Heterocyclic Syntheses with Malonyl Chloride. Part IX.[1] 2-Substituted 4-Chloro-6-pyrimidones from Certain Nitriles

By **J. A. Elvidge** * and **N. A. Zaidi,** Chemistry Department, University of Surrey, London S.W.11

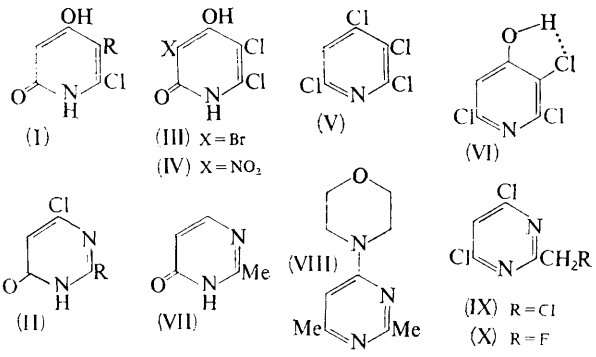
Chloroacetonitrile with malonyl chloride yielded 2,3-dichloro-4,6-dihydroxypyridine together with an unexpected product, 4-chloro-2-chloromethyl-6-pyrimidone. Further examples of this new synthesis of 2-substituted 4-chloro-6-pyrimidones were obtained with fluoro- and bromo-acetonitrile, α-bromopropionitrile, and acetonitrile. Propio- and butyro-nitrile each gave a mixture of pyridine and pyrimidine product, whilst various other nitriles gave only the pyridine products. The expected fully substituted pyrimidone was obtained from fluoroacetonitrile and chloromalonyl chloride, and from dibromoacetonitrile with bromomalonyl chloride. Some novel halogen-transfer reactions were encountered in other cases.

PREVIOUSLY we reported [2] that malonyl chloride reacts with some monosubstituted acetonitriles to give 3-substituted 4-chloro-4,6-dihydroxypyridines, considered to exist in the 2-pyridone form (I). In extending the reaction to halogenoacetonitriles, we unexpectedly obtained 2-substituted 4-chloro-6-pyrimidones (II).[3]

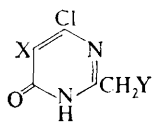
From the reaction of malonyl chloride with chloroacetonitrile two products were isolated. One, insoluble in chloroform, appeared from the analytical and spectroscopic evidence (cf. refs. 4 and 2) to be the expected 2,3-dichloro-4-hydroxy-6-pyridone (I; R = Cl). This readily gave a monobromo- (III) and a mononitro-derivative (IV), and with phosphorus oxychloride

[1] Part VIII, M. A. Butt and J. A. Elvidge, *J. Chem. Soc.*, 1963, 4483.
[2] S. J. Davis, J. A. Elvidge, and A. B. Foster, *J. Chem. Soc.*, 1962, 3638.
[3] J. A. Elvidge and N. A. Zaidi, Chem. Soc. Anniversary Meeting, Oxford, 1966.
[4] A. R. Katritzky and R. A. Jones, *J. Chem. Soc.*, 1960, 2947.

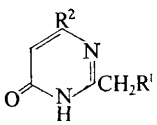
at 180° afforded the known 2,3,4,6-tetrachloropyridine (V).[5] Refluxing phosphorus oxychloride gave only a trichlorohydroxypyridine, which is probably (VI) since it lacked absorption in the 1700—1600 cm.$^{-1}$ region. The second product from the malonyl chloride reaction had the composition $C_5H_4Cl_2N_2O$. The parent peak (*m/e* 178) in the mass spectrum was the base peak, and this indication of aromatic character was supported by the u.v. and i.r. absorptions. The ^{1}H n.m.r. spectrum showed a broad band at low field for one OH or NH, a singlet from one aromatic proton, and a two-proton singlet at τ 5·62, as from a chloromethyl substituent. This last structural feature was also indicated in the mass spectrum. Thus, the new compound was the chloromethylpyrimidone (II; R = CH_2Cl), this tautomeric form being suggested by the strong i.r. bands at 1681 and 1653 cm.$^{-1}$.[6] Reductive dehalogenation to a pyrimidone hydrochloride and thence basification to give 2-methyl-4-pyrimidone [7] (VII) confirmed the structure of (II; R = CH_2Cl).



(I) (III) X = Br (IV) X = NO_2 (V) (VI) (II) (VII) (VIII) (IX) R = Cl (X) R = F



(XI) X = Y = Cl
(XII) X = Y = Br
(XIII) X = Br, Y = F
(XIV) X = Cl, Y = F



(XV) R^1 = $-\overset{+}{N}\cdot CH{:}CH\cdot CH{:}CH\cdot CH$, X^-; R^2 = Cl

(XVI) $R^1 = R^2 = -N\cdot CH_2\cdot CH_2\cdot O\cdot CH_2\cdot CH_2-$

(XVII) R^1 = F, $R^2 = -N\cdot CH_2\cdot CH_2\cdot O\cdot CH_2\cdot CH_2-$

(XVIII) R^1 = Et, $R^2 = -N\cdot CH_2\cdot CH_2\cdot O\cdot CH_2\cdot CH_2-$

The new pyrimidone (II; R = CH_2Cl) with boiling phosphorus oxychloride gave 4,6-dichloro-2-chloromethylpyrimidine (IX), whilst with chlorine the free 5-position was substituted to give 4,5-dichloro-2-chloromethyl-6-pyrimidone (XI). Bromination, however, afforded a mixture of the expected 5-bromo-compound together with some 5-bromo-2-bromomethyl derivative (XII). Evidently the chlorine of the 2-substituent was particularly reactive (more so than the 4-chlorine) and, indeed, the pure 5-bromo-2-bromomethyl-4-chloro-compound (XII) was obtained merely by treating the mixture with hydrobromic acid. As then expected, treatment of the 4-chloro-2-chloromethyl-6-pyrimidone (II; R = CH_2Cl) with sodium iodide in acetone afforded the 2-iodomethyl compound (II; R = CH_2I), and each pyrimidone with pyridine gave a monopyridinium salt (XV; X = Cl and I). Morpholine, on the other hand, replaced both chlorines in (II; R = CH_2Cl), to give a water-soluble product. This was formulated as (XVI) and not as a zwitterion because the relevant proton chemical shifts were close to those in the model compound (VIII) (Table) and were not therefore consistent with a positive charge on the 2-morpholinomethyl nitrogen. Phenylhydrazine attacked only the 2-chloromethyl group in (II; R = CH_2Cl), but with concomitant dehydrogenation,[8] to give the yellow phenylhydrazone (II; R = CH:N·NHPh).

We had found (with M. S. Stoll) that fluoroacetonitrile reacted with malonyl chloride to give a single solid product. This was now identified as 4-chloro-2-fluoromethyl-6-pyrimidone (II; R = CH_2F). Hydrogenolysis gave 2-methyl-4-pyrimidone (VII), phosphorous oxychloride gave the 4,6-dichloro-compound (X), bromine yielded the 5-bromo-derivative (XIII), and morpholine substituted the 4-chlorine to give 2-fluoromethyl-4-morpholino-6-pyrimidone (XVII).

Bromoacetonitrile reacted more slowly with malonyl chloride and gave only the 2-bromomethyl pyrimidone II; R = CH_2Br), bromination of which afforded the 5-bromo-derivative (XII) already encountered. The pyrimidone (II; R = CH_2Br) was also obtained from interaction of dibromoacetonitrile with malonyl chloride, an unexpected but reproducible result. The purity of the dibromoacetonitrile was confirmed, and so it was concluded that this compound was brominating malonyl chloride, itself thereby being converted into bromoacetonitrile, which with unchanged malonyl chloride was evidently reacting relatively more rapidly to afford (II; R = CH_2Br). In agreement, better yields were obtained with an excess of malonyl chloride. Furthermore, it was demonstrated that bromomalonyl chloride was present in the reaction mixture, together with bromoacetyl chloride and unchanged malonyl chloride.

No solid product was isolated from the reaction of malonyl chloride with di- or tri-chloroacetonitrile. That an α-methylene group was not essential for pyrimidone

[5] H. J. den Hertog, J. C. M. Schogt, J. de Bruyn, and A. de Klerk, *Rec. Trav. chim.*, 1950, **69**, 673.
[6] L. N. Short and H. W. Thompson, *J. Chem. Soc.*, 1952, 168; D. J. Brown, E. Hoerger, and S. F. Mason, *J. Chem. Soc.*, 1955, 211.
[7] A. Takamizawa, Jap.Pat., 8031/1954 (*Chem. Abs.*, 1956, **50**, 14,002).
[8] T. W. J. Taylor and W. Baker, in Sidgwick's 'Organic Chemistry of Nitrogen,' Clarendon, Oxford, 1942, p. 382.

^{1}H Nuclear magnetic resonance results at 60 Mc./sec.

