344. *Pyrimidines. Part IX.* The Ultraviolet Absorption Spectra of the Isomeric* O : 6- *and* N : 6-*Dimethyluracils.*

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The ultraviolet absorption spectra of the compounds named in the title are discussed. Thermal isomerisation of 4-hydroxy-2-methoxy-6-methyl- and of 2-hydroxy-4-methoxy-6-methyl-pyrimidine yields 3 : 6- and traces of 1 : 6-dimethyluracil respectively, together with some 6-methyluracil.

In the ultraviolet absorption spectra [1,2] of mono- and of poly-substituted pyrimidines containing not more than one potentially tautomeric group, the effect of the individual substituents on both the wavelength of maximum absorption and the extinction coefficient is approximately additive. In general the calculated values for $\lambda_{max.}$ agreed with those observed within 6 mμ (mostly within 4 mμ), unless steric hindrance prevented coplanarity of the substituent with the pyrimidine ring. However, the predicted wavelength [2] (286·5 mμ) for 4-hydroxy-2-methoxy-6-methylpyrimidine was greatly different at pH 13 from that observed [3] (263 mμ) and it was considered possible that the *O*-methyl group had migrated to one of the nitrogen atoms, under the action of the aqueous alkali or of ultraviolet light (during the measurement of the spectrum); it is known that the compound undergoes thermal isomerisation.[3] The first alternative was disproved when it was found that the 2-methoxy-compound could be recovered after one hour in solution in alkali. The alternative was investigated by studying the spectra of the isomeric *N* : 6-dimethyluracils.

Direct methylation of 6-methyluracil gives a difficultly separable mixture of 1 : 6- and 3 : 6-dimethyl- and 1 : 3 : 6-trimethyl-uracil.[4] The pure 3 : 6-dimethyl compound was made by Wheeler and McFarland's method,[5] *i.e.*, by methylating 4-hydroxy-6-methyl-2-methylthiopyrimidine with methyl iodide and hydrolysing the resulting 3 : 4-dihydro-3 : 6-dimethyl-2-methylthio-4-oxopyrimidine with concentrated hydrochloric acid. Methylation of 2 : 4-dimethoxypyrimidine is known to give 1 : 2-dihydro-1-methyl-4-methoxy-2-oxopyrimidine which can be hydrolysed to 1-methyluracil [6] and we have used the same reagents to convert 2 : 4-dimethoxy-6-methylpyrimidine into 1 : 6-dimethyluracil in good yield.

Compound	pH of aq. soln.	$\lambda_{max.}$ (mμ)	$\log_{10}\varepsilon$	$\lambda_{min.}$ (mμ)	$\log_{10}\varepsilon$
4-Hydroxy-2-methoxy-6-methylpyrimidine	13	222	3·85	242	3·51
		(222 *)	(3·83 *)		
		263	3·88		
		(263 *)	(3·87 *)		
2-Hydroxy-4-methoxy-6-methylpyrimidine	13	222	4·01	246	3·24
		275·5	3·91		
1 : 6-Dimethyluracil	13	265	3·90	241	3·48
3 : 6-Dimethyluracil	13	220	3·85	245	2·98
		280·5	4·07		
The 4-hydroxy-compound after thermal isomerisation	13	219	3·91	245	3·20
		280·5	4·07		
6-Methyluracil	13	277	3·83 *		
4-Methoxypyrimidine	6·95	247·5	3·53 †	—	—
,,	Ethanol	248	3·45	—	—

* Quoted from ref. 3. † Quoted from Brown, Hoerger, and Mason, *J.*, 1955, 211.

