the open for a number of hours the weight gradually dropped from 0.286 g. to 0.226 g. (78%); this material (XVII) was odorless. It gradually sintered with decomposition above 220°,  $\lambda_{\text{max}}^{\text{CH}_3\text{OH}}$  270 m $\mu$  ( $\epsilon$  12,140). In another run the product was collected on a sintered glass frit, then conveniently freed of hydrogen bromide by drawing air through it overnight.

*Anal.* Calcd. for C<sub>10</sub>H<sub>13</sub>BrN<sub>2</sub>O<sub>3</sub>: C, 41.54; H, 4.53; Br, 27.64; N, 9.69. Found: C, 41.93; H, 4.83; Br, 27.74; N, 9.74.

B. The reaction was run just as in the preceding experiment except that stirring was allowed to continue for 26 hr. at room temperature and the solvent was removed by evaporation at  $\leq$  40°. During the evaporation the solid dissolved, then almost immediately separated again. Washing with ether left 0.274 g. of product, m.p. 205–208°. Two recrystallizations from ethanol gave 0.111 g. (34%) of the acetate of XVII, m.p. 223–224° dec.;  $\lambda_{\text{max}}^{\text{CH}_3\text{OH}}$  268 m $\mu$  ( $\epsilon$  8,730);  $\lambda_{\text{max}}^{\text{KBr}}$  5.70, 8.15  $\mu$  (–OAc), with no appreciable absorption near 2.9  $\mu$  (–OH).

*Anal.* Calcd. for C<sub>12</sub>H<sub>15</sub>BrN<sub>2</sub>O<sub>4</sub>: C, 43.52; H, 4.57; Br, 24.13; N, 8.46. Found: C, 43.63; H, 4.69; Br, 23.76; N, 8.89, 8.35.

The first ethanolic mother liquor was allowed to evaporate somewhat. The crystals which separated (0.039 g.) were recrystallized from 2-methoxyethanol to give 0.025 g. of tiny rods which decomposed above 225° and had an infrared spectrum identical with that of 1-(*trans*-3-bromo-*cis*-4-hydroxycyclopentyl)-thymine (XVII).

**2,3'-Anhydro-1-(*cis*-3,*cis*-4-dihydroxycyclopentyl)-thymine (XVIII).**—A mixture of 0.578 g. (2.0 mmoles) of 1-(*trans*-3-bromo-*cis*-4-hydroxycyclopentyl)-thymine (XVII) and 0.339 g. (2.0 mmoles) of silver acetate in 10 ml. of 80% acetic acid was agitated on a steam-bath for 10 min., then filtered from silver bromide. An aliquot of the filtrate gave no precipitate when treated with aqueous sodium chloride, but the main solution later became purple, suggesting the presence of a silver-pyrimidine complex. The solution was saturated with hydrogen sulfide, filtered from the small amount of black solid which separated, then evaporated to dryness. The residue was agitated with 3 ml. of water, the solid collected by filtration, washed with water and then with methanol, leaving 0.121 g. (21% recovery) of crystals, m.p. 213–217° dec. The infrared spectrum was identical with that of the starting material except that four additional small peaks were also present at positions (6.86, 7.05, 11.81 and 12.0  $\mu$ ) where peaks are prominent in the *cis,cis*-oxide XIV.

Evaporation of the aqueous filtrate left a solid which was washed with acetone to give 0.187 g. (45%) of a powder, m.p. 242–246°. Crystallization from dimethylformamide returned 0.145 g. of crystals, m.p. 250–253°;  $\lambda_{\text{max}}^{\text{CH}_3\text{OH}}$  232 m $\mu$  ( $\epsilon$  8,790), 256 m $\mu$  ( $\epsilon$  8,280);  $\lambda_{\text{max}}^{\text{KBr}}$  3.05, 6.00, 6.17, 6.27, 6.35, 6.57 and 6.65  $\mu$ .

*Anal.* Calcd. for C<sub>10</sub>H<sub>12</sub>N<sub>2</sub>O<sub>3</sub>: C, 57.68; H, 5.81; N, 13.46. Found: C, 57.60; H, 6.12; N, 13.72.

When the reaction time was extended to 30 min. the yield was unchanged, even though virtually no starting material was encountered.

