Simple Pyrimidines. Part II.† 1 : 2-*Dihydro*-1-*methylpyrimidines and the Configuration of the* N-*Methyluracils.*

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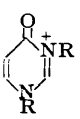
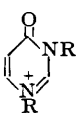
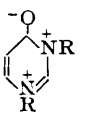
2- and 4-Hydroxypyrimidine are proved to exist in solution largely in the lactam form, by spectrographic comparison with their *N*-methyl derivatives (for differences from the *O*-methyl derivatives see Part I *). The tautomeric hydrogen of 4-hydroxypyrimidine was found to favour position 1 rather than position 1.

The preparation of the *N*-methyl derivatives involved *N*-methylation of 2- and 4-hydroxypyrimidine to (III) and (VII). The latter, as well as the missing isomer (V), were prepared from 4-hydroxy-2-mercaptopyrimidine (VIII), so that their structures might be related to those of the corresponding *N*-methyluracils, whose orientations (formerly doubtful) have now been confirmed by an unambiguous synthesis of 1-methyluracil (XI; R = H).

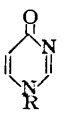
It has been shown (Brown and Short, *J.*, 1953, 331) that the substances commonly known as 2- and 4-hydroxypyrimidine have spectra very different from those of 2- and 4-methoxypyrimidine and, on these grounds, they are considered to exist largely as the tautomeric amides (II, IV, and VI) (for earlier work pointing to this conclusion see Marshall and

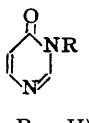

(I*a*)


(I*b*)


(I*c*)


(II; R = H)
(III; R = Me)


(IV; R = H)
(V; R = Me)


(VI; R = H)
(VII; R = Me)

Walker, *J.*, 1951, 1004; Boarland and McOmie, *J.*, 1952, 3716). To obtain more positive evidence synthesis of the three possible *N*-methyl derivatives (III, V, and VII) was undertaken. In addition, comparison of the isomers (V) and (VII) might make it possible to state to which nitrogen atom the hydrogen in " 4-hydroxypyrimidine," which is non-

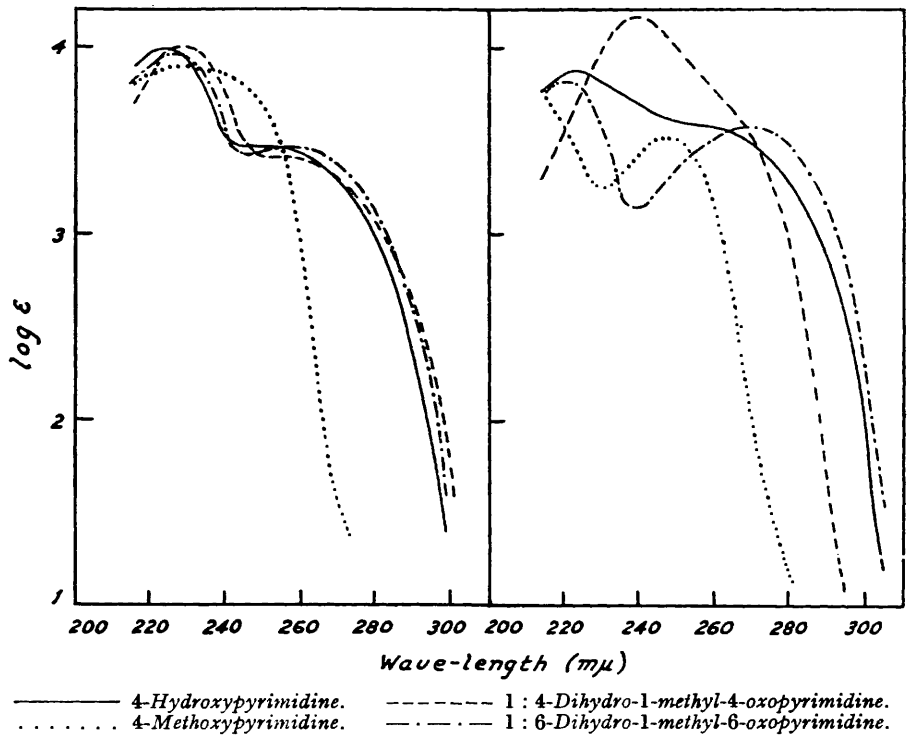
* Evans, Price, and Thomas (*Trans. Faraday Soc.*, in the press) have recently obtained evidence for the dissociation of ion pairs, R^+Cl^-, for *p*-methyl substituted triphenylmethyl chlorides in pure acetic acid.