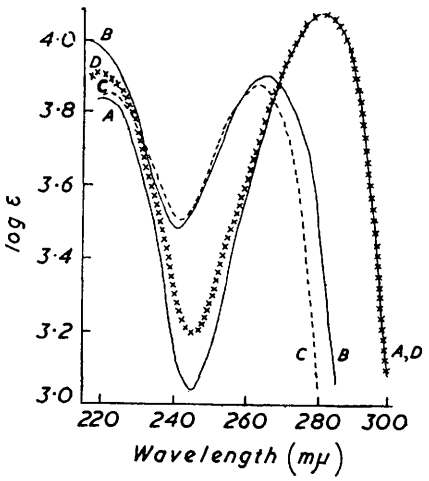
The ultraviolet absorption spectra of the pyrimidines under discussion are shown in the Table and the Figure. The spectrum of 4-hydroxy-2-methoxy-6-methylpyrimidine

* Part VIII, *J.*, 1955, 3478.

[1] Boarland and McOmie, *J.*, 1952, 3716.
[2] *Idem, ibid.*, p. 3722.
[3] Marshall and Walker, *J.*, 1951, 1004.
[4] Behrend and Thurm, *Annalen*, 1902, **322**, 165.
[5] Wheeler and McFarland, *Amer. Chem. J.*, 1909, **42**, 101.
[6] Hibbert and Johnson, *J. Amer. Chem. Soc.*, 1930, **52**, 2001.

at pH 13 agreed with that recorded by Marshall and Walker;[3] it is different from those of 1 : 6- and 3 : 6-dimethyluracil even though it closely resembles that of the former (see Figure); and we conclude that no rearrangement occurred during the measurement of its spectrum. The difference between the observed and the predicted $\lambda_{max.}$ for the 4-hydroxy-compound ($\Delta\lambda = -23{\cdot}5$ mμ) is comparable with that for compounds containing two potentially tautomeric groups, *e.g.*, 2-amino-4-hydroxypyrimidine at pH 13 has $\lambda_{max.}$ at 273 mμ,[7] whereas the predicted value would be 313·5 mμ. Other methoxypyrimidines are also anomalous: 2 : 4-dimethoxypyrimidine (in ethanol) [8] has $\lambda_{max.}$ 258 mμ (predicted 271·5 mμ) and 2 : 4 : 6-trimethoxypyrimidine [9] at pH 5·0—13 has $\lambda_{max.}$ 248 mμ (predicted 273 mμ), while 4-amino-2-methoxypyrimidine [10] at pH 7·2 has $\lambda_{max.}$ 270·5 mμ (predicted 289 mμ).

Recently [11] the additivity rule was found to apply to derivatives of pyridazine and of pyridaz-6-one which contained not more than one strongly inductive or conjugative substituent. The two isomeric 4-methoxypyridazines and the one 4-methoxypyridaz-6-one examined gave anomalous results and the 4-methoxy-group appeared to act as a strongly inductive or conjugative group. In the pyrimidine series the 2-methoxy-group causes a bathochromic shift of 21 mμ (23·5 in ethanol), whereas the 4-methoxy-group (see Table) produces a shift of only 4·5 mμ (4 in ethanol); nevertheless, the predicted $\lambda_{max.}$ (295·5 mμ) for 2-hydroxy-4-methoxy-6-methylpyrimidine at pH 13 does not agree with that observed (275·5 mμ), and it must be concluded that the additivity rule does not apply to pyrimidines containing a 2- or 4-methoxy-group as well as a potentially tautomeric substituent, nor does it apply to 2 : 4-di- or 2 : 4 : 6-tri-methoxypyrimidine.



Absorption spectra of:
A, 3 : 6-*Dimethyluracil.*
B, 1 : 6-*Dimethyluracil.*
C, 4-*Hydroxy-2-methoxy-6-methylpyrimidine.*
D, *The latter after thermal rearrangement.*

2-Hydroxy-4-methoxy-6-methylpyrimidine was made by taking advantage of the reactivity of the 2-methylsulphonyl group of 4-methoxy-6-methyl-2-methylsulphonyl-pyrimidine (cf. ref. 12), itself prepared by the action of chlorine on an ice-cold aqueous suspension of 4-methoxy-6-methyl-2-methylthiopyrimidine. The 2-methylsulphonyl group has about the same reactivity as that of the 2-chloro-group, and, like many chloro-pyrimidines, the 2-methylsulphonyl compound was lachrymatory and vesicant. Alkaline hydrolysis of the 2-methylsulphonyl compound gave the desired 2-hydroxy-4-methoxy-6-methylpyrimidine. During the work, the latter compound was described by Ochiai and

