Simple Pyrimidines. Part III. The Methylation and Structure of the Aminopyrimidines.*

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2- and 4-Aminopyrimidine are shown to exist largely in the amino-form by the comparison of their basic strengths, and ultraviolet and infrared spectra, with those of the corresponding nuclear and extra-nuclear *N*-methyl derivatives [*e.g.*, respectively (I) and (IV*a*)].

The preparation of the nuclear *N*-methyl derivatives involved the methylation of 2- and 4-aminopyrimidine to 1 : 2-dihydro-2- and 1 : 4-dihydro-4-imino-1-methylpyrimidine (I) and (II) respectively. In alkaline solution, the former rearranges to 2-methylaminopyrimidine (IV), whilst the latter is hydrolysed to 1 : 4-dihydro-1-methyl-4-oxopyrimidine.

In Part I (Brown and Short, *J.*, 1953, 331), it was shown that the potentially tautomeric 2- and 4-aminopyrimidine give ultraviolet absorption spectra similar to those of the dimethylamino-analogues, which necessarily possess the amino-structure. Such evidence that these amines in aqueous solution exist largely in the amino-form has been supplemented in the present paper by the measurement of the basic ionisation constants, and the ultraviolet spectra of the corresponding nuclear *N*-methyl derivatives (I and II) of authentic imino-structure. Moreover, the infrared spectra of these amines and their *N*-methyl derivatives show similarly that the amino-forms predominate in the solid state and in solution in non-polar solvents.

Spectroscopy.—The ultraviolet spectra of the cations of 2- and 4-aminopyrimidine are closely similar to those of the cations of the corresponding nuclear *N*-methyl derivatives (Fig. 1, Table 1). This suggests that in both cases a proton is bonded to a nuclear nitrogen

Table 1. *Ultraviolet spectra of 2- and 4-aminopyrimidine and their* N-*methyl derivatives.*

Pyrimidine deriv.	pK_a (20°)	pH	$\lambda_{max.}$ (mμ)	log $\varepsilon_{max.}$
(Pyrimidine)	1·30 [c]	7·0	238, 243, 271	3·48, 3·51, 2·63
		−0·8	242	3·74
2-Amino [a]	3·54 [c]	7·0	224, 292	4·13, 3·50
		1	221, 302—303	4·17, 3·60
2-Methylamino [a]	3·82	7·0	234, 306—307	4·23, 3·43
		1	228, 315	4·23, 3·53
2-Dimethylamino [a]	3·96	7·0	243, 318	4·26, 3·35
		1	235, 324—325	4·24, 3·47
1 : 2-Dihydro-2-imino-1-methyl	10·75 ± 0·10 [d]	13	236, 345 [g]	4·19, 3·46
		7·0	222, 301	4·12, 3·63
4-Amino [b]	5·71 [c]	13	233, 268—269	4·26, 3·72
		0	246	4·27
4-Methylamino [a]	6·12	9·0	242, 276—277	4·18, 3·54
		2·1	254	4·20
4-Dimethylamino [a]	6·35	9·3	250, 286	4·22, 3·56
		3·15	262	4·21
1 : 4-Dihydro-4-imino-1-methyl	12·22 ± 0·15 [d]	13 [f]	253, 315 [h, g]	4·21, 2·79
		7·0	250	4·21

[a] Part I (Brown and Short, *J.*, 1953, 331). [b] Boarland and McOmie (*J.*, 1952, 3716). Albert, Goldacre, and Phillips (*J.*, 1948, 2240). [d] Present work; pK_a values are for M/50-solutions, and determined potentiometrically. [c] In 4N-sulphuric acid. [f] Highest pH used with silica absorption cells. 85% of the neutral molecule is present at this pH. [g] The neutral molecules of the imines decomposed rapidly in aqueous solution. Fresh solutions were made up for every measurement at 1 mμ intervals, in the regions of maximum and minimum absorption, and for every five measurements at 5 mμ intervals elsewhere. [h] Shoulder.

atom in cations from 2- and 4-aminopyrimidine. Such a view is supported by the marked differences between the spectra of the cations of the amino-, methylamino-, and dimethylamino-pyrimidines and that of the neutral molecule of pyrimidine itself (Table 1). For if

* Part II, *J.*, 1955, 211.

the proton were bonded to the amino-group, it would be expected that the spectra of these cations would resemble that of pyrimidine (neutral molecule), just as the spectra of aniline and dimethylaniline, so different from that of benzene, become closely similar to that of

FIG. 1. *Cations of* 2-*amino-* (——) *and* 4-*amino-pyrimidine* (— — —), 1 : 4-*dihydro-*4- (. . . .), *and* 1 : 2-*dihydro-*2-*imino-*1-*methylpyrimidine* (— · — · —).