† Part I, *J.*, 1953, 331.

symmetrical, is attached. The correct orientation of the methyl group in (V) and (VII) was found by the preparation of the former from the 2-methylthio-derivative (IX) and the hydrolysis of (IX) to 1-methyluracil (XI; R = H). The orientation of 1- and 3-methyluracil in the literature was not beyond doubt, and so has been re-investigated.

Spectroscopy.—The ultra-violet absorption spectra of 2-hydroxypyrimidine resemble those of its *N*-methyl derivative (III) more closely than those of 2-methoxypyrimidine (Table), indicating that it exists largely in the amide form (II). The spectrum of the cation of 4-hydroxypyrimidine is closely similar to those of the cations of the *N*-methyl derivatives (V) and (VII) and differs from that of the cation of 4-methoxypyrimidine (Fig. 1 and Table), whilst the spectrum of its neutral molecule resembles that of the neutral molecule (VII) more closely than those of the neutral molecule (V) or 4-methoxypyrimidine

FIG. 1, *As cations.* FIG. 2, *As neutral molecules.*



(Fig. 2 and Table). Thus it is highly probable that the tautomerism in the case of 4-hydroxypyrimidine favours the lactam forms, with (VI) predominating at the expense of (IV). The spectrum of the iodide, obtained by the prolonged action of methyl iodide on 4-hydroxypyrimidine, is similar to the spectra of the cations of (V) and (VII) (see Table), suggesting that this iodide possesses the structure (I; R = Me).

The long-wave-length band of the neutral molecule of the *N*-methyl derivative (V) is more intense and lies at a shorter wave-length than that of the neutral molecule of its isomer (VII), differences which are general between the spectra of the neutral molecules of similar heterocyclic carbonyl compounds (Berson, *J. Amer. Chem. Soc.*, 1953, **75**, 3521).

The spectra of the cations of the *N*-methyl derivatives (V) and (VII) closely resemble one another, however, owing to the formation of similar chromophore systems, each being a resonance hybrid of the principal forms (I*a*, *b*, and *c*) upon the addition of a proton. The shorter wave-length of maximum absorption in the spectrum of the neutral molecule of the form (V) may be ascribed to the greater energy required for the transition from the ground state, of which (V) is the main canonical structure, to the excited state, in which the

polar structure (XII) is predominant, than for the transition from the ground state of the isomer represented principally by the homopolar structure (VII), to the excited state, which partakes heavily of the polar structure (XIV), owing to the greater separation of charge in (XII) than in (XIV). However, the greater separation of charge in (XII) confers upon the excited state of 1-methyl-4-oxo-compound a dipole moment larger than that of the excited state of its isomer, so that the difference between the dipole moments of the ground and the excited states, the transition moment, and thus the intensity of the absorption of radiation, is greater in the former than in the latter. The ratio of the dipole moments of (XII) and (XIV), and hence the ratio of the transition moments of the isomers (V) and (VII) if the contributions of (XII) and (XIV) to the ground states of these substances are small, may be taken as approximately equal to the ratio of the squares of the distances between the charged centres in each of these structures, namely, 0·35 (Berson, *loc. cit.*), a value in good agreement with the ratio of the integrated intensities of the long-wave-length bands in the spectra of the isomeric compounds, namely, 0·33. The values of the integrated intensities of the long-wave-length bands in the spectra of 2- and 4-hydroxypyrimidine, the 1-methyl-2-oxo-compound (III), and the 3-methyl-4-oxo-compound (VII) are in good quantitative agreement, again indicating that 4-hydroxypyrimidine exists largely in the form of the lactam (VI).

