

CONDENSATION REACTIONS OF MALONYL CHLORIDE
WITH NITRILES

By

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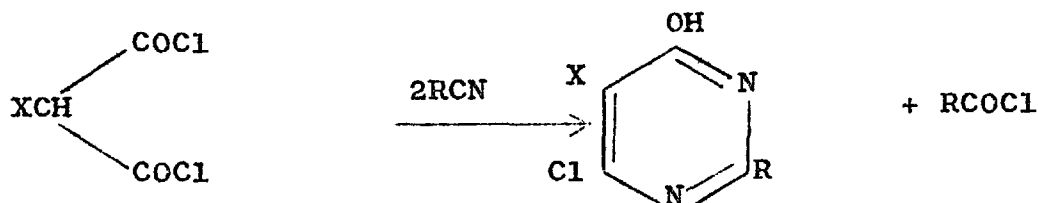
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Abstract

The study of some condensation reactions of malonyl chloride with nitriles revealed some very interesting results. It was found that fluoroacetonitrile reacted with malonyl chloride in the molar ratio of 2:1 and yielded 4-chloro-2-fluoromethyl-6-hydroxypyrimidine (65%). The reaction of malonyl chloride with chloroacetonitrile produced mainly 2-chloromethyl-4-chloro-6-hydroxy-pyrimidine along with some 2,3-dichloro-4,6-dihydroxy-pyridine. In contrast, like fluoroacetonitrile acetonitrile, bromoacetonitrile and α -bromopropio nitrile with malonyl chloride yielded exclusively their corresponding pyrimidines. The structures of these pyrimidines and pyridines were established with the aid of nuclear magnetic resonance, mass spectrometry, infrared and ultraviolet light absorption spectroscopy. Their structures were also confirmed by chemical transformations. It was found that the group attached to $C\equiv N$ in the nitrile component appeared as 2-substituent in the pyrimidine products. Propio- and butyro-nitriles yielded mainly 3-substituted-2-chloro-4,6-dihydroxy-pyridines along with some corresponding pyrimidines. Some other dinitriles with malonyl chloride produced only the corresponding pyridines.

Halogeno malonyl chlorides also reacted with some nitriles producing fully substituted pyrimidine rings.



The formation of RCOCl along with the pyrimidines has been established by nuclear magnetic resonance, isolation of a characteristic derivative, and gas-liquid chromatography.

The possible mechanisms of this new synthesis of pyrimidines have been discussed. In seeking evidence, some syntheses were performed with malonyl chloride labelled with carbon-14. The results of these experiments with labelled malonyl chloride and with halogenomalonyl chlorides showed that all the three carbon atoms of malonyl chloride appeared in the pyrimidine nucleus whilst all of the carbon atoms of the RCOCl product belonged originally to the starting nitrile.

An interesting feature of this new synthesis of pyrimidines is that it is the first direct synthesis of chloro-pyrimidines in which halogen appears at an active position of the ring.

- 4 -

To My Parents

Acknowledgments

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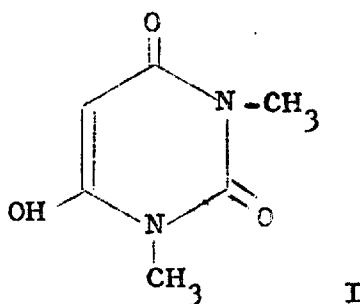
PART I

SECTION 'A' THEORETICAL

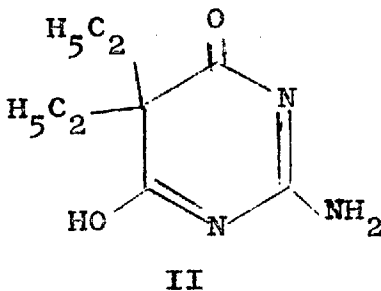
CHAPTER 1.

INTRODUCTION

Mulder¹ in 1879 found that dimethyl urea condensed with malonyl chloride in the presence of phosphoryl chloride producing 1,3-dimethyl-barbituric acid(I).