FIG. 3. *Neutral molecules of* 4-*amino-* (——), 4-*methylamino-* (— — —), 4-*dimethylamino-* (— · — · —), *and* 1 : 4-*dihydro-*4-*imino-*1-*methyl-pyrimidine* (. . . .).

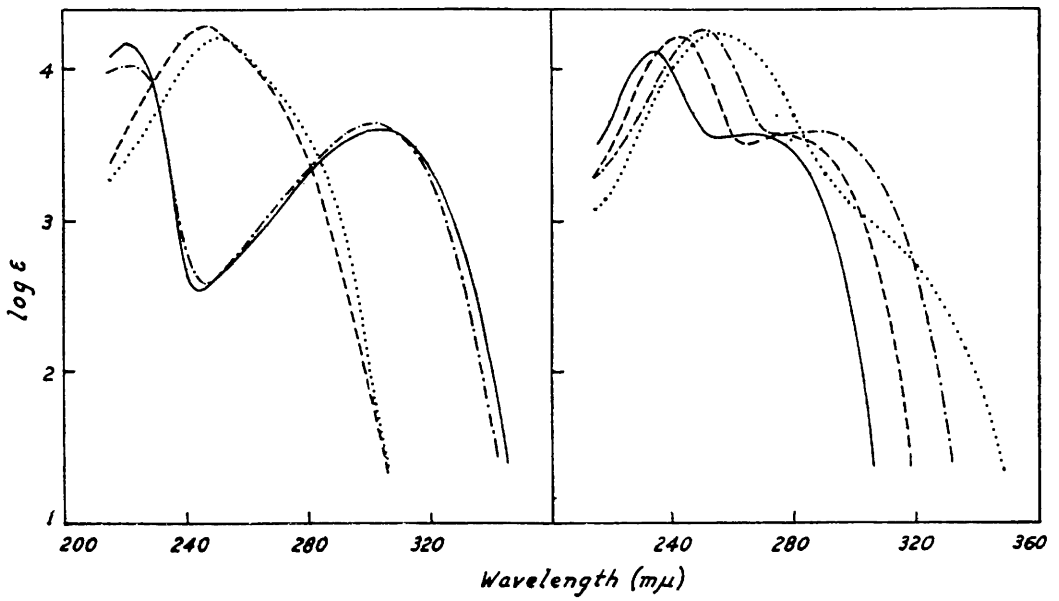
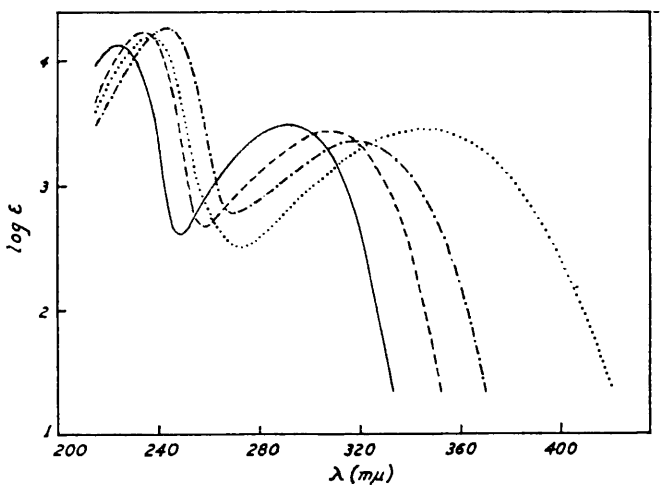


FIG. 2. *Neutral molecules of* 2-*amino-* (——), 2-*methylamino-* (— — —), 2-*dimethylamino-* (— · — · —), *and* 1 : 2-*dihydro-*2-*imino-*1-*methyl-pyrimidine* (. . . .).



benzene upon cation formation (Wohl, *Bull. Soc. chim. France*, 1939, **6**, 1312; Landolt–Bornstein, " Tabellen," Ergb. I, p. 443; Ergb. II, p. 665; Ergb. III, p. 1377). Indeed the bathochromic effect of the methyl groups in the dimethylaminopyrimidines is as much in evidence in the spectra of the cations as in the spectra of the neutral molecules (Table 1),

indicating that electronic interaction between the amino-group and the nucleus occurs in the cations, an effect that would not be possible if the proton were bonded to the amino-group.