In the infra-red region, the methyl derivatives (III), (V), and (VII), like 2- and 4-hydroxypyrimidine (Part I), possess a very strong absorption band in the 1600—1700-cm.$^{-1}$ region, due to the carbonyl bond stretching vibrations. In (III) and (VII) the band lies at 1670 and 1675 cm.$^{-1}$ respectively, *i.e.*, within the region 1700—1665 cm.$^{-1}$ typical of αβ-unsaturated ketones (Cromwell, Miller, Johnson, Frank, and Wallace, *J. Amer. Chem. Soc.*, 1949, **71**, 3337), whilst in (V) the band lies at 1653 cm.$^{-1}$, *i.e.*, within the region 1670—1650 cm.$^{-1}$ typical of αβ : α′β′-unsaturated ketones (Cromwell *et al.*, *loc. cit.*).

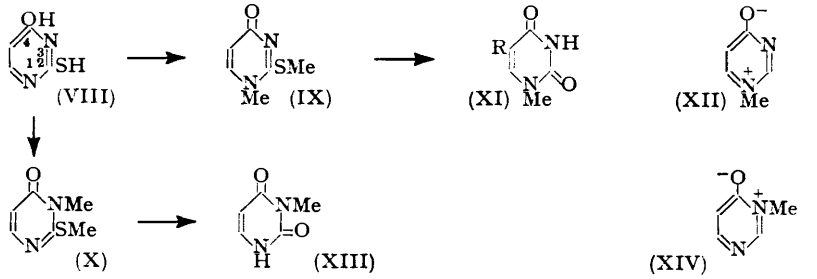
Compound	pK_a	pH	$\lambda_{max.}$ (mμ)	$\varepsilon_{max.}$	$10^7 I_a$ [f] (l. cm.$^{-2}$ mole^{-1})
2-Hydroxypyrimidine [a]	9·17 ± 0·06 [e]	13	292, 220	4550, 11,600	
		6·21	298, <215	4710, >10,000	2·10
	2·24 ± 0·04	0	309, <215	5650, >1710	
2-Methoxypyrimidine [b]	—	6·98	264	4780	1·67
		0	309, 273—274	708, 4900	
1-Methyl-2-pyrimidone	—	6·0	302, 215	5400, 10,000	2·17
	2·50 ± 0·04	0·3	313, <215	7102, >6360	
4-Hydroxypyrimidine [c]	8·60 ± 0·02 [e]	13	263, 227	3280, 11,090	
		6·2	260, 223	3740, 7320	2·3
	1·69 ± 0·04	−1 [f]	251, 224	2970, 4890	
4-Methoxypyrimidine [c]	—	6·95	247—248	3350	1·53
	2·5 ± 0·2	0	238,[h] 227—228	6800, 7740	
1 : 6-Dihydro-1-methyl-6-oxopyrimidine	—	5·0	269, 221	3900, 6810	2·20
	1·84 ± 0·03	−0·4 [g]	258, 226	2940, 9080	
1 : 4-Dihydro-1-methyl-4-oxopyrimidine	—	6·0	240	14,640	7·30
	ca. 1·8	−0·4 [g]	252,[h] 229	2640, 10,200	
1-Methyl-5-nitrouracil	7·20 ± 0·02 [e]	4·0	310, 240	11,400, 8240	—
3-Methyl-5-nitrouracil	—	4·0	298, 235	9440, 8160	—
1-Methyl-5-bromouracil	—	4·0	284, <215	9000, >9370	—
3-Methyl-5-bromouracil	—	4·0	275, <215	6960, >9720	—
1 : 4(3 : 4)-Dihydro-1 : 3-dimethyl-4-oxopyrimidinium iodide [d]	—	7	261, 230	2610, 8640	—

[a] L. N. Short, unpublished work. [b] Boarland and McOmie, *J.*, 1952, 3716. [c] Part I. [d] Corr. for iodide ion absorption. [e] Acidic pK_a. [f] In 5N-H_2SO_4. [g] In 2·5N-HCl. [h] Shoulder. [i] I, the integrated intensity, was calculated according to the approximate relation, $I = \varepsilon_{max.}\Delta\nu$, where $\Delta\nu$ is the band width in cm.$^{-1}$ at the point where $\varepsilon = \frac{1}{2}\varepsilon_{max.}$.