Pyridines (I)	τ	Intensity	Multiplicity * J in c./sec.	Assignment
R = Cl [a(e)]	3·63 (3·70)	1	s	5-H
	3·08	2	b (2·7)	NH/OH
R = CO_2Et [a]	8·73	3	t } 7·6	Me } of 3-CO_2Et
	5·73	2	q }	CH_2 }
	3·93	1	s	5-H
	−1·45	2	b (0·3)	NH/OH
R = C_6H_4·Cl-*p* [a]	3·85	1	s	5-H
	ca. 2·66	4	Unresolved	3-C_6H_4 group
	−0·9	2	b (0·4)	NH/OH
R = C_6H_4·NO_2-*p* [a]	3·82	1	s	5-H
	2·42	2	d } 8·9	*m*-H's } to NO_2 in 3-C_6H_4 group
	1·72	2	d }	*o*-H's }
	−1·15	2	b (0·4)	NH/OH
R = Me [a]	7·97	3	s	3-Me
	3·99	1	s	5-H
	−0·73	2	b (0·4)	NH/OH
R = Et [b]	8·70	3	t } 7·6	Me } of 3-Et
	7·07	2	q }	CH_2 }
	3·50	1	s	5-H
	−2·0	2	b (1·1)	NH/OH
R = CH_2Cl [a]	5·31	2	s	3-CH_2Cl
	3·80	1	s	5-H
	1·20	2	b (1·2)	NH/OH
R = CH_2Br [a]	5·30	2	s	3-CH_2Br
	3·88	1	s	5-H
R = CH_2·OEt [b]	8·77	3	t } 7	Me } of OEt
	6·31	2	q }	CH_2 }
	5·13	2	s	CH_2 at 3-position
	3·47	1	s	5-H
	−1·42	2	b (0·3)	NH/OH
R = CH_2·$N^+C_5H_5$,Br^- [a]	4·17	2	s	CH_2 at 3-position
	3·66	1	s	5-H
	1·79	2	*ca.* t } 6—7	3-, 5-H }
	1·30	1	*ca.* t }	4-H } on pyridinium ring
	0·93	2	*ca.* d }	2-, 6-H }
R = $[CH_2]_3$·CN [c]	7·93	2	*ca.* qu } 7·5	2′-CH_2 }
	7·34	2	t }	3′-CH_2·CN } of 3-substituent
	6·93	2	t }	1′-CH_2 }
	3·11	1	s	5-H
R = $[CH_2]_{13}$·CN [b]	8·75	22	*ca.* s	$[CH_2]_{11}$ }
	7·66	2	t 7	13′-CH_2·CN } of 3-substituent
	6·98	2	t 7·5	1′-CH_2 }
	3·44	1	s	5-H
	0·4	2	b (0·8)	NH/OH
R = CN [a]	3·86		s	3-H
				NH/OH not located
(XXI) [a]	3·65		s	5-H
				NH/OH not located
(V) [d]	2·63		s	5-H
(VI) [e]	3·01		s	5-H
Pyrimidines (II)				
R = CH_2Cl [f,(e),[a]]	5·52 (5·40) [5·48]	2	s	2-CH_2Cl
	3·46 (3·50) [3·45]	1	s	5-H
	−0·69	1	b (0·4)	NH/OH
R = CH_2I [a]	5·83	2	s	2-CH_2I
	3·57	1	s	5-H
				NH/OH not located
R = CH:N·NHPh [a]	3·65	1	s	5-H
	3·2—2·3	6	c	Ph + CH of 2-substituent
	−0·60	1	b (1·2)	NH/OH of ring
	−1·82	1	b (0·2)	NH of 2-substituent
R = CH_2F [b]	4·75	2	d 46	2-CH_2F
	3·55	1	s	5-H
	−1·50	1	b (0·66)	NH/OH

TABLE (*Continued*)

Pyrimidines (II)	τ	Intensity	Multiplicity * *J* in c./sec.	Assignment
R = CH_2Br [a]	5·65	2	s	2-CH_2Br
	3·48	1	s	5-H
				NH/OH not located
R = Me [f]	7·49	3	s	2-Me
	3·59	1	s	1′-CH_2
	−3·50	1	b (1·0)	NH/OH
R = Et [f]	8·66	3	t } 7	Me } of 2-Et
	7·26	2	q }	CH_2 }
	3·61	1	s	5-H
R = Pr [f]	9·13	3	t }	CH_3 }
	8·23	2	sx } 7·4	Mid CH_2 } of 2-Pr substituent
	7·32	2	t }	5-H
	3·41	1	s	5-H
	−1·5	1	b (1)	NH/OH
(VII) [g] [(VII), HCl] [g]	7·53 [7·21]	3	s	2-Me
	3·62 [3·30]	1	d } 7·5	5-H
	2·08 [1·96]	1	d }	4-H
(VIII) [d]	7·80	3	s	6-Me
	7·65	3	s	2-Me
	ca. 6·45	8	c	4-morpholino
	4·0	1	s	5-H
(IX) [d]	5·40	2	s	2-CH_2Cl
	2·67	1	s	5-H
(X) [f]	4·52	2	d 46·5	2-CH_2F
	2·60	1	s	5-H
(XI) [a]	5·46	2	s	2-CH_2Cl
	−1·39	1	b (0·3)	NH/OH
(XII) [a]	5·61		s	2-CH_2Br
				NH/OH not located
(XIII) [h]	4·73	2	d 46	2-CH_2F
	−1·0	1	b (0·5)	NH/OH
(XIV) [f]	4·52	2	d 46·5	2-CH_2F
	2·60	1	s	5-H
				NH/OH not located
(XV; X = Cl) [a]	3·93	2	s	2-CH_2
	3·37	1	s	5-H
	1·70	2	c	3′-, 5′-H }
	1·20	1	c	4′-H } on pyridinium ring
	0·77	2	*ca.* d	2′-, 6′-H }
				NH/OH not located
(XVI) [f]	7·43	4	*ca.* t	CH_2·N·CH_2 of 2-substituent
	6·58	2	s	2-CH_2
	ca. 6·3	12	c	Other CH_2's of morpholino-rings
	4·73	1	s	5-H
	0·33	1	b (0·6)	NH/OH
(XVII) [f]	6·6—6·4	4	c	CH_2·N·CH_2
	6·35—6·15	4	c	CH_2·O·CH_2
	4·79	2	d 46·5	2-CH_2F
	4·63	1	s	5-H
				NH/OH not located
(XVIII) [f]	9·00	3	t }	Me }
	8·20	2	sx } 7	Mid CH_2 } of 2-Pr substituent
	7·38	2	t }	1′-CH_2 }
	6·55—6·35	4	c	CH_2·N·CH_2 } of morpholine ring
	6·28—6·07	4	c	CH_2·O·CH_2 }
	4·65	1	s	5-H
	−3·20	1	b (0·7)	NH/OH
(XXIII) [i,(j)]	3·32 (3·63)	1	s	2-$CHBr_2$
	2·1	1	b (0·6)	NH/OH

Solutions (*ca.* 5%) in *a* Me_2SO, *b* pyridine, *c* trifluoroacetic acid, *d* CCl_4, *e* acetone, *f* $CDCl_3$, *g* D_2O, *h* dioxan, *i* diethyl carbonate, *j* $CDCl_3$ + MeOH.

* s = Singlet, d = doublet, t = triplet, q = quartet, qu = quintet, sx = sextet, c = complex, b = broad (width in p.p.m.).

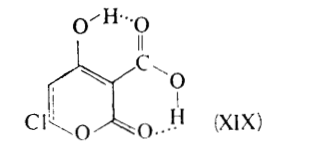
formation, however, was shown by the successful reaction with α-bromopropionitrile which gave (II; R = CHMeBr).

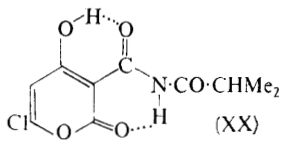
Iodoacetonitrile yielded a mixture containing iodine, even when light was excluded, and from this only the 4-chloro-2-methyl-6-pyrimidone (II; R = Me) was isolated. Because the expected product (II; R = CH_2I) had already been prepared and found stable, it appeared that reductive deiodination had occurred as part of the malonyl chloride reaction. Analogy suggests that iodoacetonitrile iodinates malonyl chloride, itself yielding acetonitrile, and that the latter reacts preferentially with unchanged malonyl chloride.

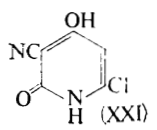
The conclusion that acetonitrile and malonyl chloride gave at room temperature the pyrimidone (II; R = Me) contradicted our earlier claim,[2] based upon ebullioscopic molecular weight (146), m.p. (233°),[9] and Cl analysis, that the product was 2-chloro-4,6-dihydroxypyridine (I; R = H). Clearly, the evidence had been insufficient; reinvestigation confirmed the earlier limited observations, added to them, and proved that the product was the pyrimidone (II; R = Me). Incidentally, a lower-melting by-product was separated from the acetonitrile–malonyl chloride reaction and identified as 6-chloro-4-hydroxy-2-oxopyran-3-carboxylic acid[10] (XIX). This was evidently formed through the induced self-condensation of malonyl chloride,[11] recognised as the first step in the higher-temperature reaction with nitriles which leads to chloropyrono-oxazines.[12]

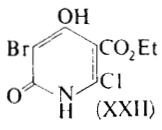
The revision of the structure for the acetonitrile product prompted reinvestigation of the related compounds described in Part VI.[2] From ethyl cyanoacetate, no product other than the previously described pyridine (I; R = CO_2Et) was isolated: the ^1H n.m.r. spectrum is now reported (Table). 4-Chloro- and *p*-nitro-benzyl cyanide, like benzyl cyanide,[2] afforded pyridine products, (I; R = C_6H_4·Cl-4 and C_6H_4·NO_2-4), proof coming from the mass and ^1H n.m.r. spectra. Similar evidence supported the pyridine structure[2] (I; R = Me) for the main product from propionitrile and malonyl chloride, a reaction now found to yield also a trace of the pyrimidone (II; R = Et). Butyronitrile likewise gave mainly the 3-ethylpyridine (I; R = Et) together with a little of the 2-propylpyrimidone (II; R = Pr) from which the 4-morpholino-derivative (XVIII) was prepared. Like γ-chlorobutyronitrile,[2] β-chloro- and β-bromo-propionitrile reacted with malonyl chloride to give the pyridines (I; R = CH_2Cl) and (I; R = CH_2Br), respectively. The halogenomethyl group in these new products was reactive and crystallisation from ethanol gave the 3-ethoxymethylpyridine (I; R = CH_2·OEt), whilst pyridine gave the pyridinium chloride and bromide (I; R = $CH_2N^+C_5H_5$, Cl^-, and Br^-).