For the neutral molecules of 2- and 4-aminopyrimidine, it can be seen (Figs. 2 and 3, Table 1) that the ultraviolet absorption curves of these amines are quantitatively displaced further along the wavelength scale from those of the corresponding nuclear *N*-methyl derivatives than from those of the extra-nuclear *N*-methyl analogues, whilst resembling both in qualitative shape. The quantitative features of these spectral data suggest that 2- and 4-aminopyrimidine in aqueous solution exist largely in the amino-form—the wavelength intervals between the two bands of their spectra, 68 and 38 mμ respectively, for example, are more nearly equal to those observed in the case of the dimethylamino-analogues, 75 and 36 mμ, than those found in the cases of the nuclear *N*-methyl derivatives, 109 and *ca.* 65 mμ—although in view of the qualitative resemblance in the shapes of the curves the possibility of some amine–imine tautomerism cannot be dismissed. Moreover, the spectral comparison in the case of 4-aminopyrimidine is to some extent uncertain in that its nuclear *N*-methyl derivative exists only to the extent of 85% neutral molecule at pH 13, the highest pH used with silica absorption cells.

The extent of such tautomerism may be calculated from the ionisation constants of the *N*-methyl derivatives fixed in the amino- and imino-forms (Angyal and Angyal, *J.*, 1952, 1461).

Since $$K_a(\text{amino}) = [\text{amine}][H^+]/[\text{cation}]$$

and $$K_a(\text{imino}) = [\text{imine}][H^+]/[\text{cation}]$$

it follows that

$$K_{\text{tautomeric}} = [\text{amine}]/[\text{imine}] = K_a(\text{amino})/K_a(\text{imino}) \quad . \quad . \quad . \quad . \quad (1)$$

By employing the ionisation constants of the nuclear and the extranuclear *N*-methyl derivatives of 2- and 4-aminopyrimidine (Table 1), it is found that the amine–imine tautomeric constant in aqueous solution is of the order of 10^6 for both these amines (cf. 2×10^5 and 2×10^3 respectively for the corresponding pyridines; Angyal and Angyal, *loc. cit.*).

This value can be only very approximate, as it is necessary in the above calculation to compare the ionisation constant of the dimethyl derivative of the amino-form with that of the monomethyl derivative of the imino-form, and it is unlikely that the ionisation constants are proportionately changed even for equal degrees of methylation. More fundamental is the objection that the methyl derivatives of the tautomers, unlike the tautomers themselves, do not possess a common cation, so that equation (1) is not strictly valid for the methyl derivatives. However, the qualitative significance of equation (1) that the less prevalent tautomer is the stronger base supports the view that 2- and 4-aminopyrimidine exist predominantly in the amino-form.

For 4-aminopyrimidine there is an added uncertainty in the above calculation, as only one of the two possible nuclear *N*-methyl derivatives was available. The other, the 3-methyl derivative, may possibly not be relevant to the present purpose, for the ready and exclusive methylation of 4-aminopyrimidine on the nuclear 1-nitrogen atom, and the similarity of the spectra of the cations of 4-amino- and 4-dimethylamino-pyrimidine and 1 : 4-dihydro-4-imino-1-methylpyrimidine, suggest that the 1-nitrogen atom is the basic centre of these compounds, and thus that the above calculation of an approximate tautomeric constant for 4-aminopyrimidine is valid within the limitations previously discussed.

In the solid state and in non-aqueous solvents 2- and 4-aminopyrimidine similarly exist largely in the amino-form, as is shown by their infrared spectra. Both amines in carbon tetrachloride solution give two strong, sharp bands at 3540 and 3430 cm.$^{-1}$, due to the asymmetric and symmetric stretching modes respectively of the unassociated NH_2 group, and two broad bands at 3320 and 3170 cm.$^{-1}$ due to the same vibration modes of the intermolecular, hydrogen-bonded NH_2 group. The intensities of the broad bands relative to those of the sharp bands increase with the concentration of the amine in solution, and in the solid state only the broad bands are observed (Table 2). 2- and 4-Methylamino-pyrimidine give only one sharp band at 3460 cm.$^{-1}$, and a broad band near to 3260 cm.$^{-1}$

which is concentration-dependent in solution and is alone observed in the solid state. For 4-methylaminopyrimidine the 3460 cm.$^{-1}$ band is a doublet with a spacing of 23 cm.$^{-1}$ between its peaks, suggesting that there is a slight difference between the N–H bond strength of the form in which the methyl group is *trans* to the 5-CH group of the nucleus and the form in which is *cis*, owing presumably to some steric hindrance in the latter form