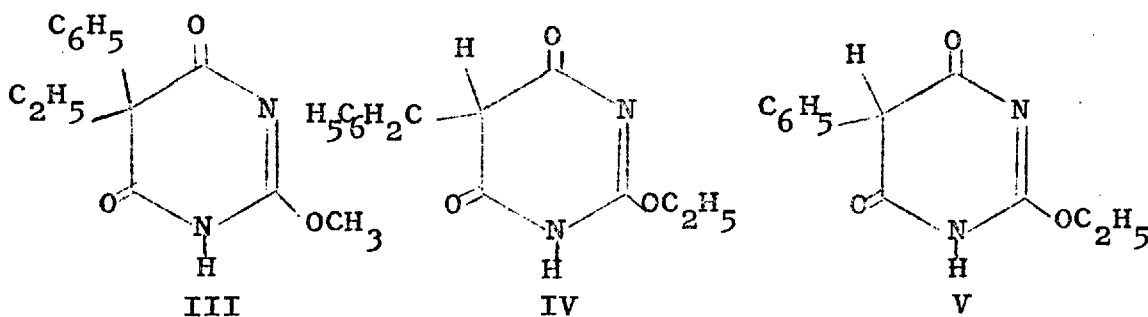


In 1902 it was reported² that diethyl malonyl chloride reacted with guanidine carbonate and yielded 2-amino-5,5-diethyl-4,6-dihydroxypyrimidine(II).



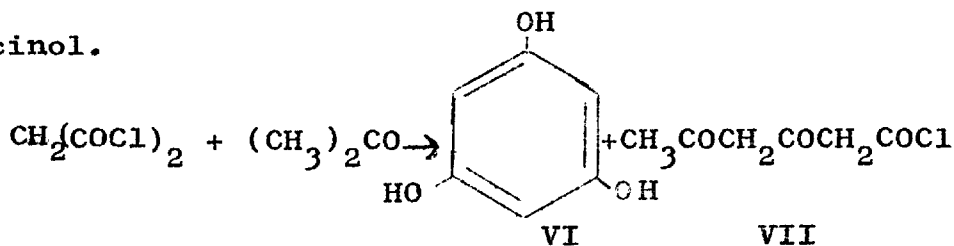
In 1912 the condensation of substituted malonyl chlorides with the alkyl ethers of isourea was reported³ to produce the derivatives of barbituric acid. Phenyl ethyl malonyl chloride with isourea methyl ether gave

2-methoxy-5-phenyl-ethyl-barbituric acid(III). Similarly benzyl malonyl chloride and phenyl malonyl chloride condensed with isourea ethyl ether yielding 2-ethoxy-5-benzyl-barbituric acid(IV) and 2-ethoxy-5-phenyl-barbituric acid(V) respectively.



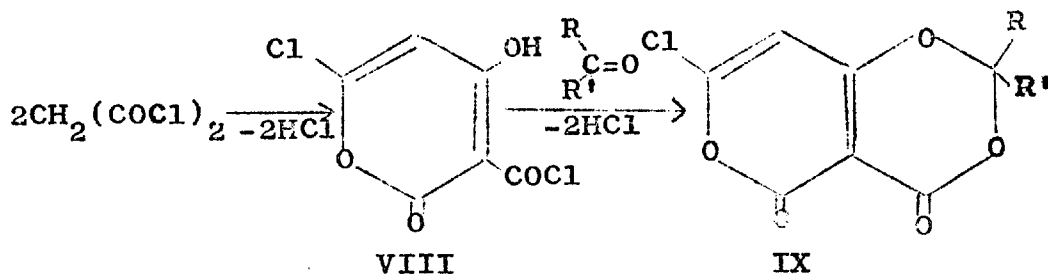
All of these cyclisations involve acylation of nitrogen.