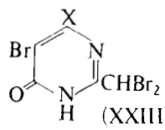
Isobutyronitrile (not previously examined) reacted with malonyl chloride when heated, and then gave a yellow product, $C_{10}H_{10}ClNO_5$, the various characteristics of which indicated the pyrone structure (XX). Comparison with the properties of an established analogue, 3-benzamidocarbonyl-4-hydroxy-6-morpholino-2-oxopyran,[12] provides convincing support. Presumably the reaction first yielded a chloropyrono-oxazine, and this was hydrolysed to (XX) during work-up.[12]


(XIX)


(XX)


(XXI)


(XXII)


(XXIII) X = Cl
(XXIV) X = Br

Previous attempts to cause succino- and glutaronitrile to react with malonyl chloride afforded only the pyrone acid (XIX) from the induced self-condensation of the chloride. New experiments with adiponitrile yielded the 3-cyanopropylpyridine (I; R = CH_2·CH_2·CH_2·CN), and 1,14-dicyanotetradecane afforded the ω-cyanotridecanylpyridine (I; R = $[CH_2]_{13}$·CN). With malonitrile, malonyl chloride reacted violently with charring, but at 0° during 7 days the product was 2-chloro-3-cyano-4,6-dihydroxypyridine [or the 2-pyridone tautomer (I; R = CN)]. This is a new positional isomer of the chlorocyanodihydroxypyridine (XXI) which results from self-condensation of cyanoacetyl chloride.[13]

Condensations with Halogenomalonyl Chlorides.—Having already shown[2] that bromomalonyl chloride with ethyl cyanoacetate afforded the fully substituted pyridine (XXII), it was of interest to determine whether halogenomalonyl chlorides were capable of yielding fully substituted pyrimidones.

Bromomalonyl chloride and fluoroacetonitrile gave a bromine-free product, identified as 4-chloro-2-fluoromethyl-6-pyrimidone (II; R = CH_2F). To account for the fate of the bromine in the bromomalonyl chloride, we suggest that the latter brominates fluoroacetonitrile and that the malonyl chloride, formed concomitantly, reacts preferentially with unchanged fluoroacetonitrile. In support, an increase in the fluoroacetonitrile increased the yield of the pyrimidone (II; R = CH_2F).

These observations prompted us to treat bromomalonyl chloride with dibromoacetonitrile. During 2 months a black mass formed, and from this the expected 5-bromo-2-dibromomethyl-4-chloro-6-pyrimidone (XXIII) was isolated. The mass spectrum of the partially purified product indicated[14] that a compound with *M* 422, containing 4 bromine atoms, was present,

[9] G. Schroeter and E. Finck, *Ber.*, 1938, **71**, 671.
[10] S. J. Davis and J. A. Elvidge, *J. Chem. Soc.*, 1952, 4109.
[11] J. A. Elvidge, *J. Chem. Soc.*, 1962, 2606.
[12] S. J. Davis and J. A. Elvidge, *J. Chem. Soc.*, 1962, 3553.
[13] G. Schroeter and C. Seidler, *J. prakt. Chem.*, 1922, **105**, 165.
[14] J. H. Beynon, 'Mass Spectrometry and Its Applications to Organic Chemistry,' Elsevier, Amsterdam, 1960, p. 298.

probably (XXIV) derived from (XXIII) by replacement of the chlorine during the prolonged preparation. A further series of peaks showed that one or more of the dibromodichloro-analogues of (XXIII) was also present.

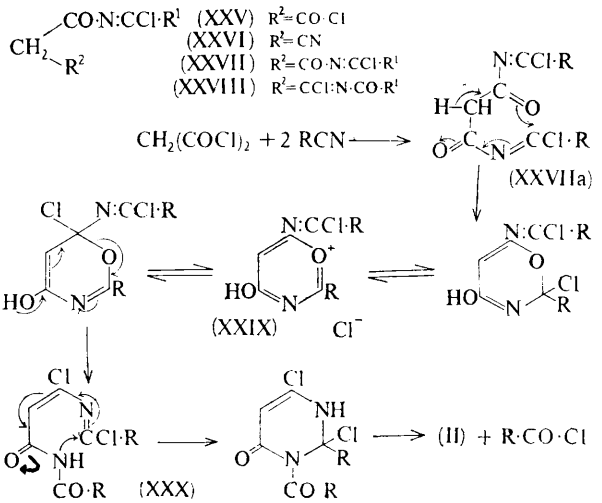
Chloromalonyl chloride with fluoroacetonitrile gave 4,5-dichloro-2-fluoromethyl-6-pyrimidone (XIV), and with chloroacetonitrile the expected 4,5-dichloro-2-chloromethyl-6-pyrimidone (XI) which had already been encountered. Difficulty was experienced in purifying the pyrimidone product in this last case, possibly because of accompanying pyridine product.

Mechanism of Formation of the Pyrimidones.—The fluoroacetonitrile–malonyl chloride reaction gave the best yield of product (II; R = CH_2F) from 2 : 1 molecular proportions (respectively). This of course agreed with the nitrile being the only source of the two nitrogen atoms of the pyrimidine ring. One molecule of nitrile provided, also, the 2-substituent and C-2 of the ring. The fate of the carbon chain of the second molecule of nitrile was indicated as RCOCl by the stoicheiometry of the reaction, $CH_2(COCl)_2 + 2RCN \longrightarrow C_4H_2ClN_2R$. Indeed, in the filtrate from the product of interaction of chloroacetonitrile and malonyl chloride the presence of chloroacetyl chloride was shown by ^1H n.m.r. and by formation of chloroacetanilide. Furthermore, in the reaction of dibromoacetonitrile with malonyl chloride, which gave the bromomethyl pyrimidone (II; R = CH_2Br), as already discussed, the concomitant formation of bromoacetyl chloride was demonstrated.

C-5 of the pyrimidine ring was provided by the methylene carbon of malonyl chloride, as shown by chloromalonyl chloride yielding (XI). The chlorine substituent which always appeared at C-4 was necessarily derived from one of the malonyl chlorocarbonyl groups. That this chlorine was introduced direct was shown by the failure of malonyl chloride to form a chloropyrimidine from 4,6-dihydroxy-2-methylpyrimidine. The present pyrimidine synthesis thus differs from the few preparations of 4(or 6)-chloropyrimidines reported,[15] which involved cyclisations with phosphorus halides. In these the nuclear halogen arises secondarily by replacement of enolic oxygen in a first-formed pyrimidone.

It seemed that the pyrimidine synthesis, like the pyridine synthesis,[2] must involve as first step acylation of the nitrile by malonyl chloride to give (XXV). At first, completion of the synthesis was envisaged as involving an exchange between (XXV) and a second molecule of nitrile to give acid chloride and the cyano-entity (XXVI), cycloisomerisation of which would yield the pyrimidone (II). However, cyanoacetyl chloride failed to yield any pyrimidine with fluoro- or chloroacetonitrile, or with either of these nitriles mixed with the corresponding acid chloride, so routes through (XXVI) were unlikely. An alternative was that an initial di-acylation product (XXVII) might undergo rearrangement to (XXVIII) from which the pyrimidone (II) would arise straightforwardly, but no reasonable mechanism for the rearrangement could be envisaged.

The second proposal, unlike the first, implied that all three carbon atoms of malonyl chloride were incorporated into the pyrimidone ring. By treating fluoroacetonitrile with malonyl chloride labelled with ^{14}C in both carbonyl groups, this implication was established. From a reaction with chloroacetonitrile, chloroacetyl chloride was isolated as the anilide and found to be devoid of radioactivity. Additionally it was shown with 4-chlorobenzyl cyanide that the pyridine product (I) from a malonyl chloride–nitrile reaction incorporated the malonyl carbons, substantiating in that respect the mechanism already proposed for the pyridine synthesis.[2]



The various observations may be accommodated as in the scheme shown. Acetylation of 2 mol. of nitrile would yield (XXVII). This might be expected to enolise more readily than an acid chloride, and so through cyclisation resulting from this capacity, as in (XXVIIa), to an entity which may be regarded as an azapyrylium salt (XXIX), and by nucleophilic attack on this by chloride, the entity (XXX) could arise. Cyclisation would then lead to the pyrimidone (II) and acid chloride through a step (shown) which hardly requires justification, simple *N*-acylpyrimidines being so labile as to be virtually unknown.[16]

Further studies are required to vindicate aspects of these suggestions. In particular, halogen exchange, as implied by stages (XXVIIa) ⟶ (XXIX) ⟶ (XXX), requires investigation: preliminary experiments failed here because of severe solubility problems. A reason for the reactions taking one or other course to a pyridine or pyrimidine product also needs finding.

EXPERIMENTAL

Mass spectra were obtained with an A.E.I. MS12 instrument. I.r. spectral data refer to Nujol mulls, and u.v. absorptions were measured with ethanol solutions (except as otherwise stated), employing Unicam SP 200 and 800 spectrometers respectively.

[15] (*a*) D. J. Brown, 'The Pyrimidines,' Interscience, New York, 1962, p. 162; (*b*) G. W. Kenner and Sir A. Todd, 'Pyrimidine and Its Derivatives,' ch. 7 in 'Heterocyclic Compounds, Wiley, New York, 1957, vol. 6.

[16] Ref. 15*a*, p. 357.