[7] Stimson and Reuter, *ibid.*, 1945, **67**, 2191.
[8] Austin, *ibid.*, 1934, **56**, 2141.
[9] Shugar and Fox, *Bull. Soc. chim. belg.*, 1952, **61**, 44.
[10] *Idem*, *Biochim. Biophys. Acta*, 1952, **9**, 199.
[11] Eichenberger, Rometsch, and Druey, *Helv. Chim. Acta*, 1954, **37**, 1298.
[12] Andrews, Anand, Todd, and Topham, *J.*, 1949, 2490.

Yamanaka [13] who made it by the action of toluene-*p*-sulphonyl chloride, followed by 10% aqueous potassium carbonate, on the *N*-oxide of 4-methoxy-6-methylpyrimidine.

That 4-hydroxy-2-methoxy-6-methylpyrimidine is isomerised by heat has been noted previously [3] and we have now shown that the product is 3 : 6-dimethyluracil, together with a little 6-methyluracil. Similar isomerisation of 2-hydroxy-4-methoxy-6-methylpyrimidine did not proceed smoothly and the chief product was 6-methyluracil. In some experiments traces of 1 : 6-dimethyluracil were obtained. Both 3 : 6- and 1 : 6-dimethyluracil were unchanged when heated under the conditions used for isomerisation of the methoxypyrimidines. The rearrangement of the 4-methoxy-compound is probably intermolecular and is in contrast with that of 4-methoxypyrimidine itself which readily yields 1 : 6-dihydro-1-methyl-6-oxopyrimidine.[14]

Experimental

1 : 6-*Dimethyluracil.*—2 : 4-Dimethoxy-6-methylpyrimidine [15] (2 g.) in methyl iodide (30 ml.) was kept for 3 days at room temperature. The solvent was evaporated, N-hydrochloric acid (50 ml.) was added, and after 1·5 hr. the solution was made neutral and evaporated to dryness (water-bath). Extraction of the residue with chloroform yielded 1 : 6-dimethyluracil (1·5 g., 82%), m. p. 218—220°, raised by recrystallisation from water to m. p. 220° alone or mixed with an authentic sample kindly supplied by Dr. W. Hepworth [16]

Thermal Isomerisation of 4-Hydroxy-2-methoxy-6-methylpyrimidine.—The 2-methoxy-compound (500 mg.) was packed into capillary m. p. tubes so that each contained about 0·5 in. of solid. These tubes were packed fairly tightly into a test-tube which was then heated in an oil-bath at the rate of 5°/min. The compound melted at 190—195° and partly resolidified; heating was continued at 205—208° for 10 min. After having been cooled, the capillary tubes were crushed and the pale brown residue extracted with boiling water (40 ml.). The aqueous extract was treated with charcoal and evaporated to *ca.* 3 ml., from which there separated needles (300 mg.), m. p. 255—260° (decomp.). After recrystallisation from water, they melted at 263—265° (decomp.). This compound was shown to be identical with 3 : 6-dimethyluracil by mixed m. p., the similarity of their spectra (see Figure), and by paper chromatography.

With solvent A (benzene–ethanol–water, 169 : 45 : 15 by vol.) the product gave two spots, when viewed under ultraviolet light, consisting of 3 : 6-dimethyluracil (R_F 0·49) and 6-methyluracil (R_F 0·08); no starting material (R_F 0·65) could be detected. With solvent B (*tert.*-butyl alcohol–benzene–water, 60 : 15 : 45) the product showed 6-methyluracil (R_F 0·63) and a spot at R_F 0·85 of 3 : 6-dimethyluracil and/or starting material.