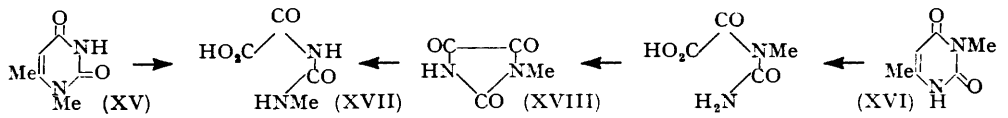
Preparations.—Methylation of 2-hydroxypyrimidine with diazomethane gave 2-methoxypyrimidine (identified as picrate) and the *N*-methyl derivative (III). The latter was also produced in small yield by heating 2-methoxypyrimidine at 190°. Similar methylation of 4-hydroxypyrimidine gave some 4-methoxypyrimidine (picrate) and a substance, m. p. 124°, which could be either (V) or (VII). The same *N*-methyl compound was formed on heating 4-methoxypyrimidine. It was identified as the isomer (VII) as follows: 2-Thiouracil (VIII) was methylated to a mixture of *N*-methyl derivatives (IX) and (X).

The latter on desulphurization with Raney nickel gave the above substance of m. p. 124°. The orientation of (X) follows from its hydrolysis to 3-methyluracil * (XIII; see below). The *N*-methyl compound (V) was not found among the methylation products of 4-hydroxypyrimidine but was obtained by the desulphurization of (IX), the orientation of which is known from its hydrolysis to 1-methyluracil (XI; R = H). When 4-hydroxypyrimidine reacted with methyl iodide, the *NN'*-dimethiodide (I; R = Me) was found in small yield. It was distinguished from the two theoretically possible *NN*-dimethyl isomers spectrographically (see p. 212).

1- *and* 3-*Methyluracil.* The position of the methyl group in the *N*-methyluracils has been accepted for nearly 50 years on the basis of Johnson and Heyl's work (*Amer. Chem. J.*, 1907, **37**, 634). Among the more important structures directly depending on these configurations are the pyrimidine nucleosides (Levene and Tipson, *J. Biol. Chem.*, 1934, **104**, 385; Bredereck, Haas, and Martini, *Chem. Ber.*, 1948, **81**, 307), the antibiotics amicetin (Flynn, Hinman, Caron, and Woolf, *J. Amer. Chem. Soc.*, 1953, **75**, 5867), and grisein (Kuehl, Bishop, Chaiet, and Folkers, *ibid.*, 1951, **73**, 1770), besides many synthetic pyrimidines. The proof of structure for 1- and 3-methyluracil advanced by Johnson and Heyl (*loc. cit.*) is not convincing. It depends on the melting point of the nitration product of the higher-melting *N*-methyluracil being nearer to that of 3-methyl-5-nitrouracil [263—265° (decomp.)] than to that of 1-methyl-5-nitrouracil [255—257° (decomp.), or even 264°; see Experimental section]. A further point was made that the methylation product had no water of crystallization whereas 1-methyl-5-nitrouracil had been reported as the monohydrate at room temperature. However, no direct comparison or mixed m. p.s appear to have been made with authentic specimens of *N*-methyl-5-nitrouracils made by an unquestionable route (Behrend and Thurm, *Annalen*, 1902, **323**, 160; Behrend and Hesse, *ibid.*, 1903, **329**, 348).