TABLE 2. *The infrared spectra of* 2- *and* 4-*aminopyrimidine and their* N-*methyl derivatives in the* N–H *stretching,* N–H *deformation, and double-bond stretching regions.*

	N–H stretching frequencies (cm.$^{-1}$)			Double-bond stretching and N–H deformation frequencies (cm.$^{-1}$)
	Free	Associated		
Pyrimidine derivative	In solution	In solution	In the solid	In the solid
2-Amino	3545 sh	3314 b	3327 b	1650 s, 1577 s
	3430 sh	3172 b	3166 b	
Same deuterated	2655 sh	2493 b	2523 b	1596 s
	2573 sh	2400 b	2395 b	
2-Methylamino	3463 sh	3280 b	3268 b	1617 s
Same deuterated	2565 sh	2416 b	2420 b	1617 s
1 : 2-Dihydro-2-imino-1-methyl	3324 sh	—	3244 b	1638 s,
Same deuterated	2455 sh	—	—	1638 s,
1 : 2-Dihydro-2-imino-1-methyl, hydriodide	—	—	3262 b	1645 s,
			3085 b	
Same deuterated	—	—	2498 b	1646 s,
			2411 b	
4-Amino	3538 sh	3322 b	3324 b	1652 s, 1594 s
	3424 sh	3180 b	3178 b	
Same deuterated	2640 sh	2498 b	2496 b	1601 s
	2561 sh	2401 b	2399 b	
4-Methylamino	3466 sh	3264 b	3245 b	1614 s
	3443 sh			
Same deuterated	2570 sh	2428 b	2445 b	1616 s
	2555 sh			
1 : 4-Dihydro-4-imino-1-methyl, hydriodide *	—	—	3260 b	1648 s
			3109 b	
Same deuterated	—	—	2500 b	1646 s
			2410 b	

* The free imine could not be isolated.

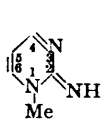
sh = sharp, b = broad, s = strong.

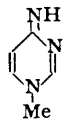
which prevents full coplanarity between the nucleus and the methylamino-group. It is unlikely that the doublet arises from amine–imine tutomerism, as 1 : 2-dihydro-2-imino-1-methylpyrimidine (the 4-isomer cannot be isolated from its salts without decomposition) absorbs at 3324 cm.$^{-1}$ in dilute solution and at 3244 cm.$^{-1}$ in the solid state.

In the double-bond stretching region, which includes the range of the N–H deformation mode, 2- and 4-aminopyrimidine show a strong band at 1650 cm.$^{-1}$ which is due to the internal deformation of the amino-group, for it disappears upon deuteration. In the same region, the salts of 1 : 2-dihydro-2- and 1 : 4-dihydro-4-amino-1-methylpyrimidine absorb strongly at 1646 cm.$^{-1}$ and the deuterated compounds show the same absorption, which is probably due therefore to the C=N stretching mode. 2- and 4-Methylaminopyrimidine give rise to a strong band near 1615 cm.$^{-1}$, but no perceptible band at higher frequencies in the N–H deformation mode and double-bond stretching mode region. This band is probably due to a ring stretching vibration, since it is unaffected by deuteration, and many other pyrimidine derivatives absorb near this band (Brownlie, *J.*, 1950, 3062; Short and Thompson, *J.*, 1952, 168). Such observations support the view that 2- and 4-amino-pyrimidine exist largely in the true amino-form since the deformation vibration of the primary amino-group generally absorbs strongly, whilst that of the secondary amino-group shows very weak absorption (Bellamy, " The Infrared Spectra of Complex Molecules," London, 1954, pp. 212 ff.).