4-*Chloro*-6-*methyl*-2-*methylthiopyrimidine.*—4-Hydroxy-6-methyl-2-methylthiopyrimidine (25 g.), phosphoryl chloride (160 ml.), and dimethylaniline (10 ml.) were boiled under reflux for 1·5 hr. The chloropyrimidine was isolated in the usual way and sublimed at 100° (bath-temp.)/25 mm., giving needles (21 g., 75%), m. p. 37—38° (lit.,[17] m. p. 39—40°).

4-*Methoxy*-6-*methyl*-2-*methylthiopyrimidine.*—The above chloropyrimidine and a solution from sodium (2 g.) in methanol (100 ml.) were boiled under reflux for 3 hr. After being cooled and filtered, the solution was distilled, giving an oil (13·3 g., 91%), b. p. 125—130°/12 mm., which crystallised (lit.,[18] b. p. 126—130°/18 mm., m. p. 137—139°).

4-*Methoxy*-6-*methyl*-2-*methylsulphonylpyrimidine.*—The above 2-methylthio-compound (3·7 g.), suspended in water (40 ml.), was cooled in ice-water, and chlorine rapidly bubbled in until all the methylthio-compound had dissolved. Meanwhile the 2-methylsulphonylpyrimidine had begun to separate and was collected. A further crop was obtained by extracting the aqueous solution with chloroform. The total *product* recrystallised from 1 : 1 (v/v) chloroform–light petroleum (b. p. 60—80°) and then had m. p. 80° (yield, 3·2 g.) (Found: C, 39·5; H, 4·7; N, 13·6. $C_7H_{10}O_3N_2S$ requires C, 41·5; H, 4·95; N, 13·85%).

2-*Hydroxy*-4-*methoxy*-6-*methylpyrimidine.*—The methylsulphonyl compound (1·0 g.) rapidly dissolved in 10% aqueous sodium hydroxide (4 ml.) on the water-bath. Water (1 ml.) was

[13] Ochiai and Yamanaka, *Pharm. Bull.* (*Japan*), 1955, **3**, 175.
[14] Brown, Hoerger, and Mason, *J.*, 1955, 211.
[15] Gabriel and Colman, *Ber.*, 1901, **32**, 2921.
[16] Ainley, Curd, Hepworth, Murray, and Vasey, *J.*, 1953, 59.
[17] Wheeler and McFarland, *Amer. Chem. J.*, 1909, **42**, 435.
[18] Matsukawa and Shirakawa, *J. Pharm. Soc. Japan*, 1951, **71**, 933.

then added and heating continued for 0·5 hr. The mixture was cooled, then neutralised with dilute hydrochloric acid, and the solid collected and recrystallised from ethanol. The 2-hydroxy-4-methoxy-6-methylpyrimidine (0·3 g.) had m. p. 210—212° (Found : C, 51·4; H, 6·1; N, 19·9; OMe, 21·2. Calc. for $C_6H_8O_2N_2$: C, 51·5; H, 5·7; N, 20·0; OMe, 22·0%) (lit.,[13] m. p. 209—211°).

Thermal Isomerisation of 2-Hydroxy-4-methoxy-6-methylpyrimidine.—The 4-methoxypyrimidine (50 mg.) was heated in m. p. tubes at a rate of *ca.* 3°/min. up to 195° and kept at this temperature for 10 min. The dark brown residue was extracted with hot ethanol, and the solution (charcoal) concentrated to 0·5 ml. Light petroleum (b. p. 40—60°) was added and the precipitate (12 mg.) collected. On a paper chromatogram, solvent A (see above) showed the presence of starting material, and of 1 : 6-dimethyluracil and 6-methyluracil whose rates of movement *relative to that of the starting material* were 0·61 and 0·18, severally; solvent B showed spots of starting material (R_F 0·69), 1 : 6-dimethyluracil (R_F 0·58), and of 6-methyluracil (R_F 0·53). No trace of 3 : 6-dimethyluracil (relative rate of movement in solvent A 0·98 and R_F in solvent B 0·78) was found. In some experiments, no 1 : 6-dimethyluracil could be detected and 6-methyluracil was always the main product.

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