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712. *Pyrimidines. Part II.* The Ultra-violet Absorption Spectra of Some Monosubstituted Pyrimidines.*

By (Miss) M. P. V. Boarland and J. F. W. McOmie.

The ultra-violet absorption spectra of a number of monosubstituted pyrimidines in aqueous buffer solutions and/or in ethanol have been measured. All the compounds examined showed bathochromic shifts which are tabulated, together with the corresponding shifts in the molecular extinction coefficients.

Although the ultra-violet absorption spectra of polysubstituted pyrimidines and purines have been fairly extensively examined, very little work has been reported on the monosubstituted compounds. Indeed, apart from the spectrum of pyrimidine itself, the spectra of only six simple monosubstituted pyrimidines have been investigated, namely, 2-hydroxy- (Brown, *Nature*, 1950, **165**, 1010), 4-hydroxy- (Albert, Brown, and Cheeseman, *J.*, 1951, 474), 2-amino- (Stimson, *J. Amer. Chem. Soc.*, 1949, **71**, 1470), 4-amino- (Williams, Ruehle, and Finkelstein, *ibid.*, 1937, **59**, 526; Cavalieri and Bendich, *ibid.*, 1950, **72**, 2587), 5-amino- (Whittaker, *J.*, 1951, 1565), and 4-methyl-pyrimidine (Marshall and Walker, *J.*, 1951, 1004). Since it seemed probable that a study of the spectra of the monosubstituted pyrimidines would throw light on the spectra of the more complex pyrimidine derivatives, the present work was undertaken and subsequently extended to include some polysubstituted pyrimidines (Part III, succeeding paper).

Table 1.

Compound	pKa_1	pKa_2	pH of aq. soln.	Water $\lambda_{max.}$ (mμ)	Water $\log_{10}\varepsilon_{max.}$	Ethanol $\lambda_{max.}$ (mμ)	Ethanol $\log_{10}\varepsilon_{max.}$
Pyrimidine	1·31 [1]	—	0·0	242	3·60 [1]	—	—
			H_2O	243	3·38	239	3·36
				272	2·46	244	3·38
						278—280	2·52
2-Methylpyrimidine	—	—	0·0	251—252	3·87	—	—
			6·98	*248*	3·46	*249*	3·45
4-Methylpyrimidine	2·0 [2]	—	0·0	244	3·70 [2]		
			7·0	*244*	3·53	*245*	3·41
2-Phenylpyrimidine	—	—	0·0	256—258	4·06	—	—
				287	3·92		
			6·98	*251*	4·18	*257*	4·28
2-Chloropyrimidine	<1·0	—	0·0	209	3·76	—	—
				251	3·43		
			6·98	209	3·75	*252*	3·19
				251	3·43	282—283	2·23
4-Chloropyrimidine hydrochloride	—	—	—	—	—	*248*	3·51
5-Chloropyrimidine	—	—	0·0	211—212	3·74	—	—
				260	3·41		
			6·98	211	3·85	*258*	3·34
				258	3·38	293	2·52

* *J.*, 1951, 1218, is considered to be Part I in this series.