Preparations.—Prolonged action of methyl iodide at 20° on 2-aminopyrimidine gave the hydriodide of 1 : 2-dihydro-2-imino-1-methylpyrimidine (I) which was converted into the

free base (at 0°). In warm alkaline solution, this rapidly rearranged to 2-methylaminopyrimidine (IV) identical with material made from 2-chloropyrimidine and methylamine (Part I, *loc. cit.*). Such rearrangement has recently been described by Carrington, Curd, and Richardson (*J.*, 1955, 1858) and others have been noticed under different conditions,


(I)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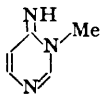
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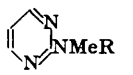
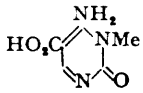

(IV; R = H)
(IV*a*; R = Me)


(V)


(VI)

e.g., during the pyrolyticdecarboxylation of 5-carboxy-3-methylcytosine (V) to 2-hydroxy-4-methylaminopyrimidine (VI) (Brown, *J. Appl. Chem.*, 1955, 358) and during nitration of 1 : 2-dihydro-2-imino-1-methylpyridine to give 2-methylamino-5-nitropyridine (Tschitschibabin and Konowalowa, *Ber.*, 1925, **58**, 1712; Tschitschibabin and Kirssanow, *ibid.*, 1928, **61**, 1223). The present rearangement clarifies the mechanism of the methylation of 2-aminopyrimidine: Overberger and Kogon (*J. Amer. Chem. Soc.*, 1954, **76**, 1065) describe a hydriodide of m. p. 241—242°, from which 2-methylaminopyrimidine was obtained by warm alcoholic alkali; this intermediate corresponds in m. p. and other properties with 1 : 2-dihydro-2-imino-1-methylpyrimidine hydriodide, and rearrangement followed during the alkaline treatment.

When 4-aminopyrimidine is methylated similarly, two products, 1 : 4-dihydro-4- and 1 : 6-dihydro-6-imino-1-methylpyrimidine (II and III), are possible, but a single 4-imino-derivative resulted. In this case the free base was very unstable: the picrate was however made. In alkaline solution no 4-methylaminopyrimidine was formed but hydrolysis occurred to 1 : 4-dihydro-1-methyl-4-oxopyrimidine. This proved the structure of the imino-derivative. An attempt to prepare 1 : 2 : 3 : 4-tetrahydro-2 : 4-di-imino-1 : 3-dimethylpyrimidine gave only a single monomethylated derivative of indeterminate structure.

Experimental

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

Spectra.—Ultraviolet absorption spectra were measured with a Hilger Uvispek H700/301 Quartz Spectrophotometer, on buffer solutions with the pH values recorded in Table 1. The solvents were 0·01M-phosphate (pH 7) and 0·1N-potassium hydroxide (pH 13).

Infrared absorption spectra were measured with a Perkin-Elmer Model 12C recording spectrometer, and lithium fluoride and sodium chloride prisms. The compounds listed in Table 2 were examined in CCl_4 solution over the approximate concentration range 0·01—0·2M in cells of 1 and 10 mm. path length, and the spectra of the solids were obtained with samples of the compounds compressed into discs with potassium bromide.

1 : 2-*Dihydro*-2-*imino*-1-*methylpyrimidine Hydriodide.*—2-Aminopyrimidine (5·0 g.), methyl iodide (10 ml.), and methanol (60 ml.) were kept for 5 days at room temperature. The precipitated hydriodide was collected (8·1 g.; m. p. 242—244°), and the filtrate stored 10 days more to obtain additional product (2·9 g.) (total yield 88%). Recrystallization from 95% ethanol (35 parts) gave thick colourless prisms of 1 : 2-*dihydro*-2-*imino*-1-*methylpyrimidine hydriodide*, m. p. 247—248° (decomp.) (Found: N, 17·75; I, 54·0. $C_5H_8N_3I$ requires N, 17·75; I, 53·55%).

1 : 2-*Dihydro*-2-*imino*-1-*methylpyrimidine.*—The hydriodide (0·23 g.), cooled at 0°, was moistened with water (2 drops), covered with purified ether (10 ml.), and then ground thoroughly (glass rod) with powdered potassium hydroxide (1 g.) added in several small portions. The ether, which became yellow, was separated by decantation. The residue was washed with ether (3 × 5 ml.). The combined ether extracts were dried (Na_2SO_4) and most of the ether was distilled off, leaving yellow crystals (about 0·1 g.) from which mother-liquor was removed by means of a filter stick to minimize exposure to the atmosphere. Recrystallization was carried out by redissolution in ether, drying (KOH), filtration through a cotton plug, concentration until crystallization began, cooling to room temperature, and filtration with a filter stick. The last traces of ether and moisture were removed by storage (2 hr.) in a desiccator ($CaCl_2$;

100 mm.), leaving very hygroscopic, thick yellow needles of 1 : 2-*dihydro*-2-*imino*-1-*methylpyrimidine*, m. p. 102—104° (Found : C, 54·95; H, 6·45; N, 38·45. $C_5H_7N_3$ requires C, 55·05; H, 6·5; N, 38·5%.)