Reaction of Chloroacetonitrile with Malonyl Chloride.—A mixture of the nitrile (9 g.) and malonyl chloride [17] (13·5 g.) was kept at room temperature for 3 days (with exclusion of moisture). Hydrogen chloride was evolved and a sticky reddish material separated, trituration of which with a mixture of dry dioxan and ether provided a crystalline mass. Under a lens, this appeared to comprise two components.

(*a*) Extraction with chloroform left insoluble 2,3-*dichloro*-4-*hydroxy*-6-*pyridone* (I; R = Cl) which was crystallised (ethanol) and sublimed, m.p. 273—274° (Found: C, 33·5; H, 1·75; Cl, 39·5; N, 7·9. $C_5H_3Cl_2NO_2$ requires C, 33·3; H, 1·7; Cl, 39·4; N, 7·7%), *m/e* 179 (P, B), 181 (65), and 183 (10%), $\nu_{max.}$ 3300—2200, 1645, 1595, 1545, 1488, 1350, 1324, and 1246 cm.$^{-1}$, $\lambda_{max.}$ 225infl. and 275 mμ (ε 4700 and 3300).

(*b*) The chloroform-soluble product was crystallised (methanol–water) and sublimed, to yield 4-*chloro*-2-*chloromethyl*-6-*pyrimidone* (II; R = CH_2Cl), m.p. 173° (Found: C, 33·8; H, 2·2; N, 15·75. $C_5H_4Cl_2N_2O$ requires C, 33·55; H, 2·2; N, 15·65%), *m/e* 178 (P, B), 180 (65), 182 (10·2), and 129 (49%), $\nu_{max.}$ 3200—2200, 1676s, 1658, 1590, 1260w, 1220w, 1155, and 1130s cm.$^{-1}$, $\lambda_{max.}$ 228 and 282 mμ (ε 4500 and 3500) (cf. ref. 18).

Reactions of the Pyridine Product.—(a) *Bromination.* A solution of the pyridine (I; R = Cl) (0·5 g.) in ethanol (5 ml.) containing bromine (0·3 ml.) was heated under reflux for 30 min. and then cooled. Crystallisation of the product from ethanol–water, and sublimation, afforded 5-*bromo*-2,3-*dichloro*-4-*hydroxy*-6-*pyridone* (III), m.p. 230° (decomp.) (Found: C, 23·3; H, 0·5; N, 5·6. $C_5H_2BrCl_2NO_2$ requires C, 23·2; H, 0·8; N, 5·4%), $\lambda_{max.}$ 245sh, 282, and 312sh mμ (ε 3900, 3550, and 650).

(b) *Nitration.* The pyridine (I; R = Cl) (0·48 g.) was heated in 50% nitric acid (5 ml.) at 75° for 25 min., and the solution poured on ice. Sublimation of the product (0·46 g.) gave bright yellow crystals, m.p. 215° (decomp.), of 2,3-*dichloro*-4-*hydroxy*-5-*nitro*-6-*pyridone* (IV) (Found: C, 27·1; H, 0·9; Cl, 31·5; N, 12·5. $C_5H_2Cl_2N_2O_4$ requires C, 26·5; H, 0·9; Cl, 31·5; N, 12·5%), $\lambda_{max.}$ 283 and 355sh mμ (ε 3150 and 1700).

(c) *With phosphorus oxychloride.* (*i*) The pyridine (I; R = Cl) (2 g.) was heated with phosphorus oxychloride (15 ml.) in a sealed tube at 180° for 24 hr. By steam-distillation and crystallisation from methanol, 2,3,4,6-tetrachloropyridine (1·8 g.) was isolated, m.p. 38° (lit.,[5] 37·5—38°) (Found: C, 27·9; H, 0·7; N, 6·5. Calc. for C_5HCl_4N: C, 27·65; H, 0·5; N, 6·45%), $\nu_{max.}$ ($CHCl_3$) 1550, 1545sh, 1396, 1320s, 1282w, and 1145 cm.$^{-1}$, $\lambda_{max.}$ 231, 274sh, 281·5, and 288 mμ (ε 6300, 2100, 3350, and 3100). (*ii*) The pyridine (I; R = Cl) (0·5 g.), dimethylaniline (0·6 ml.), and phosphorus oxychloride (8 ml.) were refluxed together for 7 hr. Excess of the oxychloride was distilled off under reduced pressure and the residue poured on ice. Ether extraction and crystallisation of the extract from chloroform gave 2,3,6-*trichloro*-4-*hydroxypyridine* (VI) (0·16 g.), m.p. 193—195° (Found: C, 30·3; H, 1·3; Cl, 53·9; N, 7·4. $C_5H_2Cl_3NO$ requires C, 30·2; H, 1·1; Cl, 53·6; N, 7·0%), $\nu_{max.}$ (CCl_4) 3580w, 3200—2400, 1592s, 1570sh, 1540sh, 1458s, 1429w, 1417w, 1342, 1220, and 1155 cm.$^{-1}$, $\lambda_{max.}$ 231sh and 293 mμ (ε 7300 and 5700).

Reactions of the Pyrimidine Product.—(a) *Hydrogenolysis.* Hydrogenation of the pyrimidine (II; R = CH_2·Cl) (1 g.) in 85% ethanol (100 ml.) over 10% palladium–charcoal catalyst (0·05 g.) at atmospheric pressure and room temperature effected the theoretical uptake (2 mol.) in 105 min. Filtration, evaporation to dryness, and sublimation afforded 2-*methyl*-4-*pyrimidone hydrochloride* (0·5 g., 70%), m.p. 259—260° (decomp.) (Found: C, 40·9; H, 4·9; Cl, 24·7; N, 19·3. $C_5H_7ClN_2O$ requires C, 41·0; H, 4·8; Cl, 24·2; N, 19·1%), $\lambda_{max.}$ 223 and 268 mμ (ε 6050 and 3000). Dissolution of the hydrochloride in 10% sodium hydroxide, acidification with acetic acid, extraction with chloroform, sublimation, and crystallisation ($CHCl_3$) gave 2-methyl-4-pyrimidone, m.p. 213·7—214·3° (lit.,[7] 214°) (Found: C, 54·2; H, 5·4; N, 25·5. Calc. for $C_5H_6N_2O$: C, 54·5; H, 5·5; N, 25·4%), *m/e* 110 (P), $\lambda_{max.}$ 220 and 275 mμ (ε 8000 and 4800), $\nu_{max.}$ ($CHCl_3$) 2875br, 1676s, 1606, 1557w, 1480w, and 1320 cm.$^{-1}$, identical with an authentic preparation (i.r. spectrum, mixed m.p.) described below.

(b) *With phosphorus oxychloride.* The pyrimidine (II; R = CH_2Cl) (0·5 g.), dimethylaniline (0·3 ml.), and phosphorus oxychloride (4 ml.) were refluxed for 4 hr., and a product was isolated (as above). From ethanol, 4,6-*dichloro*-2-*chloromethylpyrimidine* (IX) formed needles, m.p. 40° (Found: C, 30·8; H, 1·7; Cl, 54·2; N, 14·5. $C_5H_3Cl_3N_2$ requires C, 30·4; H, 1·5; Cl, 53·9; N, 14·2%), $\lambda_{max.}$ 252sh, 257, and 263sh mμ (ε 3300, 3550, and 2800).

(c) *Chlorination.*[19] The pyrimidine (II; R = CH_2Cl) (0·53 g.), *N*-chlorosuccinimide (0·448 g.), and benzoyl peroxide (0·18 g.) were refluxed together in chloroform (10 ml.) for 12 hr. Concentration of the solution under reduced pressure gave 4,5-*dichloro*-2-*chloromethyl*-6-*pyrimidone* (XI) which, after being washed (H_2O) and crystallised ($CHCl_3$), formed needles (0·48 g.), m.p. 217—220° (Found: C, 27·9; H, 1·1; Cl, 50·0; N, 12·9. $C_5H_3Cl_3N_2O$ requires C, 28·1; H, 1·4; Cl, 49·65; N, 13·1%), *m/e* 212 (P), 214 (100), and 216 (32%), $\lambda_{max.}$ 240 and 290 mμ (ε 3200 and 3100).

(d) *Bromination.* The pyrimidine (II; R = CH_2Cl) (0·5 g.) was refluxed in ethanol (5 ml.) containing bromine (0·4 ml.). After 45 min., the solution was cooled and the product collected: it was a mixture (Br analysis, ^{1}H n.m.r.). The material was refluxed for 2 hr. with conc. hydrogen bromide in acetic acid (2·5 ml.), the solution cooled, and 5-*bromo*-2-*bromomethyl*-4-*chloro*-6-*pyrimidone* (XII) (0·67 g., 80%) collected and sublimed (m.p. 260—261°) (Found: C, 19·6; H, 1·0; N, 9·0. $C_5H_3Br_2ClN_2O$ requires C, 19·8; H, 1·0; N, 9·25%), *m/e* 300 (P), 302 (232), 304 (168), and 306 (31%), $\nu_{max.}$ 1675, 1660s, 1590s, 1549, 1335, 1220, and 1190s cm.$^{-1}$, $\lambda_{max.}$ 244 and 298 mμ (ε 4600 and 8800).

(e) *With sodium iodide and then pyridine.* The pyrimidine (II; R = CH_2Cl) (0·5 g.) in acetone (8 ml.) was refluxed with a solution of sodium iodide (0·5 g.) in acetone (3·5 ml.) for 4 min. Dilution with water gave 4-*chloro*-2-*iodomethyl*-6-*pyrimidone* (II; R = CH_2I) (0·6 g., 80%), m.p. 205—207° (decomp.) (from ethanol) (Found: C, 22·2; H, 1·6; Cl, 13·0; I, 46·8; N, 10·5. $C_5H_4ClIN_2O$ requires C, 22·2; H, 1·5; Cl, 13·1; I, 46·9; N, 10·35%), $\nu_{max.}$ 1660, 1630sh, 1580, 1540sh, and 1120 cm.$^{-1}$, $\lambda_{max.}$ 240 and 295 mμ (ε 5300 and 6100).