Kuehl *et al.* (*loc. cit.*) oxidized 3-methyluracil to ω-methyloxaluric acid (XVII). Apart from the confusion in formulæ 1 and 2 of that paper, which show the relation of the oxidation product not to 3-methyluracil but to 1-methyluracil, it is reasonable to expect that *either* 1- or 3-methyluracil would give ω-methyloxaluric acid on permanganate oxidation. For example, both the 6-methyl analogues, 1 : 6- (XV) and 3 : 6-dimethyluracil (XVI) gave ω-methyloxaluric acid (XVII) on oxidation (Behrend and Dietrich, *Annalen*, 1899, **309**, 268; Behrend and Hufschmidt, *ibid.*, 1905, **343**, 162), the latter presumably by way of methylparabanic acid (XVIII), the ring opening more easily at the methylamide than at the amide bond (Behrend and Henkel, *ibid.*, 1911, **378**, 180). This evidence for the



structure of 3-methyluracil is thus inconclusive. Whitehead's synthesis of 3-methyluracil (*J. Amer. Chem. Soc.*, 1952, **74**, 4267) is also ambiguous.

However, the following synthesis is unambiguous. Methyl β-methylaminopropionate

* Uracil is here considered as 2 : 4-dihydroxypyrimidine, and cytosine as 4-amino-2-hydroxypyrimidine.

was heated with cyanic acid to give on ring closure 5 : 6-dihydro-1-methyluracil. The 5-bromo-derivative of this was dehydrobrominated on melting, to 1-methyluracil (XI; R = H), which was converted into 5-bromo-1-methyl- (XI; R = Br) and 1-methyl-5-nitrouracil (XI; R = NO_2). Comparison by mixed m. p., paper-chromatography, and ultra-violet spectra (see Table) with the two *N*-methyluracils and the nitro- and bromo-derivatives prepared from them showed that the structure assigned by Johnson and Heyl was correct. The isomer, m. p. *ca.* 175°, is 3-methyluracil (XIII); that of m. p. *ca.* 233° is 1-methyluracil (XI; R = H).

Another related doubtful structure was investigated. Johns (*J. Biol. Chem.*, 1912, **11**, 73) methylated 5-nitrocytosine. The *N*-methyl derivative on acid hydrolysis was said, without direct comparison, to give 1-methyl-5-nitrouracil (XI; R = NO_2). Repetition and direct comparison with both 1- and 3-methyl-5-nitrouracil showed Johns's formulation of his product as 1-methyl-5-nitrocytosine to be correct. It follows that Johns's 4 : 5-diamino-1-methyl-2-pyrimidone (Johns, *ibid.*, 1914, **17**, 1) is also correctly designated. There is no longer any doubt of the orientation of the *N*-methylation products of cytosine (Johnson and Clapp, *ibid.*, 1909, **5**, 49; Hilbert, *J. Amer. Chem. Soc.*, 1934, **56**, 190) or of 2-hydroxy-4-methylamino-5-nitropyrimidine (Johns, *J. Biol. Chem.*, 1913, **14**, 3; 1914, **17**, 1) as direct comparisons were made with substances whose orientation has been confirmed above.

Experimental

Analyses were by Mr. P. R. W. Baker, Beckenham.

Spectra.—Ultra-violet absorption spectra were measured with a Hilger Uvispek H700/301 Quartz Spectrophotometer, with buffer solutions having the pH values recorded in the Table. The solvents were 0·01M-acetate buffer (for pH 3·8—5·7), and 0·01M-phosphate buffer (for pH 6·0—7·9), together with 0·1N-potassium hydroxide (pH 13) and N-hydrochloric acid (pH 0).

Infra-red absorption spectra were measured with a Perkin–Elmer Model 12C recording spectrometer, with a sodium chloride prism, the compounds being compressed into a disc with potassium bromide.