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TABLE 1—*continued.*

Compound	pKa_1	pKa_2	pH of aq. soln.	Water $\lambda_{max.}$ (mμ)	Water $\log_{10}\varepsilon_{max.}$	Ethanol $\lambda_{max.}$ (mμ)	Ethanol $\log_{10}\varepsilon_{max.}$
5-Bromopyrimidine	—	—	0·0	219·5	3·94	—	—
				265	3·58		
			6·98	216·5	4·02	217·5	3·87
				261	3·46	*261*	3·33
						294	2·53
2-Methylthiopyrimidine	—	—	0·0	214·5	3·39	—	—
				255	4·16		
				310	3·54		
			6·98	*250*	4·12	*251*	4·20
						286	3·30
2-Methoxypyrimidine	—	—	0·0	273—274	3·69	—	—
				309	2·85		
			6·98	*264*	3·68	*267·5*	3·65
2-Aminopyrimidine	3·54 [3]	—	3·0	220	4·10 [4]	—	—
				300	3·58		
			7·0	225	4·04	227	4·22
				292	3·51	*297*	3·59
4-Aminopyrimidine	5·71 [3]	—	0·0	246	4·27 [5]	—	—
			7·73	234	4·08 [6]	236	4·30
				268	3·55	*272—273*	3·71
			13	233	4·26 [5]	—	—
				268—269	3·72		
5-Aminopyrimidine	2·60 [7]	—	1·0	253	4·16 [7]	—	—
				332	3·57		
			H_2O	236	4·04	246	4·10
				298	3·49	*315*	3·50
2-Hydroxypyrimidine	2·24	9·17 [8]	0·3	309	3·75 [8,9]	—	—
			6·1	215	4·0		
				299	3·66		
			13	*290*	3·66		
4-Hydroxypyrimidine	1·85	8·59 [9]	0·0	225	4·18	—	—
				252—254	3·65		
			4·88	227·5	3·97		
				258 inf.	3·74		
			13	227	4·04		
				264—265	3·56		
2-Mercaptopyrimidine	~1·3	7·2	0·0	208	3·87	—	—
				285	4·51		
				378	3·18		
			4·9	278	4·33		
				346	3·42		
			13	231	3·69		
				270	4·23		
4-Mercaptopyrimidine	<1	6·7	0·0	306	4·30	—	—
			4·5	285	4·03		
				327	3·91		
			13	*292—294*	4·04		
Pyrimidine-4-carboxylic acid	—	—	0·0	257	3·57	—	—
			13	*253*	3·51		
Pyrimidine-5-carboxylic acid	—	—	13	*245—246*	3·31	—	—

[1] Jones and Whittaker, forthcoming publication. [2] Marshall and Walker, *J.*, 1951, 1004. [3] Albert, Goldacre, and Phillips, *J.*, 1948, 2240. [4] Stimson, *J. Amer. Chem. Soc.*, 1949, **71**, 1470. A redetermination in 1952 gave 3·51 as $\log_{10}\varepsilon$ for the 292-mμ band for the neutral molecule (private communication). [5] Williams, Ruehle, and Finkelstein (*ibid.*, 1937, **59**, 526) report for 4-aminopyrimidine in acid and alkaline solution the values 246, 4·05, and 232, 4·00; 274, 3·56 respectively. [6] Cavalieri and Bendich (*ibid.*, 1950, **72**, 2587) give the values 232, 4·05; 265, 3·58, for the neutral molecule. [7] Whittaker, *J.*, 1951, 1565. [8] Brown, *Nature*, 1950, **165**, 1010. [9] Albert, Brown, and Cheeseman (*J.*, 1951, 474) give the following values for 4-hydroxypyrimidine at pH 0·3, 6·3, and 13; cation, 225, 4·00; neutral molecule, 225, 3·83; anion, 229, 4·07, and 265, 3·68.

As Marshall and Walker (*loc. cit.*) have observed, much of the earlier work on pyrimidine derivatives containing one or more potentially tautomeric groups (OH, SH, or NH_2) is of doubtful value since the measurements were made without reference to pK_a values and often without control of pH. Consequently, the results obtained referred to a mixture

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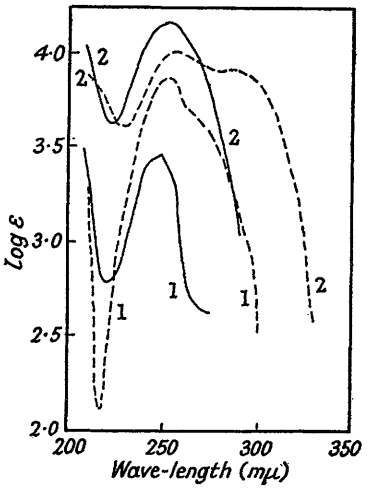
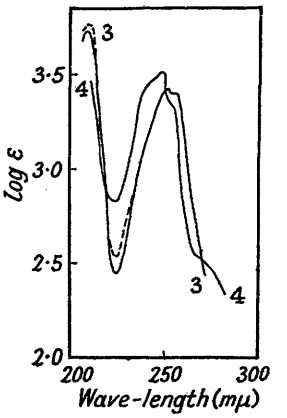
of ions and neutral molecules, whose composition was unknown. In the present work, following the procedure of Marshall and Walker, the pK_a value of the pyrimidine to be examined determined the pH of the buffer solution to be used as the solvent. The pK_a values, the wave-lengths of maximum extinction, and the logarithms of the molecular extinction coefficients are recorded in Table 1 and the Figures. In addition, the light absorptions of the non-tautomeric pyrimidines were measured in ethanol, since the maxima