**1-(*cis*-3,*cis*-4-Dihydroxycyclopentyl)-thymine (XIX).**—A solution of 0.208 g. of 2,3'-anhydro-1-(*cis*-3,*cis*-4-dihydroxycyclopentyl)-thymine (XVIII) in 5 ml. of 0.3 *N* sodium hydroxide was heated at 100° for 30 min., cooled, and agitated with enough (0.401 g.) Dowex-50 polysulfonic acid resin to make the solution acidic to phenolphthalein. The solution was filtered, evaporated to dryness and the residue crystallized from ethanol to give 0.179 g. (79%) of needles, m.p. 201–203° or m.p. 203° after recrystallization;  $\lambda_{\text{max}}^{\text{CH}_3\text{OH}}$  272 m $\mu$  ( $\epsilon$  10,300);  $\lambda_{\text{max}}^{\text{KBr}}$  2.91, 2.99  $\mu$ .

*Anal.* Calcd. for C<sub>10</sub>H<sub>14</sub>N<sub>2</sub>O<sub>4</sub>: C, 53.09; H, 6.24; N, 12.38. Found: C, 52.70; H, 6.46; N, 12.48.

**1-(*cis*-4-Hydroxy-*trans*-3-methoxycyclopentyl)-thymine (XX).**—A suspension of 0.208 g. of finely divided 1-(*cis*-3,*cis*-4-oxidocyclopentyl)-thymine (XIV) in 15 ml. of methanol containing 0.1 ml. of 72% perchloric acid was stirred for 14.5 hr. The resulting solution was neutralized with 0.4 ml. of 2 *M* aqueous potassium carbonate, then evaporated to dryness. Extraction of the residue with 4  $\times$  4 ml. of chloroform, evaporation of the extracts and crystallization of the residue from butanone gave 0.168 g. (70%) of rods, m.p. 184–185° or m.p. 184–186° after recrystallization,  $\lambda_{\text{max}}^{\text{CH}_3\text{OH}}$  272 m $\mu$  ( $\epsilon$  10,300).

*Anal.* Calcd. for C<sub>11</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub>: C, 54.99; H, 6.71; N, 11.66. Found: C, 55.12; H, 7.04; N, 11.76.

***N*-(*trans*-2-Hydroxy-*trans*-4-(1-thyminyl)-cyclopentyl)-pyridinium Hydroxide, Inner Salt (XXI).**—A solution of 0.208 g. of 1-(*cis*-3,*cis*-4-oxidocyclopentyl)-thymine (XIV) in 3.33 ml. of 50% aqueous pyridine was heated at 100° for 75 min., then evaporated to dryness with no more heat than necessary. The residual brown glass partly dissolved in 1.5 ml. of hot ethanol, then crystallized; yield 0.217 g. (76%) of a brown solid, m.p. 208–210° dec.;  $\lambda_{\text{max}}^{\text{H}_2\text{O}}$  262(sh), 267 and 280(sh) m $\mu$  ( $\epsilon$  13,300, 13,800 and 9,180)<sup>33</sup>;  $\lambda_{\text{max}}^{\text{KBr}}$  2.92, 3.16 (uncommonly weak), 3.7–4.1, 6.00, 6.06, 6.20, 6.32sh, 6.36sh, 6.42sh, 6.46 and 6.66  $\mu$ . The product was very soluble in water giving a solution of pH *ca.* 11. Satisfactory recrystallization methods for this compound and its salts with hydrochloric and acetic acids (below) were not found.

*Anal.* Calcd. for C<sub>16</sub>H<sub>17</sub>N<sub>3</sub>O<sub>3</sub>: C, 62.70; H, 5.96; N, 14.63. Found: C, 62.11; H, 5.82; N, 14.23.

***N*-(*trans*-2-Hydroxy-*trans*-4-(thymine-1-yl)-cyclopentyl)-pyridinium Chloride (XXII).**—A suspension of 0.057 g. (0.2 mmole) of the above inner salt XXI in 1 ml. of ethanol almost all dissolved when 0.022 g. (0.22 mmole) of 37.6% hydrochloric acid was added. The solution was filtered immediately, and the product immediately began to separate from the filtrate. The product was 0.041 g. of a brown solid which sintered and decomposed above 315°;  $\lambda_{\text{max}}^{\text{H}_2\text{O}}$  262(sh), 267 and 280(sh) m $\mu$  ( $\epsilon$  12,530, 13,040 and 8,500)<sup>33</sup>. In comparison with the above inner salt XXI, the infrared absorption at 3.15  $\mu$  was much enhanced, the sharp 6.0  $\mu$  band was broadened (5.9–6.0  $\mu$ , with a shoulder at 6.10  $\mu$ ) and the other bands listed for XXI were gone.

