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EVIDENCE FOR ZWITTERIONIC STRUCTURES FOR ANHYDRONUCLEOSIDE DERIVATIVES OF THYMINE AND URACIL

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PYRIMIDINE anhydronucleosides,[1] obtained by intramolecular displacement reactions of sterically suitable nucleoside esters (sulfonates,[2,3] halides,[4-6] and pyrophosphates[7]) or epoxides,[8] have become increasingly valuable in enabling structural assignments and as intermediates for stereo-

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[1] D.M. Brown, A. Todd and S. Varadarajan in Ciba Foundation Symposium on the Chemistry and Biology of Purines (Edited by G.E.W. Wolstenholme and C.M. O'Connor) p. 108. J. and A. Churchhill, London (1957); J.J. Fox and I. Wempen in Advances in Carbohydrate Chemistry (Edited by M.L. Wolfrom) Vol. 14, p. 214. Academic Press, New York (1959).

[2] V.M. Clark, A.R. Todd and J. Zussman, J. Chem. Soc. 2952 (1951); W. Anderson, D.H. Hayes, A.M. Michelson and A.R. Todd, Ibid. 1882 (1954).

[3a] D.M. Brown, A. Todd and S. Varadarajan, J. Chem. Soc. 2388 (1956); [b] D.M. Brown, D.B. Parihar, A. Todd and S. Varadarajan, Ibid. 3028 (1958); [c] J.J. Fox, N. Yung and A. Bendich, J. Amer. Chem. Soc. 79, 2775 (1957); [d] J.J. Fox, J.F. Codington, N.C. Yung, L. Kaplan and J.O. Lampen, Ibid. 80, 5155 (1958); [e] J.F. Codington, R. Fecher and J.J. Fox, Ibid. 82, 2794 (1960); J. Org. Chem. 27, 163 (1962); [f] N.C. Yung and J.J. Fox, J. Amer. Chem. Soc. 83, 3060 (1961); [g] R. Letters and A.M. Michelson, J. Chem. Soc. 1410 (1961).

[4] A.M. Michelson and A.R. Todd, J. Chem. Soc. 816 (1955).

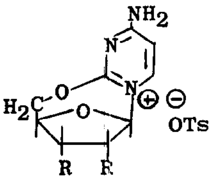
[5] G.B. Brown and A. Bendich in ref. 1a, pp. 116, 117; D.M. Brown, D.B. Parihar, C.B. Reese and A. Todd, J. Chem. Soc. 3035 (1958); D.M. Brown, D.B. Parihar and A. Todd, Ibid. 4242 (1958).

[6] D.M. Brown, A.R. Todd and S. Varadarajan, J. Chem. Soc. 868 (1957); J.P. Horwitz and A.J. Tomson, Abstracts of Papers presented at the American Chemical Society Meeting, Chicago, 1961, pp. 14-O.

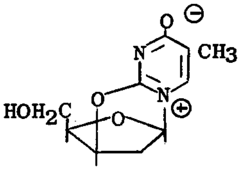
[7] E.R. Walwick, W.K. Roberts and C.A. Dekker, Proc. Chem. Soc. 84 (1959).

[8] R. Fecher, J.F. Codington and J.J. Fox, J. Amer. Chem. Soc. 83, 1889 (1961); E.J. Reist, J.H. Osiecki, L. Goodman and B.R. Baker, Ibid. 83, 2208 (1961).

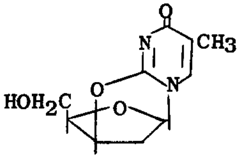
regulated transformations in the sugar moieties of the nucleosides. They have also been considered as possible intermediates in the biosynthesis of the deoxyribonucleotides.[5,9] The first pyrimidine anhydronucleosides, obtained by Todd and co-workers from cytosine derivatives, were p-toluenesulfonate salts which were necessarily assigned ionic structures (I).[2]



I



IIa



IIb

Analogously, anhydrothymidines free of an external anion were initially pictured as zwitter ions such as IIa.[4] But in subsequent publications dealing with anhydronucleoside derivatives of thymine and uracil the Todd group and others have tacitly rejected dipolar representations in favor of covalent structures analogous to IIb.[1,3,5-8] We now wish to submit evidence favoring zwitterionic representations for such compounds.