In 1918 Komninos⁴ reported that, in the presence of marble, malonyl chloride and acetone reacted vigorously and produced phloroglucinol(VI) and 3,5-dioxohexanoyl chloride(VII). It was also reported that 3,5-dioxo-hexanoyl chloride when boiled with water and some more calcium carbonate was converted into phloroglucinol.



These reactions were apparently carbon-acylations.

Davis and Elvidge⁵ reinvestigated Komninos's work and found that neither of the two reported products was formed. They proved that the product was a new unsaturated hetero-dicyclic compound, a chloropyrono-1,3-dioxin (IX). The reaction was found a general one for aliphatic and aromatic ketones yielding 2,2-disubstituted derivatives of the same unsaturated hetero-dicyclic compound. Evidence was obtained⁶ indicating that the reaction proceeded in two stages. In the first stage the ketone as a very weak base induced a self condensation of malonyl chloride to 6-chloro-4-hydroxy-2-oxopyran-3-carbonylchloride (VIII). In the second stage of the reaction this acid chloride reacted with one molecule of ketone to produce the bicyclic heterocycle. Hence both C- and O- acylations were involved.



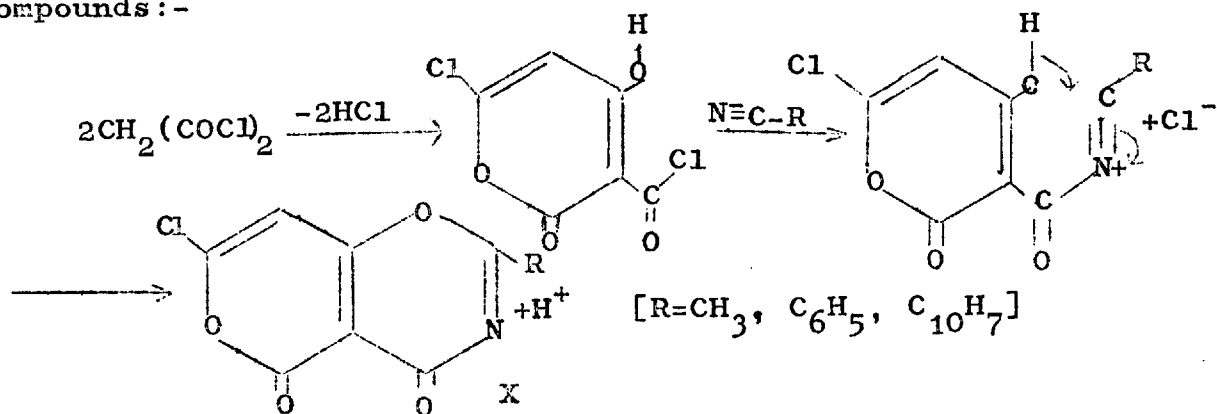
Davis and Elvidge (loc. cit.) found that weakly enolic ethyl acetoacetate and ethyl pyruvate readily produced pyrono-dioxins. On the other hand, the unsaturated oxo-ester

$\text{H}_5\text{C}_2\text{O}_2\text{C}.\text{CH}=\text{CH}.\text{CO}.\text{CH}(\text{CO}_2\text{C}_2\text{H}_5)_2$, failed to react with malonyl chloride to produce a pyronodioxin, this unsaturated oxoester evidently being insufficiently basic to induce the self condensation of malonyl chloride to pyrone acid chloride.

Davis and Elvidge⁷ also found that the 1,3-diketone, acetyl acetone, afforded a chlorine free compound, isomeric with dehydroacetic acid, whilst a 1,4-diketone, acetonyl acetone, converted malonyl chloride vigorously into malonic acid.