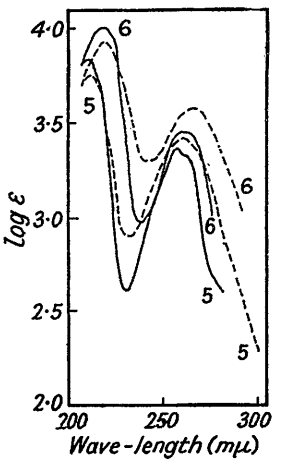
FIGS. 1—2. (1) 2-*Methyl-*; (2) 2-*phenyl-pyrimidine.*



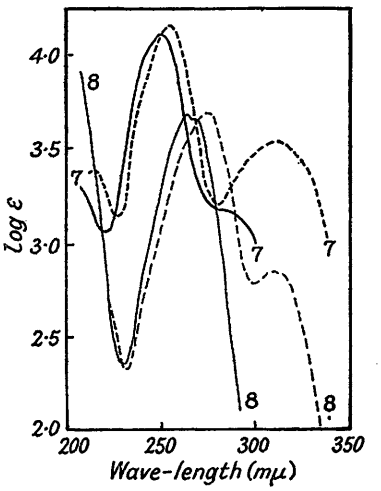
FIGS. 3—4. (3) 2-*Chloro-pyrimidine*; (4) 4-*chloro-pyrimidine hydrochloride.*



FIGS. 5—6. (5) 5-*Chloro-*; (6) 5-*bromo-pyrimidine.*



FIGS. 7—8. (7) 2-*Methylthio-*; (8) 2-*methoxypyrimidine.*



In these and all other Figures, — — — *refers to acid,* ——— *to neutral, and* · · · · *to alkaline solution.*

for many compounds are usually displaced in this medium which was frequently used by earlier workers.

The curves are in general very similar to those reported by Marshall and Walker, confirming their view that the extra methyl group in their compounds would have very little effect on the characteristic spectrum of a pyrimidine containing a potentially tautomeric group. From a comparison of these graphs with those of Marshall and Walker, the same conclusions as those reached by them may be drawn concerning the structure of potentially tautomeric monosubstituted pyrimidines in neutral solution. For example, the light-

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extinction curve of 2-methylthiopyrimidine (Fig. 7) in neutral solution is very similar to that of 2-mercaptopyrimidine (Fig. 9) in alkaline solution. It is quite different from the light-extinction curve of the neutral 2-mercaptopyrimidine molecule (Fig. 9) which is closely similar to that of 1 : 4 : 6-trimethyl-2-pyrimidthione. It seems probable therefore that 2-mercaptopyrimidine in neutral solution exists mainly in the thione structure. From similar arguments, it is likely that 2- and 4-hydroxy- and 4-mercapto-pyrimidine also exist in the 2- and 4-pyrimidone and the 4-pyrimidthione form respectively. The anions