This iodide (0·2 g.) was heated in pyridine (1 ml.) for 1 hr. on a steam-bath, and the solution evaporated under reduced pressure. Crystallisation of the residue from

[17] *Org. Synth.*, Coll. Vol. IV, 1963, p. 263.
[18] M. P. V. Boarland and J. F. W. McOmie, *J. Chem. Soc.*, 1952, 3716; D. J. Brown and L. N. Short, *ibid.*, 1953, 331.
[19] Cf. J. A. Carbon, *J. Org. Chem.*, 1960, **25**, 1731.

aqueous ethanol gave the *pyridinium iodide* (XV; X = I) (0·24 g.) as needles, m.p. 260° (decomp.) (Found: C, 34·5; H, 2·7; N, 11·9. $C_{10}H_9ClIN_3O$ requires C, 34·3; H, 2·6; N, 12·0%), $\lambda_{max.}$ 256sh, 261, and 268sh mμ (ε 3900, 4100, and 3400). Similarly, the 2-chloromethylpyrimidone (II; R = CH_2Cl) (0·5 g.) with boiling pyridine (5 ml.) for 2 hr. afforded the corresponding *chloride* (XV; X = Cl) (0·65 g.) as needles (aq. EtOH), m.p. 270° (decomp.) (Found: C, 46·3; H, 4·0; Cl, 27·2; N, 16·1. $C_{10}H_9Cl_2N_3O$ requires C, 46·5; H, 3·5; Cl, 27·5; N, 16·3%), $\lambda_{max.}$ 256sh, 261, and 269sh mμ (ε 6150, 6400, and 5100).

(f) *With morpholine.* The pyrimidine (II; R = CH_2Cl) (0·4 g.) was stirred with morpholine (4 ml.), and the excess of the latter was then distilled off under reduced pressure. Crystallisation of the residue (0·47 g., 77%) from ethanol gave leaflets of 4-*morpholino*-2-*morpholinomethyl*-6-*pyrimidone* (XVI), m.p. 182—183° (Found: C, 55·4; H, 7·3; N, 19·6. $C_{13}H_{20}N_4O_3$ requires C, 55·7; H, 7·1; N, 20·0%), $\lambda_{max.}$ 234 and 270 mμ (ε 21,600 and 8800). The compound (VIII), required for ^1H n.m.r. comparison, was similarly obtained from 6-chloro-2,4-dimethylpyrimidine.[20]

(g) *With phenylhydrazine.* The pyrimidine (II; R = CH_2Cl) (0·5 g.) in ethanol (5 ml.) was refluxed with phenylhydrazine (0·5 g.) for 2 hr. Water was added and the mixture extracted with ether to yield 4-*chloro*-2-*phenylhydrazonomethyl*-6-*pyrimidone* (II; R = CH:N·NHPh) which formed yellow crystals (0·48 g.), m.p. 290° (decomp.) (from ethanol) [Found: C, 53·1; H, 3·8; N, 22·3%; *M* (mass spectrum), 248. $C_{11}H_9ClN_6O$ requires C, 53·1; H, 3·6; N, 22·5%; *M*, 248], $\lambda_{max.}$ 239, 246sh, 258sh, 275, 293sh, 302sh, and 395 mμ (ε 7700, 7200, 5100, 3700, 2600, 2000, and 19,000).

Authentic Pyrimidines.—Acetamidine hydrochloride [21] was converted into 4,6-dihydroxy-2-methylpyrimidine,[22] m.p. 300°, and thence into 4,6-dichloro-2-methylpyrimidine (4 g.), m.p. 47·5—48°,[23] which on hydrolysis gave 4-chloro-2-methyl-6-pyrimidone (II; R = Me) (1·44 g.), m.p. 233°,[24] $\lambda_{max.}$ 226 and 279 mμ (ε 6300 and 5000), $\nu_{max.}$ 3200—2300, 1830w, 1690, 1660s, 1640sh, 1600s, 1548w, 1530w, 1430s, 1365s, 1330w, 1315, 1220, 1128s, and 1050 cm.$^{-1}$. Hydrogenation of the last compound (0·3 g.) in 80% ethanol (50 ml.) over 10% palladium–charcoal catalyst at room temperature and pressure, filtration, and evaporation gave a sticky solid. Basification (aq. $NaHCO_3$) and extraction with hot chloroform and concentration yielded 2-methyl-4-pyrimidone (VII) (0·13 g.), m.p. 214° (lit.,[7] 214°), $\nu_{max.}$ 2875br, 1676s, 1606, 1567w, 1480w, 1320, 990, and 846 cm.$^{-1}$.

Reaction of Fluoroacetonitrile with Malonyl Chloride.—Malonyl chloride (6·75 g.) was kept with fluoroacetonitrile [25] (5·7 g.) (with exclusion of moisture) for 24 hr. There was no obvious evolution of hydrogen chloride. The product was collected and washed with dry dioxan–ether (yield 5 g., 65%). Crystallisation from methanol and sublimation gave 4-*chloro*-2-*fluoromethyl*-6-*pyrimidone* (II; R = CH_2F), m.p. 192·5—193° (Found: C, 37·2; H, 2·5; Cl, 22·3; N, 17·3. $C_5H_4ClFN_2O$ requires C, 36·9; H, 2·5; Cl, 21·8; N, 17·2%), *m/e* 162 (P) and 164 (31·8%), $\nu_{max.}$ 3200—2300, 1650br,s, 1585s, 1545, 1337w, 1277w, 1230, 1192, 1120s, and 1036 cm.$^{-1}$, $\lambda_{max.}$ 228 and 281 mμ (ε 5500 and 4200).

Under other conditions, and with other proportions of the reagents, the yield of pyrimidine (II; R = CH_2F) was inferior. At 100°, the product was formed in 51% yield in 20 min., but was contaminated with dark red material. Use of nitromethane as a solvent provided no advantage.

Reactions of 4-Chloro-2-fluoromethyl-6-pyrimidone.—(a) *With phosphorus oxychloride.* The pyrimidone (II; R = CH_2F) (0·3 g.) was refluxed with phosphorus oxychloride (3 ml.) and dimethylaniline (0·2 ml.) for 5 hr., excess of the acid chloride was distilled off under reduced pressure, and ice was added to the residue which was then extracted with ether. The ether was washed with aqueous sodium carbonate, dried (Na_2SO_4), and evaporated. Crystallisation of the residue (0·1 g.) from methanol–water, and sublimation, gave needles of 4,6-*dichloro*-2-*fluoromethylpyrimidine* (X), m.p. 56° (Found: C, 33·0; H, 1·85. $C_5H_3Cl_2FN$ requires C, 33·15; H, 1·7%), $\lambda_{max.}$ 209 and 256 mμ (ε 5800 and 4600).

(b) *Bromination.* Bromine (0·6 ml.) was added in drops to the pyrimidine (II; R = CH_2F) (0·6 g.) in ethanol (5 ml.) and the solution was refluxed for 30 min. and then cooled. After sublimation, the 5-*bromo*-4-*chloro*-2-*fluoromethyl*-6-*pyrimidone* (0·71 g.) had m.p. 220° (Found: C, 24·9; H, 1·2; N, 11·2. $C_5H_3BrClFN_2O$ requires C, 24·85; H, 1·2; N, 11·6%), *m/e* 240 (P), 242 (131), and 244 (33·5%), $\nu_{max.}$ 3300—2500, 1670—1650s, 1585, 1540, 1305, 1265, 1240w, 1185s, 1045s, and 1025s cm.$^{-1}$, $\lambda_{max.}$ 241 and 292 mμ (ε 2600 and 3400).

(c) *Hydrogenolysis.* Hydrogenation of the pyrimidine (II; R = CH_2F) (0·5 g.) and work-up, by the methods already described, gave 2-methyl-4-pyrimidone hydrochloride, m.p. 259° (decomp.) (Found: C, 40·9; H, 4·9; Cl, 19·5; N, 18·7%), basification of which yielded 2-methyl-4-pyrimidone, m.p. and mixed m.p. 214°. The i.r. and ^1H n.m.r. spectra were identical with those of authentic (VII).

(d) *With morpholine.* The pyrimidine (II; R = CH_2F) (0·5 g.) was stirred with morpholine (5 ml.). The excess of morpholine was distilled off under reduced pressure, and the residue (0·46 g.) was crystallised from aqueous methanol to give needles of 2-*fluoromethyl*-4-*morpholino*-6-*pyrimidone* (XVI), m.p. 260° (Found: C, 50·9; H, 5·8; N, 19·5. $C_9H_{12}FN_3O$ requires C, 50·7; H, 5·6; N, 19·7%), $\nu_{max.}$ 3200—2300, 1650—1615s, 1565, 1343, 1305, 1270w, 1245s, and 1110s cm.$^{-1}$, $\lambda_{max.}$ 239 and 269 mμ (ε 10,650 and 7050).