Davis and Elvidge (loc. cit.) showed that an aliphatic aldehyde could induce the self-condensation of malonyl chloride but the second stage of the reaction to a chloropyronodioxin appeared not to take place. In contrast, benzaldehyde reacted with malonyl chloride to yield the expected chloropyronodioxin, whilst other aromatic aldehydes condensed with the methylene group yielding α - β -unsaturated acids. The formation of these α , β -unsaturated acids from aromatic aldehydes and malonyl chloride proceeded more quickly than by the conventional Doebner procedure. In their further investigations, Davis and Elvidge⁸ showed that some nitriles behaved like ketones and with malonyl chloride produced another new bicyclic system, a chloro-oxopyrano-oxazine. Benzo-, aceto-, and naphtho nitriles reacted with

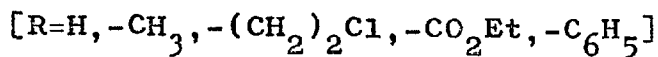
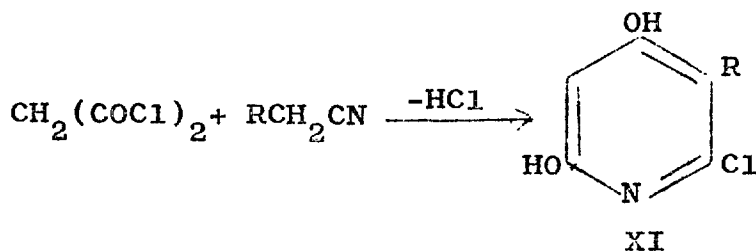
two mols. of malonyl chloride at 100° and yielded 2-substituted-7-chloro-, 4,5-dioxopyrano[3,4-e]-[1,3]-oxazines(X). The following mechanism was suggested for the formation of these compounds:-



It was also shown that preformed pyrone acid chloride reacted with benzonitrile to produce the same bicyclic product as obtained from the reaction of benzonitrile and malonyl chloride. They also studied some reactions of these chloro-oxopyrano-oxazines. The chlorine substituent of these products was found to be very reactive. Amines and water yielded 7-amino and 7-hydroxy derivatives respectively. Amines also cleaved the pyrone ring and yielded bicarbonyl amide derivatives of 4-oxo-1,3-oxazines.

Later Davis, Elvidge and Foster⁹ investigated the reaction of nitriles with malonyl chloride at room temperature. They found that nitriles having cyanomethylene group yielded under these conditions 3-substituted 2-chloro-4,6-dihydroxy-pyridine with slow evolution of hydrogen chloride.

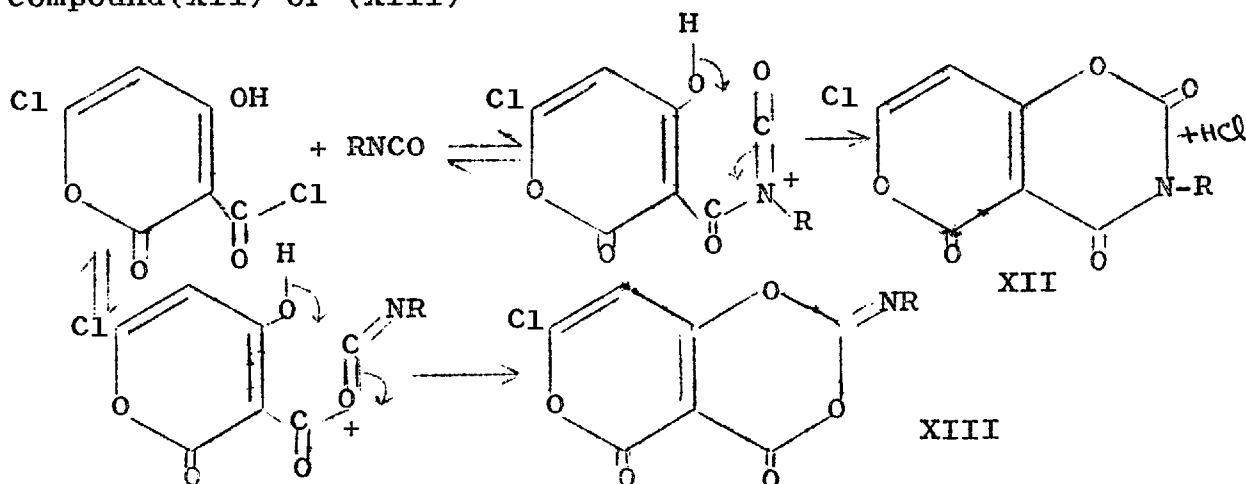
Thus acetonitrile and some monosubstituted aceto nitriles reacted with one molecular proportion of malonyl chloride and yielded 2-chloro-4,6-dihydroxy pyridines(XI). The α -substituent of the acetonitrile appeared at position 3 of the pyridine ring.