The *picrate* was prepared from the hydriodide (0·22 g.), picric acid (0·21 g.), and water (5 ml.). Recrystallization from ethanol (20 parts) gave yellow granules, m. p. 198—200° (Found : N, 24·95. $C_{11}H_{10}O_7N_6$ requires N, 24·85%), identical (mixed m. p.) with the picrate prepared from the free base.

2-*Methylaminopyrimidine* (*by Rearrangement*).—A solution of 1 : 2-dihydro-2-imino-1-methylpyrimidine hydriodide (1·0 g.) in aqueous N-sodium hydroxide (12 ml.) was heated on a steam-bath for 10 min., then cooled and extracted with chloroform (2 × 10 ml.). Evaporation and recrystallization of the residue from light petroleum (b. p. 60—80°; 10 parts) gave 71% of 2-methylaminopyrimidine, m. p. 59—60° (Found : C, 54·95; H, 6·45; N, 38·8. Calc. for $C_5H_7N_3$: C, 55·05; H, 6·5; N, 38·5%). The m. p. was undepressed by authentic material (Part I).

The picrate, recrystallised from methanol (70 parts), had m. p. 191° (Overberger and Kogon, *loc. cit.*, give 195—196°) (Found : N, 25·0. Calc. for $C_{11}H_{10}O_7N_6$: N, 24·85%). A mixed m. p. with 1 : 2-dihydro-2-imino-1-methylpyrimidine picrate showed depression but there was none with authentic 2-methylaminopyrimidine picrate.

1 : 4-*Dihydro*-4-*imino*-1-*methylpyrimidine Hydriodide*.—4-Aminopyrimidine (5·0 g.), methyl iodide (5 ml.), and methanol (25 ml.) were refluxed for 1 hr. The precipitate which formed upon cooling (10·0 g., 80%; m. p. 204—205°), recrystallised from ethanol (20 parts), gave 1 : 4-*dihydro*-4-*imino*-1-*methylpyrimidine hydriodide*, m. p. 205—206° (Found : N, 17·75; I, 53·35. $C_5H_8N_3I$ requires N, 17·75; I, 53·55%). In another preparation the reactants were set aside for three days at room temperature. A different crystalline form of the hydriodide was at first obtained, having m. p. 163—164°. Recrystallization from ethanol (20 parts) or storage for 3 days gave the other form, m. p. 205—206°.

The *picrate* was prepared from the hydriodide (0·24 g.), picric acid (0·23 g.), water (10 ml.), and N-sodium hydroxide (1 ml.). Recrystallization from ethanol (100 parts) gave yellow needles, m. p. 172—173° (Found : N, 24·8. $C_{11}H_{10}O_7N_6$ requires N, 24·85%).

Hydrolysis of 1 : 4-*Dihydro*-4-*imino*-1-*methylpyrimidine*.—The hydriodide (0·9 g.) and 0·1N-sodium hydroxide (80 ml.) were set aside for 10 hr. at 20—25°. The solution was brought to pH 5 with hydrochloric acid and evaporated to dryness *in vacuo*, moistened with a little benzene, and re-evaporated. The residue was dissolved in ethanol, filtered from salt, and added to saturated alcoholic picric acid (20 ml.). The precipitate (55%) was recrystallised from ethanol (90 parts), giving a yellow solid, m. p. 164—166°.

1 : 4-*Dihydro*-1-*methyl*-4-*oxopyrimidine picrate* made from authentic base (Part II, *loc. cit.*) also had m. p. 164—166° (Found : N, 20·4. $C_{11}H_9O_8N_5$ requires N, 20·65%). The two specimens showed no mixed m. p. depression, but each depressed the m. p. of 1 : 6-dihydro-1-methyl-6-oxopyrimidine picrate (Part II, *loc. cit.*).

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