FIG. 9. 2-*Mercaptopyrimidine.*

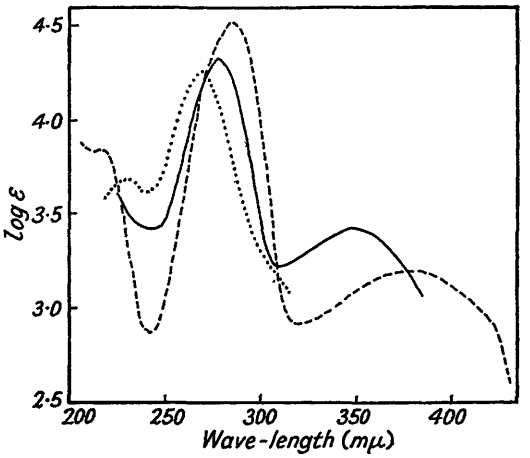
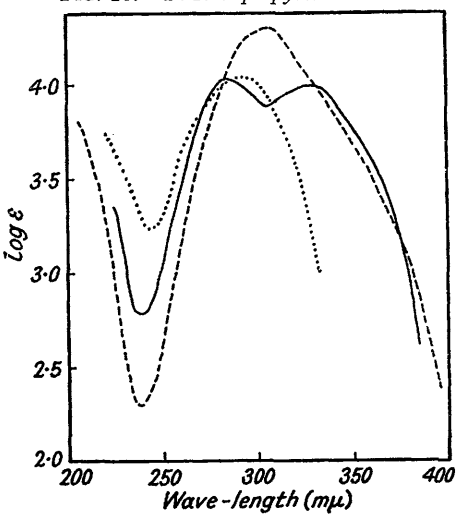
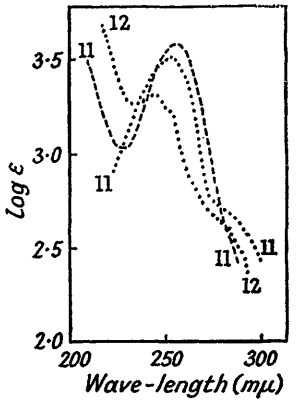


FIG. 10. 4-*Mercaptopyrimidine.*





FIGS. 11—12. (11) *Pyrimidine-4-*; (12) *pyrimidine-5-carboxylic acid.*

will, of course, have the same structures whether they are derived from hydroxy-(mercapto-)pyrimidines or from pyrimidones (pyrimidthiones).

The ultra-violet absorption spectrum of pyrimidine in aqueous solution consists of at least three bands, one below 200 (probably of high intensity, by analogy with benzene), one at 243 (log $\varepsilon = 3{\cdot}38$), and a broad band between 260 and 290 mμ with a maximum at 272 mμ (log $\varepsilon = 2{\cdot}46$) (Jones and Whittaker, forthcoming publication; see also Halverson and Hirt, *J. Chem. Phys.*, 1951, **19**, 711, which contains earlier references). It will be seen from Table 1 and the Figures that nuclear substitution causes a bathochromic shift of the absorption bands and that, with the possible exception of 2-mercaptopyrimidine, the bands of longer wave-length have lower intensities than those of shorter wave-length for a given compound. It thus seems reasonable to suppose that the bands whose maxima are italicised in Table 1 are due to the displacement of the 243- or 244-mμ band of pyrimidine

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in water and alcohol respectively. In the same way, the bands of shortest and longest wave-length are probably related to the bands <200 and >270 mμ of pyrimidine. Doub and Vandenbelt (*J. Amer. Chem. Soc.*, 1947, **69**, 2714; 1949, **71**, 2414) have similarly correlated the ultra-violet absorption spectra of mono- and poly-substituted benzenes with benzene itself. The bathochromic shifts for a single substituent in different positions in the pyrimidine nucleus are given in Table 2. It may be seen that for a single substituent, the bathochromic shift varies according to the position of the substituent in the pyrimidine ring. Thus, the 2-substituents form a series which may be written in the order of increasing bathochromic shift : Me < MeS < Ph < Cl < MeO < S^- ≪ O^- < NH_2. A similar series is obtained for the 4-substituents : Me < Cl < CO_2^- < O^- < NH_2 ≪ S^-. Andrisano

TABLE 2.[1]

	Shift in wave-length, Position						Shift in mol. extinction coeff. (× 10^{-3}), Position					
	2		4		5		2		4		5	
Radical												
Me	5	(5)	1	(1)	—		0·48	(0·42)	0·99	(0·17)	—	
MeS	7	(7)	—		—		10·8	(13·4)	—		—	
Ph	8	(13)	—		(12) [5]		12·6	(16·6)	—		(9·7)	
CO_2^-	—		10		2·5		—		0·84		−0·36	
Cl	9·5 [3]	(8)	5 [2]	(4) [2]	15	(14)	0·29	(−0·85)	0·84	(0·84)	0·03	(−0·22)
Br	—		—		18	(17)	—		—		0·47	(−0·26)
MeO	21	(23·5)	—		—		2·39	(2·07)	—		—	
S^-	27		48		—		14·6		8·6		—	
O^-	47		21·5		—		2·17		1·23		—	
NH_2 [4]	49	(53)	25	(28·5)	55	(71)	0·86	(1·49)	1·13	(2·73)	0·69	(0·73)