*Anal.* Calcd. for C<sub>15</sub>H<sub>15</sub>ClN<sub>3</sub>O<sub>3</sub>: C, 55.64; H, 5.60; Cl, 10.95; N, 12.98. Found: C, 54.55; H, 6.09; Cl, 10.77; N, 12.20.

***N*-(*trans*-2-Hydroxy-*trans*-4-(thymine-1-yl)-cyclopentyl)-pyridinium acetate** was prepared by the same procedure used for the chloride XXII (above), using decolorizing charcoal and two equivalents of acetic acid instead of hydrochloric acid. The cream-colored product had a m.p. of 158–162° dec. It was very hygroscopic and easily soluble in water;  $\lambda_{\text{max}}^{\text{H}_2\text{O}}$  262(sh), 267, 280(sh) m $\mu$  ( $\epsilon$  13,200, 13,600, 9,600)<sup>33</sup>.

(33) The ultraviolet absorption is probably a summation from two independent chromophores. The values  $\lambda_{\text{max}}^{\text{H}_2\text{O}}$  209 m $\mu$  ( $\epsilon$  5000) and 256 m $\mu$  ( $\epsilon$  5000) for 1-ethyl-pyridinium bromide were reported by H. B. Kleveris, *J. Polymer Sci.*, **10**, 97 (1953).

The infrared absorption spectrum resembled that of the above chloride except for a peak at  $6.3 \mu$  ( $\text{CH}_3\text{COO}^-$ ).

*Anal.* Calcd. for  $\text{C}_{17}\text{H}_{21}\text{N}_3\text{O}_3$ : C, 58.78; H, 6.09; N, 12.10; O, 23.03. Found: C, 57.14; H, 6.39; N, 12.28; O, 23.27.

**1-(trans-3-Amino-cis-4-hydroxycyclopentyl)-thymine (XX-III).**—A sealed tube containing 0.208 g. of finely divided 1-(cis-3,cis-4-oxidocyclopentyl)-thymine (XIV) and 5 ml. of methanolic ammonia (saturated at  $0^\circ$ ) was heated for 2 hr. in an oil-bath kept at  $123\text{--}127^\circ$ . The resulting solution was cooled, evaporated to dryness, and the residue was washed with methanol. The product (0.169 g., 75%) sintered with decomposition from 216 to  $222^\circ$ ;  $\lambda_{\text{max}}^{\text{CH}_3\text{OH}}$  272  $\mu$  ( $\epsilon$  9,340);  $\lambda_{\text{max}}^{\text{KBr}}$  2.90 ( $-\text{OH}$ , shoulder, uncommonly weak), 2.96, 3.00 and  $6.22 \mu$  ( $-\text{NH}_2$ ).

*Anal.* Calcd. for  $\text{C}_{10}\text{H}_{15}\text{N}_3\text{O}_3$ : C, 53.32; H, 6.71; N, 18.66. Found: C, 53.26; H, 6.91; N, 17.90.

A strictly comparable reaction run with concentrated aqueous ammonia gave 0.164 g. of product, m.p.  $215\text{--}220^\circ$  dec. It gave an infrared spectrum identical with that of the analytical sample.