Reaction of Bromoacetonitrile with Malonyl Chloride.—The nitrile [26] (4·8 g.) and chloride (2·8 g.) during 2 days afforded a solid which was washed with dioxan–ether and crystallised from methanol to give needles of 2-*bromomethyl*-4-*chloro*-6-*pyrimidone* (II; R = CH_2Br) (2·3 g., 52%), m.p. 194—195° (decomp.) (Found: C, 26·8; H, 1·8; Br, 35·7; Cl, 15·7; N, 12·7. $C_5H_4BrClN_2O$ requires C, 26·9; H, 1·8; Br, 35·9; Cl, 15·9; N, 12·5%), *m/e* 222 (P), 224 (131·5), and 226 (32·8%), $\nu_{max.}$ 3200—2100, 1845w, 1665s,br, 1590s, 1320w, 1225, 1145, and 1122s cm.$^{-1}$, $\lambda_{max.}$ 232 and 288 mμ (ε 5300 and 4500). Treatment of this pyrimidone (0·5 g.) in boiling ethanol (8 ml.) with bromine (0·2 ml.) for 1 hr. and then addition of water to the solution gave 5-bromo-2-bromomethyl-4-chloro-6-pyrimidone (XII) (0·57 g., 84%), sublimation of which provided crystals, m.p. 261°, identical (mixed m.p., i.r. spectrum) with compound (XII), above.

[20] E. Ochiai and Y. Ito, *J. Pharm. Soc. Japan*, 1937, **57**, 579.
[21] *Org. Synth.*, Coll. Vol. I, 1951, p. 5.
[22] A. W. Dox and L. Yoder, *J. Amer. Chem. Soc.*, 1922, **44**, 361.
[23] J. Baddiley, B. Lythgoe, D. McNeil, and A. R. Todd, *J. Chem. Soc.*, 1943, 383.
[24] F. R. Basford, F. H. S. Curd, and F. L. Rose, *J. Chem. Soc.*, 1946, 713.
[25] F. J. Buckle, R. Heap, and B. C. Saunders, *J. Chem. Soc.*, 1949, 912.
[26] W. Steinkopf, *Ber.*, 1905, **38**, 2694.

Reaction with Dibromoacetonitrile.—(*a*) This nitrile [27] (4 g.) and malonyl chloride (3·5 g.) during 2 days gave a reddish brown solid which was triturated with ether–dioxan and then crystallised from ethanol. Needles of 2-bromomethyl-4-chloro-6-pyrimidone (1·2 g.) were obtained, m.p. 194—195° undepressed by compound (II; R = CH_2Br) described above (Found: C, 27·1; H, 1·9; Br, 35·7; Cl, 15·8; N, 12·4%). The dibromoacetonitrile was nevertheless pure, b.p. 70—72°/20 mm., n_D^{25} 1·5419, τ ($CDCl_3$) 4·16 only (Found: C, 12·1; H, 0·4; Br, 80·4; N, 6·9. Calc. for C_2HBr_2N: C, 12·1; H, 0·5; Br, 80·4; N, 7·0%).

(*b*) A mixture of the nitrile (2·6 g.) and malonyl chloride (2 g.) was kept for 3 days, and then methanol (1·5 ml.) was added in drops, with shaking and cooling of the mixture. The liquid was chromatographed (0·1 μl. aliquots) in nitrogen (10 ml./18 sec.) at 140° on a column of 10% Carbowax 1000 on Celite, using a gas-density balance detector. The chromatogram comprised a strong peak from methanol followed by 5 sharp peaks, the last of which had a retention time of 5·36 min. A succession of mixed chromatograms with added authentic esters (0·1 μl. portions) showed that the 2nd, 3rd, and 5th components were methyl bromoacetate, dimethyl malonate, and dimethyl bromomalonate, respectively.

Reaction with α-Bromopropionitrile.—From the nitrile [28] (3 g.) and malonyl chloride (3·1 g.), kept in the dark for 2 days, a product was isolated in the usual way. From ethanol, 2-(1-*bromoethyl*)-4-*chloro*-6-*pyrimidone* (1·6 g., 60%) crystallised as needles, m.p. 178—180° (Found: C, 30·5; H, 2·6; Br, 33·5; Cl, 14·9; N, 11·6. $C_6H_6BrClN_2O$ requires C, 30·3; H, 2·5; Br, 33·7; Cl, 14·95; N, 11·8%), *m/e* 236 (P), 238 (130), and 240 (32%), $\nu_{max.}$ 3100—2400, 1675s,br, 1580, 1550w, 1445, 1260, 1215w, 1130s, and 1050s cm.$^{-1}$, $\lambda_{max.}$ 232 and 288 mμ (ε 3400 and 3000).

Reaction with Iodoacetonitrile.—The product from interaction (2 days) of the nitrile [29] (3·3 g.) with malonyl chloride (2·9 g.) was washed with dioxan–ether and triturated with chloroform to remove iodine. Crystallisation from ethanol gave needles of 4-chloro-2-methyl-6-pyrimidone (0·28 g., 20%), m.p. 233—234° (Found: C, 41·5; H, 3·6; Cl, 24·4; N, 19·1. Calc. for $C_5H_5ClN_2O$: C, 41·5; H, 3·5; Cl, 24·6; N, 19·4%), $\lambda_{max.}$ 226 and 279 mμ (ε 6300 and 5000), *m/e* 144 (P, B), identical (mixed m.p., i.r. spectrum) with the authentic pyrimidone (II; R = Me) described above.

Reaction with Acetonitrile.—A mixture of acetonitrile (4 g.) and malonyl chloride (7 g.) was kept for 3 days. The product was triturated with dioxan–ether, washed with ether, and sublimed to give minor (m.p. 110—120°) and major fractions (m.p. 200—220°). The latter fraction crystallised from ethanol as needles: it was 4-chloro-2-methyl-6-pyrimidone (2·2 g., 32%), m.p. 233° (Found: C, 41·7; H, 3·8; Cl, 24·3; N, 19·1%), *m/e* 144 (P) and 146 (32%), identical (mixed m.p., i.r. spectrum) with the authentic compound (II; R = Me) already described. The minor sublimate crystallised from light petroleum (b.p. 100—120°) as needles: it was 6-chloro-4-hydroxy-2-oxopyran-3-carboxylic acid [10] (XIX), m.p. 135—136° (Found: C, 37·9; H, 1·8; Cl, 18·5. Calc. for $C_6H_3ClO_5$: C, 37·9; H, 1·6; Cl, 18·4%), $\nu_{max.}$ ($CHCl_3$) 1717s, 1676s, 1620s, 1554s, and 1526sh cm.$^{-1}$, τ ($CDCl_3$) 3·58 (1H) and −4·0vbr (2H).[30]

Reaction with p-*Chlorophenylacetonitrile.*—A mixture of the nitrile (3·4 g.) and malonyl chloride (3·8 g.) was kept for 2 days, and the solid was triturated with ether–dioxan and crystallised from ethanol. 2-*Chloro*-3-(p-*chlorophenyl*)-4-*hydroxy*-6-*pyridone* (I; R = C_6H_4·Cl-*p*) (1·8 g.) had m.p. >300° (Found: C, 51·5; H, 3·1; Cl, 27·6; N, 5·3. $C_{11}H_7Cl_2NO_2$ requires C, 51·6; H, 2·7; Cl, 27·8; N, 5·5%), $\nu_{max.}$ 3200—2100, 1645, 1610w, 1595w, 1570bs, 1545sh, 1500w, 1320, 1300, 1263, 1230s, 1200, 1092, and 1023 cm.$^{-1}$, $\lambda_{max.}$ 239 and 293sh mμ (ε 9700 and 2000).

Reaction with p-*Nitrophenylacetonitrile.*—This nitrile (2 g.) was heated with malonyl chloride at 60° for 4 hr. and the product collected and washed with dioxan–ether. From ethanol, 2-*chloro*-4-*hydroxy*-3-(p-*nitrophenyl*)-6-*pyridone* (I; R = C_6H_4·NO_2-*p*) (1·3 g., 40%) formed bright yellow needles, m.p. >300° (Found: C, 49·7; H, 2·65; Cl, 13·3; N, 10·5. $C_{11}H_7ClN_2O_4$ requires C, 49·5; H, 2·6; Cl, 13·3; N, 10·5%), *m/e* 266 (P), $\nu_{max.}$ 3300—2200, 1640sh, 1610—1590s, 1520, 1500w, 1345, 1295, 1260sh, and 1230s cm.$^{-1}$, $\lambda_{max.}$ 273 and 293 mμ (ε 5200 and 5300).

Reactions with Propio- and Butyro-nitrile.—Propionitrile (2·5 g.) interacted with malonyl chloride (7 g.) for 2 days. After being washed with dioxan–ether, the product was heated at 140—150°/10 mm. to give a small sublimate of 4-*chloro*-2-*ethyl*-6-*pyrimidone* (II; R = Et), m.p. 162° (from ethanol) (Found: C, 45·6; H, 4·6; Cl, 22·3; N, 17·5. $C_6H_7ClN_2O$ requires C, 45·6; H, 4·4; Cl, 22·15; N, 17·7%), *m/e* 158 (P), $\nu_{max.}$ 3200—2400, 1695s, 1655s, 1600s, 1550sh, 1270, and 1130s cm.$^{-1}$. The residue, which crystallised from methanol, was 2-chloro-4-hydroxy-3-methyl-6-pyridone (I; R = Me), m.p. 304° (lit.,[2] 302°), *m/e* 159 (P) and 161 (32%).

