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APPLICATION OF NMR SPECTROSCOPY IN DISTINGUISHING BETWEEN N_1- AND N_3-SUBSTITUTED 2,4-DIOXO-1,2,3,4,-TETRAHYDROPYRIMIDINES.

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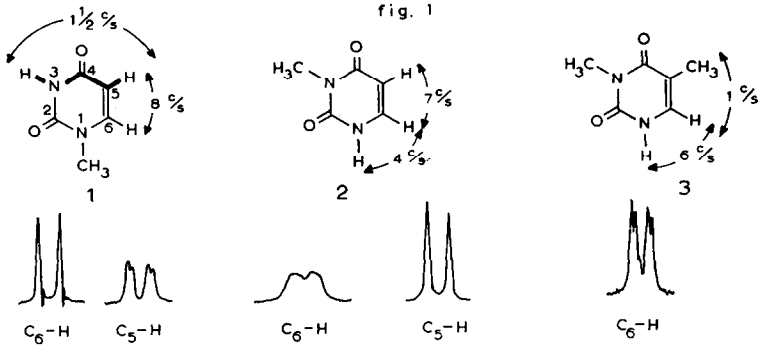
The classical method of distinguishing between N_1- and N_3-substituted uracil and thymine derivatives makes use of the correlation between structure - of the positional isomer - and the pH-dependent shift of the UV maximum.[3] The method is, at best, cumbersome in practice and suffers from the usual restrictions of solubility in the desired media.

In the course of our studies on nucleotide analogues[4] we were confronted with the requirement of a simple and rapid method for recognizing the positional isomers of N-substituted uracils and thymines. Of the various available spectral approaches to the problem, the use of NMR spectroscopy appeared to us to be most promising in view of its potential information-content.

fig. 1



An examination of the spectrum of N_1-methyluracil (1) in $CDCl_3$ showed that although both C_5- and C_6-protons appeared as doublets, the doublet from H_5 was diffused while that from H_6 consisted of two sharp peaks. In dry DMSO-d_6, the H_5 signal sharpened into a weakly coupled doublet. In contrast to this pattern the spectrum of N_3-methyluracil (2) exhibited the H_5 as a sharp doublet and the H_6 as two considerably broadened peaks. The

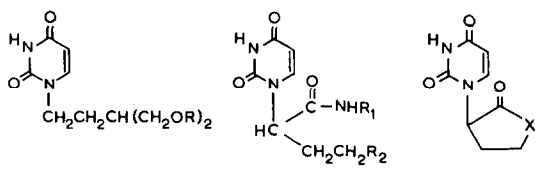
spectrum of N_3-methylthymine (3) gave a pair of weakly coupled peaks for the C_6-proton. The essential features of the spectra of 1, 2 and 3 are shown in fig. 1.

The small coupling of H_5 in 1 (J= 1.5 c/s) arises from the long-range interaction with N_3-H. Such coupling has been frequently observed for protons located at the ends of W-shaped bonds.[5] Exchange of the N_3-proton by deuterium or irradiation at N-H (double resonance) removed this splitting and showed H_5 as a sharp doublet (J= 8 c/s).

In 2, H_6 is coupled with both H_5 and N_1-H (J= 4 c/s) and in 3, the corresponding proton is coupled strongly with N_1-H (J = 6 c/s) and weakly with the allylic protons of the C_5-CH_3 group (J= 1 c/s). These coupling constants have been evaluated by deuterium exchange of N-H and double resonance techniques.

The long-range coupling of H_5 with N_3-H has been observed by us in the case of a large number of N_1-substituted uracil derivatives (Chart I). It would appear, therefore, that NMR spectroscopy is a convenient technique for identifying the positional isomers of N-substituted uracils and thymines.

Chart I*



R	R_1	R_2	X
1 H	5 $CH_2C_6H_5$	OH	9 O
2 $COCH_3$	6 $CH_2C_6H_5$	Cl	10 $NCH_2C_6H_5$
3 $CH_2C_6H_5$	7 $CH_2CH_2OCH_2C_6H_5$	OH	11 NCH_2CH_2Cl
4 $C(C_6H_5)_3$	8 $CH_2CH_2OCH_2C_6H_5$	Cl	12 $NCH_2CH_2OCCH_3$ (O)
			13 $NCH_2CH_2OCH_2C_6H_5$

* (a) In compounds 1-13 $J_{H_3H_5}$ varies between 1.5 - 2 c/s and $J_{H_5H_6}$ is ~ 8 c/s. All spectra were measured in DMSO-d_6.

(b) Correct analyses and spectral data have been obtained for the compounds described. Their syntheses will be presented elsewhere.

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