**1-(cis-4?-Cyano-cis-3?-hydroxycyclopentyl)-thymine (XXIV).**—A mixture of 0.208 g. (1.0 mmole) of 1-(cis-3,cis-4-oxidocyclopentyl)-thymine (XIV) and 0.098 g. (2.0 mmoles) of sodium cyanide in 2 ml. of water was stirred and heated under reflux until the solid had all dissolved (20 min.) and then for another 5 min. The solution was cooled, weakly acidified with 0.3 ml. of acetic acid, then evaporated to dryness. The residue was subjected to partition chromatography<sup>25b</sup> with the system ethyl acetate-heptane-methanol-water (4:3:3:2). A peak eluted in the second hold-back-volume (H.B.V.) was evaporated to dryness. The residue (0.037 g.) was washed with acetone, leaving 0.010 g. of crystals with a m.p. of  $156\text{--}165^\circ$  and an infrared absorption spectrum identical with that of 1-(3-cyclopenten-1-yl)-thymine (I).<sup>34</sup> A small peak centered in the fifth H.B.V. was not investigated. Compounds remaining on the column were removed with methanol, the methanol was evaporated and the residue subjected to partition chromatography with the system ethyl acetate-methanol-water (8:2:1). A peak centered in the second H.B.V. gave 0.015 g. of residual solid, m.p.  $251\text{--}257^\circ$ , with an infrared spectrum identical with that of the starting *cis,cis*-oxide XIV. The eluate corresponding to a peak in the third H.B.V. was concentrated to a volume of ca. 3 ml. This solution deposited 0.106 g. of crystals, m.p.  $262\text{--}265^\circ$  dec. Recrystallization from 1.5 ml. of 2-methoxyethanol gave 0.010 g. of crystals, m.p.  $250\text{--}254^\circ$ , with an infrared spectrum identical with that of the *trans*-4-cyano-*cis*-3-hydroxy compound XXV (below). The 2-methoxyethanol mother liquor was evaporated to dryness and the residue crystallized from pyridine-ether; yield 0.080 g. (34%), m.p.  $258\text{--}265^\circ$  or m.p.  $265\text{--}272^\circ$  after recrystallization;  $\lambda_{\text{max}}^{\text{CH}_3\text{OH}}$  270  $\mu$  ( $\epsilon$  9,480), min. 237  $\mu$  ( $\epsilon$  1,830),  $\epsilon_{\text{max}}/\epsilon_{\text{min}}$  5.18;  $\lambda_{\text{max}}^{\text{KBr}}$  2.91 ( $-\text{OH}$ ), 3.17 ( $-\text{NH}$ ) and 4.44  $\mu$  ( $-\text{CN}$ ), distinguished from isomers XXV and XXVI by a peak at 9.71  $\mu$  and the absence of appreciable absorption between 10 and 10.6  $\mu$ .

*Anal.* Calcd. for  $\text{C}_{11}\text{H}_{13}\text{N}_3\text{O}_3$ : C, 56.16; H, 5.57; N, 17.86. Found: C, 56.02; H, 5.96; N, 17.70.

**1-(trans-4-Cyano-cis-3-hydroxycyclopentyl)-thymine (XXV).**—A suspension of 0.208 g. of 1-(cis-3,cis-4-oxidocyclopentyl)-thymine (XIV) in 15 ml. of water and 15 ml. of tetrahydrofuran containing 2.0 ml. of hydrogen cyanide and 0.2 ml. of diisopropylmethylamine was stirred and heated under reflux ( $64^\circ$ ) for 22 hr. The resulting solution was very dark and a dark solid was present. (The *cis,cis*-oxide had all dissolved just before refluxing began. This gave a pale yellow, homogeneous solution, but at the reflux temperature two liquid phases were present. On slight cooling these gave a single phase again.) The solution was allowed to cool and filtered from 0.045 g. of black solid which was discarded. The filtrate was received into a flask containing 0.5 ml. of acetic acid in an attempt to prevent further polymerization of hydrogen cyanide. This filtrate

was evaporated almost to dryness. The residue was dissolved in 10 ml. of hot water, the resulting solution ( $\text{pH } 5$ ), was filtered from a dark solid, then freeze-dried, leaving 0.355 g. of a dark, gummy solid. This was augmented with material extracted from the above dark solids with 15 ml. of hot ethanol. Recrystallizations from 2-methoxyethanol and from ethanol using decolorizing charcoal gave a total of 0.015 g. of recovered *cis,cis*-oxide XIV, identified by its infrared spectrum. The residue from evaporation of the combined mother liquors was fractionated by partition chromatography<sup>25b</sup> with the system ethyl acetate-heptane-water (8:2:1). Evaporation of an eluate peak fraction from the second hold-back-volume (H.B.V.) left a residue which was washed with benzene, leaving 0.007 g. of needles, m.p.  $254\text{--}261^\circ$ , with an infrared spectrum identical with that of the starting *cis,cis*-oxide. Another peak was centered at the end of the third H.B.V., with a shoulder extending into the fifth H.B.V. Residues from the two eluate fractions from this range were separately subjected to another partition chromatography. The peak eluate fractions gave residues which were washed with benzene and with ethanol, leaving crystals (0.004 g., m.p.  $257\text{--}259^\circ$ , and 0.005 g., m.p.  $257\text{--}259^\circ$ ) which showed identical infrared absorption spectra:  $\lambda_{\text{max}}^{\text{KBr}}$  2.96 ( $-\text{OH}$ ), 3.11 ( $-\text{NH}$ ) and 4.45  $\mu$  ( $-\text{CN}$ ), with peaks at 10.30, 11.02 and 12.22  $\mu$  (broad) which distinguished this compound from its isomers XXIV and XXVI. The ultraviolet absorption maximum in methanol was at 270  $\mu$  ( $\epsilon$  10,050), the minimum at 237  $\mu$  ( $\epsilon$  2,440),  $\epsilon_{\text{max}}/\epsilon_{\text{min}}$  4.12.