The product (3·65 g.) from interaction of butyronitrile (4·2 g.) and malonyl chloride (8·4 g.) for 3 days was triturated with ether–dioxan and fractionally crystallised from ethanol. The major, less-soluble component was 2-*chloro*-3-*ethyl*-4-*hydroxy*-6-*pyridone* (I; R = Et) (2·45 g.), m.p. 285° (decomp.) (Found: C, 48·1; H, 4·8; Cl, 20·3; N, 7·9. $C_7H_8ClNO_2$ requires C, 48·4; H, 4·6; Cl, 20·5; N, 8·1%), $\nu_{max.}$ 3300—2200, 1660s, 1620w, 1595s,br, 1550sh, 1260, 1230s, 1180, and 1080 cm.$^{-1}$, $\lambda_{max.}$ 280infl. and 291 mμ (ε 3700 and 4100). The more-soluble component was 4-*chloro*-2-*propyl*-6-*pyrimidone* (II; R = Pr) (0·5 g.) which formed fine needles, m.p. 171° (Found: C, 48·6; H, 5·9; Cl, 20·5; N, 16·25. $C_7H_9ClN_2O$ requires C, 48·7; H, 5·2; Cl, 20·6; N, 16·2%). Morpholine (1 ml.) was added to the preceding pyrimidine (0·45 g.) in chloroform (2·5 ml.), and the solution was washed with water and evaporated. Crystallisation of the residue from ethanol gave fine needles of 4-*morpholino*-2-*propyl*-6-*pyrimidone* (XVIII) (0·4 g.), m.p. 238° (decomp.) (Found: C, 59·4; H, 7·7; N, 18·75. $C_{11}H_{17}N_3O_2$ requires C, 59·2; H, 7·6; N, 18·8%), $\nu_{max.}$ 3100—2400, 1680s, 1615s, 1565, 1310w, 1235s, 1180w, and 1110s cm.$^{-1}$, $\lambda_{max.}$ 233 and 270 mμ (ε 30,500 and 13,500).

Reaction with β-*Chloro- and* β-*Bromo-propionitrile.*—A mixture of β-chloropropionitrile [31] (6 g.) and malonyl chloride (9·4 g.) was kept for 5 days. After being triturated with dioxan–ether and crystallised from acetone, the 2-chloro-3-chloromethyl-4-hydroxy-6-pyridone (I; R = CH_2Cl) (5·2 g., 40%) had decomp. 198°, $\nu_{max.}$ 2670, 1670s, 1640s, 1600s, 1560w, 1273, 1250, 1225, 1155, and 1120 cm.$^{-1}$.

[27] *Org. Synth.*, Coll. Vol. IV, 1963, p. 254.
[28] C. Moureu and R. L. Brown, *Bull. Soc. chim. France*, 1920, **27**, 901.
[29] R. Scholl, *Ber.*, 1896, **29**, 2415.
[30] Cf. M. A. Butt, J. A. Elvidge, and A. B. Foster, *J. Chem. Soc.*, 1963, 3069 (i.r. data in Table 1 of this reference are for $CHCl_3$ solutions, not Nujol mulls as stated).
[31] E. Chapman and H. Stephen, *J. Chem. Soc.*, 1925, **127**, 885.

When refluxed in ethanol it afforded *2-chloro-3-ethoxymethyl-4-hydroxy-6-pyridone* (I; R = CH_2·OEt) (60%), m.p. 210° (decomp.) (from ethanol) (Found: C, 46·95; H, 5·4; Cl, 17·3; N, 6·9. $C_8H_{10}ClNO_3$ requires C, 47·2; H, 4·9; Cl, 17·4; N, 6·8%), and when heated with pyridine at 95° for 1 hr. it gave needles of *N-(2-chloro-4,6-dihydroxy-3-pyridylmethyl)pyridinium chloride* (I; R = $CH_2N^+C_5H_5,Cl^-$) (2·1 g., 74%), m.p. >300° (from aqueous ethanol) (Found: C, 48·1; H, 3·9; Cl, 25·2; N, 9·9. $C_{11}H_{10}Cl_2N_2O_2$ requires C, 48·35; H, 3·7; Cl, 25·7; N, 10·25%): a wet test for ionic chlorine was strongly positive.

Similarly, β-bromopropionitrile [32] (4 g.) and malonyl chloride (4·5 g.) during 7 days afforded 3-bromomethyl-2-chloro-4-hydroxy-6-pyridone which was triturated with dioxan and then crystallised from acetone (yield, 2·1 g.), decomp. 220°, $\nu_{max.}$ 3200—2300, 1640s, 1600s, 1562w, 1430, 1315s, 1250w, 1212s, 1180, and 1132 cm.$^{-1}$. This with boiling ethanol gave 2-chloro-3-ethoxymethyl-4-hydroxy-6-pyridone (50%), m.p. 210° (decomp.) $\nu_{max.}$ 3300—2200, 1790br,w, 1660s, 1620sh, 1595s, 1250, 1223, 1183, 1115w, and 1100 cm.$^{-1}$ (Found: C, 46·9; H, 4·7; N, 6·45%), identical (mixed m.p., i.r. spectrum) with that already described. With hot pyridine for 2 hr. the β-bromopropionitrile product gave the *pyridinium bromide* (I; R = $CH_2N^+C_5H_5,Br^-$) (65%), m.p. >300° (from aqueous ethanol) (Found: C, 39·5; H, 2·9; Br, 24·1; Cl, 10·7; N, 8·5. $C_{11}H_{10}BrClN_2O_2$ requires C, 39·3; H, 3·5; Br, 23·8; Cl, 10·6; N, 8·3%).

Reaction with Isobutyronitrile.—A mixture of isobutyronitrile (6·5 g.) and malonyl chloride (6 g.) appeared not to interact during several days. After 4 hr. at 60° and then overnight at room temperature, the mixture had deposited solid. This was washed with ether and crystallised from ethyl acetate to give light-yellow needles of *6-chloro-4-hydroxy-3-isobutyramidocarbonyl-2-oxopyran* (XX), m.p. >300° (Found: C, 46·1; H, 3·9; Cl, 13·6; N, 5·5. $C_{10}H_{20}ClNO_5$ requires C, 46·1; H, 3·8; Cl, 13·6; N, 5·4%), $\lambda_{max.}$ 225, 266, and 333 mμ, $\nu_{max.}$ 3300, 1715, 1690, 1525s, 1410, and 1260s cm.$^{-1}$.

Reactions of Dinitriles with Malonyl Chloride.—(a) *Adiponitrile.* This dinitrile (4·3 g.) with malonyl chloride gave during 2 days a dark brown product which was triturated with acetone and repeatedly crystallised from methanol. Crystalline *2-chloro-3-(3-cyanopropyl)-4-hydroxy-2-pyridone* (I; R = $[CH_2]_3$·CN) (1·5 g.), m.p. 190° (decomp.), was obtained (Found: C, 51·0; H, 4·3; Cl, 16·5; N, 13·0. $C_9H_9ClN_2O_2$ requires C, 50·8; H, 4·2; Cl, 16·7; N, 13·2%), *m/e* 212 (P), 214 (32·4%), and 158 (B), $\nu_{max.}$ 3300—2300, 2250 (C≡N), 1650, 1615, 1580s,br, 1420w, 1345w, 1270, 1235s, 1192, and 1157 cm.$^{-1}$, $\lambda_{max.}$ 230sh, 276, and 287 mμ (ε 2700, 2100, and 2100).

(b) *1,14-Dicyanotetradecane.* A mixture of this dinitrile [33] (2·5 g.) and malonyl chloride (4 g.) gave a product during 6 days. Trituration of the solid with dioxan–ether and crystallisation from ethanol gave *2-chloro-3-(13-cyanotridecanyl)-6-pyridone* (I; R = $[CH_2]_{13}$·CN) (2·1 g., 21%), m.p. 250° (decomp.) (Found: C, 64·35; H, 8·4; Cl, 10·2; N, 7·8. $C_{19}H_{29}ClN_2O_2$ requires C, 64·8; H, 8·2; Cl, 10·1; N, 7·9%), $\nu_{max.}$ 2670br, 2260w (C≡N), 1673s, 1615, 1595s, 1560w, 1340w, 1250, and 1230 cm.$^{-1}$, $\lambda_{max.}$ 230sh, 280infl., and 290 mμ (ε 3200, 2800, and 3000).

[32] V. N. Mikhailova and V. V. Pigulevskii, *Zhur. obshchei Khim.*, 1958, **28**, 3112.

[33] S. Bergström, G. Aulin-Erdtman, B. Rolander, E. Stenhagen, and S. Östling, *Acta Chem. Scand.*, 1952, **6**, 1157.

(c) *Malononitrile.* The dinitrile (2·1 g.) with malonyl chloride (4·5 g.) during 7 days at 0° gave a viscous red liquid. This was dissolved in a minimum of dry dioxan, ether was added, and the amorphous precipitate filtered off. Evaporation of the filtrate to small bulk and chilling at 0° afforded a crystalline mass, sublimation of which provided *2-chloro-3-cyano-4,6-dihydroxypyridine* [or tautomer, (I; R = CN)], m.p. 218—219° (Found: C, 41·9; H, 1·8; Cl, 20·7; N, 16·1. $C_6H_3ClN_2O_2$ requires C, 42·2; H, 1·8; Cl, 20·8; N, 16·4%), *m/e* 170 (P, B), 172 (33), 142 (55), and 135 (45%), $\nu_{max.}$ 3615s, 3420s, 2550br, 2230 (C≡N), 1610sh, 1590s, 1500w, 1295w, 1270, 1200s cm.$^{-1}$, $\lambda_{max.}$ 222 and 249 mμ (ε 8700 and 4100).

Self-condensation of Cyanoacetyl Chloride.—Cyanoacetyl chloride [34] (10 g.), kept at room temperature, evolved hydrogen chloride after *ca.* 20 hr. and gave a solid mass within 4 hr. more. Extraction of this with hot water, and concentration of the extract, afforded 2-chloro-5-cyano-4-hydroxy-6-pyridone (I; R = CN) (10 g., 60%), as needles (from water), m.p. 190° (decomp.) (lit.,[13] 187—190°), $\nu_{max.}$ 3400br, 2240 (C≡N), 1640s,br, 1565, 1356w, 1260, 1175, and 1120 cm.$^{-1}$.