1 : 2-*Dihydro*-1-*methyl*-2-*oxopyrimidine*.*—2-Hydroxypyrimidine (1·0 g.; Brown, *Nature*, 1950, **165**, 1010) was suspended in ethereal diazomethane (from 5 g. of *N*-nitrosomethylurea, 70 ml. of ether, and 20 ml. of 40% potassium hydroxide solution). Evolution of nitrogen was slow and the crystals were crushed occasionally; a new solid gradually appeared. After 2 days at room temperature the product (52%; m. p. 122—123°) was collected. Repeated recrystallization from acetone (10 parts; charcoal) gave colourless 1 : 2-*dihydro*-1-*methyl*-2-*oxopyrimidine*, m. p. 127—128° (Found : C, 54·65; H, 5·4; N, 25·45. $C_5H_6ON_2$ requires C, 54·55; H, 5·5; N, 25·45%). The *picrate* recrystallized from ethanol (80 parts) as yellow needles, m. p. 162—164° (Found : C, 39·0; H, 2·75. $C_{11}H_9O_8N_5$ requires C, 38·95; H, 2·65%).

The ethereal filtrate from the reaction mixture was distilled, to give 2-methoxypyrimidine (17%, b. p. 70—80°/20 mm.). It was redistilled and its picrate made. Authentic 2-*methoxypyrimidine picrate*, from ethanol (15 parts), had m. p. 105—106° (Found : N, 20·7. $C_{11}H_9O_8N_5$ requires N, 20·65%).

2-Methoxypyrimidine (1 g.) was heated at 190—200° for 3 hr. Unchanged 2-methoxypyrimidine (0·7 g.) was distilled off (bath 120°; 10 mm.). The crystalline residue was identified as 1 : 2-dihydro-1-methyl-2-oxopyrimidine by its picrate.

1 : 6-*Dihydro*-1-*methyl*-6-*oxopyrimidine*.—(a) *By methylation.* 4-Hydroxypyrimidine (1·0 g.) was methylated as was the 2-isomer. After 2 days the solid was removed and concentration almost to dryness gave a second crop (total yield, 51%). Several recrystallizations from chloroform (5 parts) gave thick colourless prisms of the 6-*oxo*-derivative, m. p. 125—126° (Found : C, 54·8; H, 5·4; N, 25·4%). The *picrate*, from ethanol (100 parts), had m. p. 175—176° (Found : N, 20·8. $C_{11}H_9O_8N_5$ requires N, 20·65%).

From the combined mother-liquors (above) there was obtained 4-methoxypyrimidine (9%; b. p. 70—80°/20 mm.; Brown and Short, *loc. cit.*), identified as picrate. Authentic 4-*methoxypyrimidine picrate*, from ethanol (30 parts), had m. p. 123—124° (Found : C, 39·0; H, 3·2; N, 20·0. $C_{11}H_9O_8N_5$ requires C, 38·95; H, 2·65; N, 20·65%).

(b) *From* 4-*methoxypyrimidine.* 4-Methoxypyrimidine (13 mg.) was heated at 190—195°

* This compound might elsewhere be named 1-methyl-2-pyrimidone. Similar alternative names might be used elsewhere for analogous compounds.

(sealed tube) for 2 hr. Sublimation (bath 100°; 20·mm.) then gave the *N*-methyl compound (6 mg.; m. p. 121—124°), identified by mixed m. p. with the previous product.

(c) *By desulphurization.* 1 : 6-Dihydro-1-methyl-2-methylthio-6-oxopyrimidine (see below; 1·5 g.) was boiled in water (25 ml.) with Raney nickel (8 g., wet) for 2 hr. The filtered solution was saturated with sodium chloride and extracted with chloroform (continuously for 24 hr.). The residue from the evaporated extract recrystallized from *cyclo*hexane (120 ml.), giving the above-mentioned product (34%), m. p. 123—124°.

1:4(3:4)-*Dihydro*-1:3-*dimethyl*-4-*oxopyrimidinium Iodide.*—A solution of 4-hydroxypyrimidine (200 mg.), methyl iodide (0·4 ml.; 2·7 mols.), and methanol (4 ml.) was stored for 30 days at room temperature. Removal of solvent (reduced pressure) left a red oil which solidified. Recrystallization from ethanol (100 parts) gave 17% of tan-coloured *iodide*, m. p. 205—206° (Found : N, 11·1; I, 50·6. $C_6H_9ON_2I$ requires N, 11·1; I, 50·35%).