*Anal.* Calcd. for  $\text{C}_{11}\text{H}_{13}\text{N}_3\text{O}_3$ : C, 56.16; H, 5.57; N, 17.86. Found: C, 56.10; H, 5.64; N, 18.00.

**1-(cis-4-Cyano-trans-3-hydroxycyclopentyl)-thymine (XXVI).**—The reaction procedure paralleled that of the preceding experiment on a tenfold larger scale, using 2.082 g. of 1-(*trans*-3,*trans*-4-oxidocyclopentyl)-thymine (XV).<sup>30</sup> The heating period was reduced to 15 hr. The reaction mixture was evaporated to dryness, then evaporated to dryness thrice more with 25-ml. portions of ethanol to remove the last of the residual volatile reagents. The residue was heated with 100 ml. of ethanol, cooled and the solution filtered from 0.997 g. of a dark brown solid which was discarded. The solution was evaporated to dryness and the residue (2.935 g.) fractionated by partition chromatography<sup>25b</sup> with the system ethyl acetate-heptane-water (8:2:1). A peak in the first hold-back-volume (H.B.V.) gave a substantial amount of a semi-crystalline, brown residue which was shown by paper chromatography to be a complex mixture of blue- and yellow-fluorescing substances. A peak centered in the second H.B.V. had a small shoulder in the latter part of the first H.B.V. From this shoulder was obtained a residue which was crystallized from butanone to give 0.015 g. of a brown solid, m.p.  $245\text{--}254^\circ$ ; the infrared spectrum showed it to be 1-(*cis*-3,*cis*-4-oxidocyclopentyl)-thymine (XIV). The rest of the peak gave a residue which crystallized from butanone as a yellow-tan solid (0.406 g., 20% recovery), m.p.  $205\text{--}210^\circ$ . The infrared absorption spectrum was that of the starting *trans,trans*-oxide XV with additional small bands at 7.82 and 8.37  $\mu$ . A peak centered at the end of the fourth H.B.V. gave a residue which crystallized from butanone as 0.443 g. (19%) of a tan solid, m.p.  $228\text{--}231^\circ$ . Colorless material from a similar experiment<sup>35</sup> had an identical infrared spectrum and a m.p. of  $231\text{--}233^\circ$ ;  $\lambda_{\text{max}}^{\text{CH}_3\text{OH}}$  270  $\mu$  ( $\epsilon$  10,200), min. 239  $\mu$  ( $\epsilon$  3,720),  $\epsilon_{\text{max}}/\epsilon_{\text{min}}$  2.74;  $\lambda_{\text{max}}^{\text{KBr}}$  2.93 ( $-\text{OH}$ ), 3.18 ( $-\text{NH}$ ) and 4.49  $\mu$  ( $-\text{CN}$ ) with bands at 8.06, 10.12 and 11.52  $\mu$  that were not present in the isomers XXIV and XXV. Paper chromatography generally did not distinguish this compound from its isomers, but with the system benzene-methanol- $\text{H}_2\text{O}$  (2:1:1)<sup>36</sup> at  $36^\circ$  the  $R_f$  was 0.01 (1.1 cm./29 hr.) vs.  $R_f$  0.02 (2.2 cm./29 hr.) for both of the other isomers.

*Anal.* Calcd. for  $\text{C}_{11}\text{H}_{13}\text{N}_3\text{O}_3$ : C, 56.16; H, 5.57; N, 17.86. Found: C, 56.21; H, 5.80; N, 17.72.

The column was eluted with 4 l. of methanol. The methanol was evaporated and the resulting residue washed with dimethylformamide and with ether, leaving 0.413 g. of

(34) This compound may well have been present as a trace contaminant in the starting *cis,cis*-oxide XIV. A weak infrared absorption peak at 14.33  $\mu$  was seen for all samples of *cis,cis*-oxide which were checked except those isolated by partition chromatography. The olefin I has a strong absorption at 14.33  $\mu$ .

(35) In the similar experiment a substantial decolorization was achieved prior to the partition chromatography by agitating an ethanolic solution of the crude product with four parts by weight of Dowex-50 polysulfonic acid resin.