Reactions of Bromomalonyl Chloride (b.p. 30°/0·35 mm., n_D^{21} 1·5478.[2,35])—(a) *With fluoroacetonitrile.* These reagents (4 g. and 2 g., respectively), kept together for 3 days, afforded a solid which was triturated with ether–dioxan and crystallised from ethanol to give 4-chloro-2-fluoromethyl-6-pyrimidone (1·5 g.) as leaflets, m.p. 193°, *m/e* 162 (P), and 164 (32%), identical (i.r. spectrum, mixed m.p.) with the compound (II; R = CH_2F) already described.

(b) *With dibromoacetonitrile.* Bromomalonyl chloride (2 g.) and dibromoacetonitrile (3·5 g.) were kept together, with exclusion of moisture and light, for 2 months. The dark solid was triturated with acetone and then crystallised from ethanol to give *5-bromo-2-dibromomethyl-4-chloro-6-pyrimidone* (XXIII) (0·95 g.), decomp. >300° (Found: C, 15·9; H, 0·5; Br, 62·8; Cl, 9·5; N, 7·4. $C_5H_2Br_3ClN_2O$ requires C, 15·7; H, 0·5; Br, 63·0; Cl, 9·3; N, 7·35%), *m/e* 378 (P), 380 (310), 382 (400), 384 (190), and 386 (32%), $\nu_{max.}$ 3200—2400, 1670s, 1630sh, 1570, 1530, 1350w, 1310, 1225, 1172, 1145w, 1110, 1068, and 1020 cm.$^{-1}$, $\lambda_{max.}$ 240 and 295 mμ (ε 5600 and 5100).

Reactions of Chloromalonyl Chloride [35] (cf. ref. 2).—(a) *With fluoroacetonitrile.* After 5 days, a mixture of the reagents (5 g. and 3·5 g., respectively) had given a crystalline solid. This was triturated with ether–dioxan and crystallised from ethanol to afford *4,5-dichloro-2-fluoromethyl-6-pyrimidone* (XIV) (2·48 g., 44%), m.p. 195—196° (Found: C, 30·7; H, 1·3; Cl, 35·7; N, 13·8. $C_5H_3Cl_2FN_2O$ requires C, 30·45; H, 1·5; Cl, 36·0; N, 14·2%), *m/e* 196 (P), 198 (64·1), and 200 (10·3%), $\nu_{max.}$ 3300—2500, 1680—1660s, 1585s, 1550s, 1445w, 1310, 1265, 1243, and 1190s cm.$^{-1}$, $\lambda_{max.}$ 232, 289, and 300sh mμ (ε 4000, 4900, and 3900).

(b) *With chloroacetonitrile.* The nitrile (3·3 g.) was mixed with chloromalonyl chloride (4 g.). After 7 days, the product was triturated with ether–dioxan and repeatedly crystallised from ethanol, to give 4,5-dichloro-2-chloromethyl-6-pyrimidone (1·58 g., 32%), m.p. 216—218°, identical (mixed m.p., i.r. spectrum) with the compound (XI) above.

Experiments Concerning the Mechanism of Formation of the 4-Chloro-6-pyrimidones.—The product from a reaction

[34] *Org. Synth.*, 1961, **41**, 5.

[35] M. Conard and H. Reinbach, *Ber.*, 1902, **35**, 1813.

of malonyl chloride with chloroacetonitrile was filtered off and washed well with dry ether, the washings being kept separate. A portion of the initial filtrate in deuteriochloroform (solution, *ca.* 5%) showed singlets at τ 5·82 and 5·40. The proton chemical shifts of chloroacetonitrile and chloroacetyl chloride under similar conditions were τ 5·85 and 5·40. A mixture of the two compounds (in $CDCl_3$) showed the same chemical shifts. Malonyl chloride had τ 5·60. The foregoing ether washings were cooled, and aniline was added in drops until reaction ceased. The product was collected, washed well with water, dried, and sublimed at 110—120°/15 mm. After crystallisation from 50% aqueous ethanol, needles of chloroacetanilide were obtained, m.p. and mixed m.p. 134—135° (Found: C, 56·4; H, 4·8; Cl, 20·8; N, 8·2. Calc. for C_8H_8ClNO: C, 56·7; H, 4·7; Cl, 20·9; N, 8·3%), τ($CDCl_3$) 5·85 (2H, s; $COCH_2Cl$), *ca.* 2·6 (5H,c; Ph), and 1·75 (1H,br; NH).

A mixture of malonyl chloride (4 ml.) and 4,6-dihydroxy-2-methylpyrimidine (1 g.) was kept at room temperature (with exclusion of moisture) for 5 days. The acid chloride was distilled off under reduced pressure, and the residue was triturated with dry ether–dioxan and then crystallised from ethanol. The starting pyrimidine was obtained (0·768 g.), m.p. >300°, and not the mono- or the di-chloro-compound (described above).

A mixture of cyanoacetyl chloride (3 g.) and fluoroacetonitrile (4 g.) was kept (with exclusion of moisture) at room temperature for several days. A dark tar formed from which no solid product was isolated. The same lack of success followed the keeping of a mixture of cyanoacetyl chloride (2·2 g.), fluoroacetonitrile (3 g.), and fluoroacetyl chloride [36] (2·5 g.) for 4 days.

A mixture of fluoroacetonitrile (3·5 g.), malonyl chloride (4·2 g.), and tetrabutylammonium iodide (5·5 g.) was kept at room temperature. The iodide did not appear to dissolve. After 1 day, the solid was collected, triturated with dioxan–ether, and extracted several times with hot chloroform. Evaporation of the chloroform and crystallisation of the residue from ethanol afforded 4-chloro-2-fluoromethyl-6-pyrimidone, m.p. and mixed m.p. 193°. By sublimation of the chloroform-insoluble material, 6-chloro-4-hydroxy-2-oxopyran-3-carboxylic acid was obtained, m.p. and mixed m.p. 135°.

Experiments with Sodium [1,1-$^{14}C_2$]*Malonate*.—The labelled sodium malonate (0·05 mc) (Radiochemical Centre, Amersham) was dissolved in water (10 ml.) to which malonic acid (5 g.) was added. The solution was evaporated at 35—40°/14 mm., and malonic acid (10 g.) was added to the dried residue which was then employed for the preparation [27] of malonyl chloride, b.p. 51°/21 mm., n_D^{20} 1·4582 (yield 50%).

A portion (1·5 g.) was allowed to hydrolyse in the air and the malonic acid was crystallised from ether–acetone. Treatment of the acid (0·8 g.) in methanol with sodium hydroxide (0·6 g.) in methanol precipitated sodium malonate, which was washed with methanol and dried. For counting by an end-window anti-coincidence counter (2080 counter and 1805 II scaler; Isotope Development Ltd.) the sodium malonate (250 mg.) was slurried in ethanol (2 ml.) and dried to constant weight in a planchette by means of a heat lamp. Sets of 10 counts were measured on each of 2 planchettes, and corrected [37] for the background (114 ± 10·6/100 sec.) (mean count rate = 6729 ± 82/100 sec.; standard proportional error, 1·2%).

4-Chloro-2-fluoromethyl-6-pyrimidone was prepared from a portion of the labelled malonyl chloride and counted similarly. For preparation of planchettes, the pyrimidone was slurried with 3 : 2 carbon tetrachloride–light petroleum (b.p. 60—80°) (mean count rate = 5967 ± 77/100 sec.; standard proportional error, 1·3%. Calculated count rate = 6147/100 sec.; discrepancy in observed counts, −2·9%).

2-Chloro-3-(*p*-chlorophenyl)-4,6-dihydroxypyridine was prepared from a further portion of the labelled malonyl chloride. Planchettes were prepared by slurrying the product with 4 : 1 ethanol–light petroleum (b.p. 60—80°) (mean count rate = 3758 ± 61/100 sec.; standard proportional error, 1·6%. Calculated count rate = 3889/100 sec.; discrepancy in observed counts, −3·3%).

In a further set of experiments, [1,1-$^{14}C_2$]malonyl chloride was converted (as above) into sodium malonate and counted (mean count rate = 3072 ± 55/1000 sec.; standard proportional error, 1·8%). From a portion of the malonyl chloride, 4-chloro-2-fluoromethyl-6-pyrimidone was prepared (mean count rate = 2757 ± 52/1000 sec.; standard proportional error 1·9%. Calculated, 2806/1000 sec.; discrepancy in observed counts, −1·7%). The labelled malonyl chloride was also treated with chloroacetonitrile, and, from the filtrate from the reaction product, chloroacetanilide was obtained (as described earlier). For preparation of planchettes, this anilide was slurried with 2 : 3 carbon tetrachloride–light petroleum (b.p. 60—80°) but was found not to be radioactive.

We thank the Government of Pakistan for a maintenance grant (to N. A. Z.), and the S.R.C. for a grant towards the cost of the Perkin-Elmer R10 n.m.r. spectrometer.

Subsequent to the completion of our work, Professor E. Bernatek, Oslo, kindly told us of his independent discovery of this pyrimidine synthesis.

[8/358 *Received, March 13th,* 1968]

[36] E. Gryszkiewicz-Trochimowski, A. Sporzynski, and J. Wnuk, *Rec. Trav. chim.*, 1947, **66**, 419.

[37] J. A. Elvidge and P. G. Sammes, 'Modern Techniques of Organic Chemistry,' Butterworths, London, 1966, p. 215.