[1] The values in parentheses refer to the measurements made in ethanol. [2] The bathochromic shift and the increment of the molecular extinction coefficient for 4-chloropyrimidine were calculated from the measurement made on the hydrochloride in ethanol. It is assumed by analogy with other chloro- and bromo-pyrimidines that the value thus obtained will not differ appreciably from those which would be observed in an aqueous medium. [3] This value is calculated from the $\lambda_{max.}$ of the envelope of the extinction curve instead of the observed $\lambda_{max.}$ (cf. Fig. 3). [4] The infra-red spectra of 2- and 4-aminopyrimidines indicate that these compounds probably exist in the NH_2 form rather than the tautomeric = NH form (Short and Thompson, *J.*, 1952, 168). [5] Maggiolo and Russell, *J.*, 1951, 3297.

and Modena (*Gazzetta*, 1951, **81**, 405), from a study of 2-substituted 4 : 6-dimethylpyrimidines, have reported the following bathochromic shifts produced by the 2-substituent : MeS (4) < Me,Ph (5) < Cl (8·5) < MeO (18) < SH (32·5) < NH_2 (41) < OH (48). The order of the series for substituents in the 2-position in these compounds is very similar to that obtained from the monosubstituted compounds except for the first three members where the differences are only of the order of 1 mμ. In the calculation of the bathochromic shifts for 2-hydroxy- and 2-mercapto-4 : 6-dimethylpyrimidine, Andrisano and Modena use the wave-length of maximum extinction obtained at pH 5·6. At this pH both these compounds will exist as neutral molecules which are not strictly comparable with the non-tautomeric pyrimidines (4 : 6-dimethyl-2-pyrimidthione has an acidic pK_a value of 8·5 and 4 : 6-dimethyl-2-pyrimidone will be less acidic). If the bathochromic shifts for these substituents are calculated from the wave-length maxima at pH 12·9, when the compounds should exist entirely as anions, the values 23 mμ for S^- and 43 mμ for O^- are obtained which are in better agreement with the values obtained from the monosubstituted pyrimidines. It is seen that the bathochromic shifts obtained from a study of the dimethylpyrimidines are less than those obtained from the monosubstituted derivatives. This is in agreement with our observations on polysubstituted pyrimidines, where it has frequently been found that methyl groups in the 4- and the 6-position prevent other substituents from exerting their full bathochromic effect.

Following Stimson's suggestion (*J. Amer. Chem. Soc.*, 1949, **71**, 1470), Andrisano and Modena (*loc. cit.*) classified the 4 : 6-dimethylpyrimidines which they examined as symmetrical, quasi-symmetrical, or asymmetrical. A pyrimidine which is symmetrically disposed about a plane perpendicular to the plane of the ring and passing through carbon atoms 2 and 5 is termed symmetrical. According to Andrisano and Modena, the wave-length of maximum extinction in a symmetrical pyrimidine remains constant throughout

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the pH range, although the extinction coefficient varies. They termed compounds which are formally symmetrical and whose wave-length maxima varied with pH to a certain extent, quasi-symmetrical. Substituents falling into the latter class were Me, Ph, and SMe. The 2-substituted 4 : 6-dimethylpyrimidines whose maximum wave-length varied continuously with pH were termed asymmetrical by Andrisano and Modena who placed substituents such as OH, OMe, SH, and NH_2 in this class. Stimson (*loc. cit.*), on the other hand, classified pyrimidines such as barbituric acid and 5-ethyl-4 : 6-dihydroxy-2-mercapto-pyrimidine as symmetrical pyrimidines. She did not however record measurements made above pH 11 which is probably below at least one of the acidic dissociation constants of this type of compound. It is likely therefore that at higher pH values the maximum would be shifted. In the simpler compounds containing only one tautomeric group, studied in the present work and by Andrisano and Modena, the only pyrimidines which are observed to be symmetrical in the strict sense defined by the latter authors are the 2-chloro-compounds. These have exceptionally low basic pK_a values and probably do not form cations in acid solution. It seems therefore that the shifting of the maximum with pH depends, not so much on the actual symmetry of the molecule, as on the formation of an anion or cation.