(36) I. B. Bush, *Biochem. J.*, **50**, 370 (1952).

crystals. These were extracted with 5 ml. of water. Evaporation of the extract left 0.327 g. (16%) of crystals, m.p. 239–241° or m.p. 237–239° after crystallization from di-

methylformamide. This material gave an infrared spectrum identical with that of 2,3'-anhydro-1-(*cis*-3,*trans*-4-dihydroxycyclopentyl)-thymine (XII).

[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO., PEARL RIVER, N. Y.]

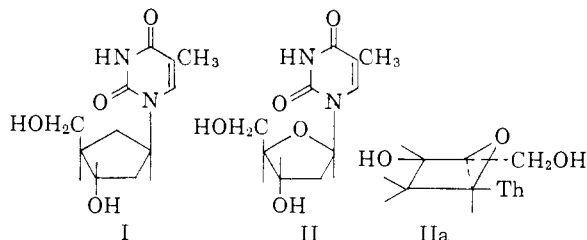
## Synthesis and Proof of Structure of the Cyclopentane Isostere of Thymidine. Steric Control in the Prins Condensation of Formaldehyde with a Cyclopentenylthymine<sup>1</sup>

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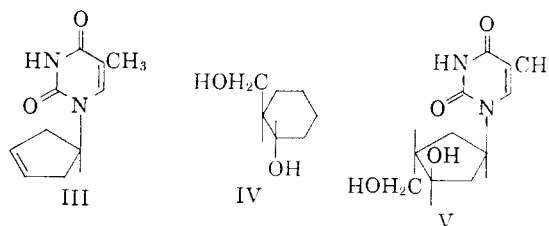
1-(3-Cyclopenten-1-yl)-thymine (III) was converted stereospecifically to the cyclopentane isostere I of thymidine. A convenient reaction sequence developed for this transformation included: (a) sulfuric acid-catalyzed condensation with paraformaldehyde in acetic acid, (b) reaction with acetic anhydride and sulfuric acid for the acetolysis of cyclic formals and (c) methanolysis of acetate groups. The isolation of intermediates was not required. The relative configurations at the three asymmetric centers of the diol I were established by two sequences of reactions leading to definitive intramolecular ring closures. The resulting cyclized products IX, X and XIV are anhydronucleoside analogs. It is postulated that the stereospecificity in the synthesis of I results from the formation of a non-classical carbonium ion intermediate such as XVb in which formaldehyde is bound to the thymine group. The cyclopentane isostere XVIII of thymidylic acid was synthesized.

Antimetabolites or possible metabolic substitutes for thymidine are of special interest because the enzyme systems required for the incorporation of thymidine into deoxyribonucleic acid seem to be uniquely associated with the capacity for rapid cell proliferation.<sup>2a</sup> We hoped to prepare the cyclopentane isostere I of thymidine(II) as a likely tool for cancer chemotherapy,<sup>2b</sup> for the induction of mutations,<sup>3</sup> or for the study of nucleic acid metabolism.<sup>4</sup> The steric relationships in I and II should be very similar. A comparison of



results from X-ray, molecular polarizability and proton magnetic resonance studies of nucleosides and other compounds shows the expected similarities in bond lengths and angles in tetrahydrofuran<sup>5</sup> and cyclopentane<sup>6</sup> ring systems. In both

systems there are favored conformations in which four of the ring atoms are approximately coplanar while a fifth atom is puckered about 0.5 Å. out of the plane of the other four. From proton magnetic resonance spectroscopic data it has been concluded that thymidine has considerable conformational rigidity, with the oxygen atom of the tetrahydrofuran ring puckered up as indicated in conformation IIa.<sup>5b</sup> From an inspection of molecular models an analogous conformation would also be predicted as the most stable form for the cyclopentane isostere I, since it should minimize non-bonded interactions between the substituents on the cyclopentane ring. Syntheses leading to 1-(3-cyclopenten-1-yl)-thymine (III) are reported separately.<sup>7</sup> A stereospecific approach to the problem of the three



asymmetric centers in the diol I *via* an epoxide derivative of the olefin III was theoretically attractive but experimentally impractical.<sup>8</sup> Another possible approach to the diol I was to apply the Prins reaction to the olefin III. This reaction, the acid-catalyzed condensation of olefins with formaldehyde, has been used occasionally for the synthesis of 1,3-diols. Reaction in sulfuric acid has given 1,3-diols in fair to good yields, predominantly in

(1) Presented at the 141st Meeting of the American Chemical Society, Washington, D. C., March, 1962.

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