In 83 per cent sulfuric acid at room temperature 1-(3-cyclopenten-1-yl)thymine[10] (III, m.p. 168°-169°) is rapidly isomerized. The distinctive spectral properties of the isomer [IV, 79% yield, m.p. 236°-237°; $\lambda_{max}^{H_2O}$ 230 mμ(ε 6,950) and 258 mμ(ε 7,790); λ_{max}^{KBr} 6.02, 6.16, 6.36 and 6.55 μ, with neither the 3.15 μ (NH) or 14.3 μ (*cis* olefin) band of III] show [cf. 3d,f] that it is very closely related to the pyrimidine anhydronucleosides.[11] 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

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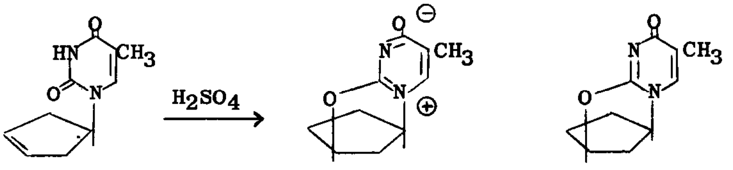
[9] P. Reichard, J. Biol. Chem. 234, 2719 (1959).

[10] K.C. Murdock and R.B. Angier, J. Org. Chem. in press.

[11] Supporting spectral data and satisfactory analytical results for at least three elements were obtained for all new compounds mentioned.

not be obscured by effects due to the hydroxyl groups or other substituents usually present in anhydronucleosides. In contrast with III, 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.[12] In chloroform it dissolved to an extent of just 2 per cent, compared to 33 per cent for III (wt./wt. at 23°). Solubility 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 was confirmatory. Experience with a variety of 1-substituted thymines[13] and other compounds in the system butanone-water, 9:1, has shown that R_f values show a good inverse correlation with the polarities that would be anticipated from the nature of the substituents. The R_f values obtained concurrently for III 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



III **IVa** **IVb**

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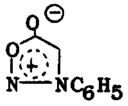
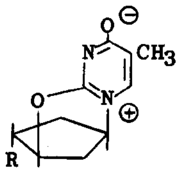
[12] In addition to IVa and IVb, other probable contributing resonance forms would include the alternative Kekulé form and structures with negative charge on the nitrogen atom not at the bridgehead and/or positive charge on the ethereal oxygen atom, making a total of at least ten possible forms. A systematic name for IVa is 6,7,8,9-tetrahydro-2-hydroxy-3-methyl-6,9-methanopyrimido-[2,1-b]-[1,3] oxazapin-5-ium hydroxide, inner salt.

[13] K.C. Murdock and R.B. Angier, papers in press.

structure, IVb.[14] Thus the physical properties of IV indicate that it is even more polar than phenylsydnone (V) and related 5-membered heterocycles, compounds with valency requirements allowing them to be represented plausibly only with zwitterionic structures.[15]



V



VI

Compounds analogous to IVa in their spectra and other properties were formed with a facility consonant with the formation of aromatic structures. Reaction of the olefin III with perbenzoic acid in benzene gave a pair of isomeric epoxides. One of these epoxides (m.p. 214°-216°) could be converted to a hydroxyanhydro compound (VIa, R = OH, m.p. 251°-253°) merely by treatment with hot water. The olefin III and hypobromous acid (from N-bromoacetamide and perchloric acid in dioxane) reacted at room temperature to give a bromoanhydro compound (VIb, R = Br, m.p. 169°-170°).

Some reactions of IVa and a synthesis of the cyclopentane isostere of thymidine will be reported in complete form.

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[14] In a control study the observed and calculated values for III 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 American Cyanamid Co., Stamford, Conn. Because of solubility limitations the measured figures were obtained from 2 per cent 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 per cent lower than chloroform solutions.

[15] W. Baker and W.D. Ollis, Quart. Rev. 11, 15 (1957).