Dihydro-N-*methyl*-2-*methylthio*-*oxopyrimidines.*—To 2-thiouracil (50 g.) in 5N-sodium hydroxide (220 ml.) methyl sulphate (5 × 20 ml.) was added at <50°. The mixture was finally warmed to 70°, then chilled overnight. 1 : 6-*Dihydro*-1-*methyl*-2-*methylthio*-6-*oxopyrimidine* (19·4 g.; m. p. 122—123°) was filtered off, the filtrate repeatedly extracted at room temperature with chloroform, and the chloroform distilled off, leaving crystalline residues. The first 3 extracts (25 ml. each) gave impure material from which, by recrystallization from ethanol, more of the previous lactam (3·2 g.; m. p. 120—122°) was obtained (total yield, 37%). Recrystallization from water (10 parts) gave colourless plates, m. p. 122—123° (Found : C, 46·2; H, 4·95; N, 18·0. $C_6H_8ON_2S$ requires C, 46·15; H, 5·15; N, 17·95%).

The next few extracts (100 ml. each) yielded progressively higher melting material until at the ninth extraction nearly pure 1 : 4-*dihydro*-1-*methyl*-2-*methylthio*-4-*oxopyrimidine* was obtained (1·7 g.; m. p. 166—167°). Seventeen further extractions (100 ml. each) gave diminishing amounts of comparable material. Thereafter, further extractions gave less pure material (*e.g.*, 49th extract: 0·03 g., m. p. 110—132°). The purer residues were combined and recrystallized from ethanol (4 parts). Lower-melting fractions were repeatedly recrystallized and mother-liquors reworked, the total yield being 38%. Final recrystallization gave colourless plates, m. p. 168—169° (Found : C, 46·3; H, 5·2; N, 17·9%).

1-*Methyluracil.*—The last-mentioned compound (1·0 g.) was refluxed for 2½ hr. with hydrochloric acid (*d* 1·1; 8 ml.) and brought to pH 3 with 10N-sodium hydroxide (yield, 72%). Recrystallization from water (22 parts) gave colourless needles of 1-methyluracil, m. p. 232—233° (Found : C, 47·5; H, 4·4; N, 22·6. Calc. for $C_5H_6O_2N_2$: C, 47·6; H, 4·8; N, 22·2%). It was identical (mixed m. p.; paper chromatography) with authentic material prepared as below.

1 : 4-*Dihydro*-1-*methyl*-4-*oxopyrimidine.*—1 : 4-Dihydro-1-methyl-2-methylthio-4-oxopyrimidine (2 g.) was boiled with Raney nickel (10 g.; weighed wet) in water (30 ml.) for 1½ hr. Evaporation of the filtered solution, and extraction of the dry residue with boiling *iso*butyl methyl ketone (120 ml.), gave almost colourless needles (57%) of 1 : 4-*dihydro*-1-*methyl*-4-*oxopyrimidine*, m. p. 155—156° (Found : C, 54·1; H, 5·3; N, 25·45. $C_5H_6ON_2$ requires C, 54·5; H, 5·5; N, 25·45%).

3-*Methyluracil.*—1 : 6-Dihydro-1-methyl-2-methylthio-6-oxopyrimidine (0·97 g.) was refluxed for 1 hr. with hydrochloric acid (*d*, 1·1; 10 ml.), then evaporated to dryness *in vacuo*. Recrystallization from ethanol (6 parts) gave 83% of colourless 3-methyluracil, m. p. 179° (Found : N, 22·25%). It was also made (mixed m. p.) according to Whitehead (*loc. cit.*).