Experimental

Source of Pyrimidines.—2-Methylpyrimidine was kindly supplied by Dr. E. C. Kornfeld, of Lilly Research Laboratories, U.S.A.

4-Methylpyrimidine was kindly supplied by Dr. James Walker, National Institute for Medical Research, London.

2-Chloropyrimidine, 4-chloropyrimidine hydrochloride, 2- and 4-mercaptopyrimidine, and pyrimidine-5-carboxylic acid were prepared by known methods (Boarland and McOmie, *J.*, 1951, 1218).

5-Chloropyrimidine, 2-phenylpyrimidine, and pyrimidine oxalate were generously supplied by Dr. B. Lythgoe of Cambridge.

2-Aminopyrimidine. The commercial product of Eastman Kodak Company was recrystallised from benzene before use.

4-Aminopyrimidine was a gift from Dr. D. J. Brown, Australian National University, London.

4-Hydroxypyrimidine was prepared from 2-thiouracil by Brown's method (*J. Soc. Chem. Ind.*, 1950, **69**, 353).

A solution of pyrimidine in alcohol was obtained by dissolving pyrimidine oxalate (4·0 mg.) in ethanol (9·95 c.c.) and N-sodium hydroxide (0·05 c.c.). The ethanol in the control cell contained an equivalent quantity of sodium oxalate.

For 5-bromopyrimidine and pyrimidine-4-carboxylic acid see McOmie and White, forthcoming publication.

2-*Methylthiopyrimidine.* 2-Mercaptopyrimidine (2·2 g.) and methyl sulphate (2·0 c.c.) were shaken in aqueous sodium hydrogen carbonate (1·65 g. in 40 c.c.) at room temperature for 2 hours. The pyrimidine slowly dissolved, the colour fading to pale yellow. Extraction with ether (150 c.c.) gave a bright yellow oil. Three distillations under reduced pressure gave 2-methylthiopyrimidine as a colourless liquid, b. p. 109°/28 mm. (1·54 g., 62%), n_D^{14} 1·5880. Johnson and Joyce (*J. Amer. Chem. Soc.*, 1916, **38**, 1385) report b. p. 99—100°/14 mm., n_D^{20} 1·5856, for the compound prepared by zinc dust reduction of 4-chloro-2-methylthiopyrimidine.

2-*Methoxypyrimidine.* 2-Chloropyrimidine (5·0 g.) in methanol (20 c.c.) was added to a solution of sodium methoxide [from sodium (1·0 g.)] in methanol (30 c.c.). An exothermic reaction took place with immediate separation of sodium chloride. After several hours at room temperature, the solution was filtered and the methanol removed by distillation. The residue was distilled under reduced pressure from a quantity of sodium chloride which had separated from the methanolic solution. 2-Methoxypyrimidine was obtained as a colourless liquid (3·0 g., 63%), b.p. 72·5°/22 mm., n_D^{14} 1·5023, in good agreement with Albert and Brown's observations (personal communication).

Physical Measurements.—Absorption spectra. These were measured with a Unicam S.P. 500 quartz spectrophotometer at the pH values recorded in the Table. The buffer solutions were : 0·2N-acetate (for pH 4·0—5·0), M/15-phosphate (pH 6·98), together with N- (pH 0) and 0·1N-hydrochloric acid (pH 1·0), and 0·1N-sodium hydroxide (pH 13). Values of wave-lengths below 235 mμ are probably only correct to within ±2 mμ owing to the initial incorrect adjustment of the instrument.

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Potentiometric titrations. The pH of the solution was measured during titration with a Doran pH Indicator standardised against 0·05M-potassium hydrogen phthalate buffer solutions, a Doran Linear (0—13 pH) Alkacid glass electrode being used. The pK_a values were calculated from the pH readings and are probably correct within $\pm$0·2 pH unit.

The authors thank Professor A. Albert and Mr. G. E. Coates for their helpful advice on potentiometric titrations, Mr. M. Marshall for the measurement of some of the ultra-violet spectra, and the Department of Scientific and Industrial Research for the award of a Maintenance Grant to one of them (M. P. V. B.)

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