5 : 6-*Dihydro*-1-*methyluracil.*—Methyl β-methylaminopropionate (33 g.; Lindsay and Cheldelin, *J. Amer. Chem. Soc.*, 1950, **72**, 828) was dissolved in hydrochloric acid (1·0N; 295 ml.). Sodium cyanate (19 g.) was added and the solution refluxed for 24 hr. The water was distilled off (water-bath; 25 mm.) and the residue extracted with boiling ethyl acetate (2 × 350 ml.) (yield, 10 g.). Recrystallization from ethyl acetate (50 parts) gave colourless needles of 5 : 6-*dihydro*-1-*methyluracil*, m. p. 170—172° (Found : C, 46·9; H, 6·15; N, 22·0; O, 24·8. $C_5H_8O_2N_2$ requires C, 46·9; H, 6·3; N, 21·9; O, 24·95%).

5-*Bromo*-5 : 6-*dihydro*-1-*methyluracil.*—5 : 6-Dihydro-1-methyluracil (3·1 g.) and bromine (1·45 ml.) were refluxed in glacial acetic acid (45 ml.), for about 7 min. The residual oil, after evaporation *in vacuo* on the water-bath, was diluted with water (10 ml.) and brought to pH 5 with 10N-sodium hydroxide. After refrigeration the solid (4 g.) was filtered off and washed with ice-water. Recrystallized from ethanol (carbon), 5-*bromo*-5 : 6-*dihydro*-1-*methyluracil* was white (Found : C, 28·95; H, 3·2; N, 13·5; Br, 38·7. $C_5H_7O_2N_2Br$ requires C, 29·0; H, 3·4; N, 13·55; Br, 38·6%). It melted at 140—144° with loss of hydrogen bromide, and resolidified, remelting at about 225°.

1-*Methyluracil* (*Unambiguous Synthesis*).—5-Bromo-5 : 6-dihydro-1-methyluracil (0·6 g.) was plunged into a bath at 155—160°. It was removed 2 min. after resolidifying. The crude material was dissolved in water and neutralized, and, after evaporation to dryness, the residue was extracted with boiling *iso*butyl methyl ketone (15 ml.), the extract giving 1-methyluracil on cooling. The crude product was also brominated and nitrated, giving respectively 5-bromo-1-methyluracil (Found : C, 29·4; H, 2·65. Calc. for $C_5H_5O_2N_2Br$: C, 29·3; H, 2·45%) and 1-methyl-5-nitrouracil (Found : N, 24·6. Calc. for $C_5H_5O_4N_3$: N, 24·55%) (mixed m. p.s). The former, prepared from pure 1-methyluracil by bromination in water (Hilbert, *loc. cit.*) and recrystallized from water (50 parts), had m. p. 266° (decomp.).

3-Methyl-5-bromouracil, prepared as was the 1-methyl isomer and recrystallized from water (35 parts), had m. p. 228—229°, depressed strongly by authentic 1-methyl-5-bromouracil.

1-*Methyl-5-nitrouracil*.—Nitric acid (*d* 1·52; 0·25 ml.) was added to 1-methyluracil (0·5 g.) dissolved in concentrated sulphuric acid (1 ml.) at room temperature. After 20 min. the solution was poured on ice, giving 0·58 g. of 1-methyl-5-nitrouracil. Recrystallized from water (17 parts), it melted slowly with decomp. from 256° to 264°, according to rate of heating. It showed no depression with material prepared as above. Identical material was prepared by hydrolysis of 1-methyl-5-nitrocytosine (Johns, *J. Biol. Chem.*, 1912, **11**, 73).

3-Methyl-5-nitrouracil, prepared from 3-methyluracil (cf. the 1-methyl isomer) in 93% yield and crystallized from water, had m. p. 263—265° (decomp.), depressed by the 1-methyl isomer. Nitration at 100° according to Johnson and Heyl (*loc. cit.*) gave no nitro-derivative.

1 : 3-Dimethyl-5-nitrouracil (formerly prepared by methylation of nitrouracil or indirectly) when obtained from 1 : 3-dimethyluracil as above (80% yield) had m. p. 155° (decomp.).

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