The structures of these pyridine derivatives were confirmed by chemical transformations of the products obtained from the reactions of propionitrile and cyanoethyl acetate with malonyl chloride.

Butt, Elvidge and Foster¹⁰ also investigated the reaction of isocyanates with malonyl chloride. Malonyl chloride with isocyanate produced bicyclic heterocycles which were proved to be 3-substituted 7-chloro-3,4-dihydro-2,4,5-trioxo-2H,5H-pyrano[3,4-e]-1,3-oxazines (XII). Again it was suggested that the reaction proceeded in two main stages. In the first stage the weakly basic isocyanates induced the

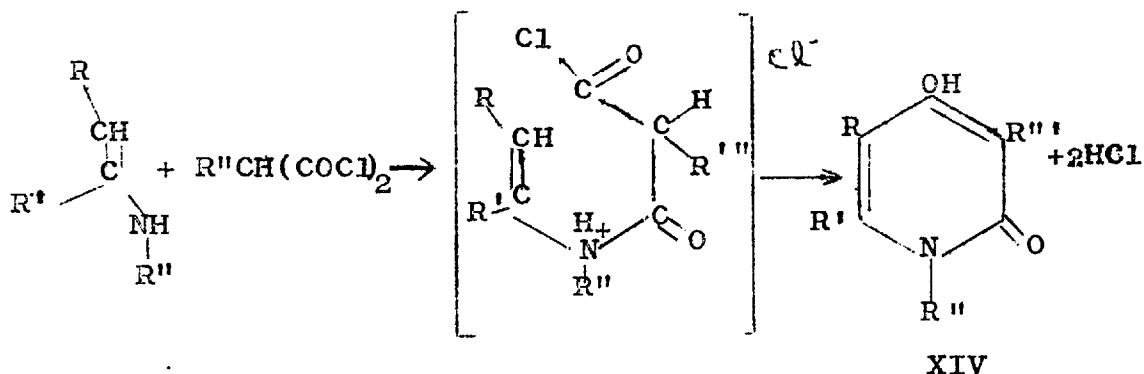
self condensation of malonyl chloride to pyrone acid chloride. The second stage involved the acylation of either nitrogen or oxygen of isocyanates and then cyclization yielded either compound(XII) or (XIII)



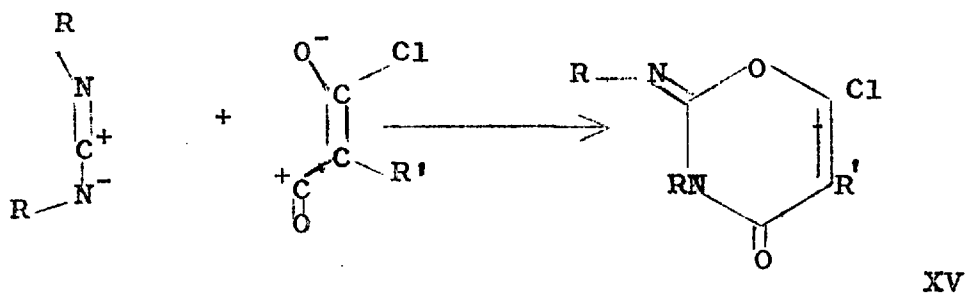
But on the basis of degradation products with alcohol the structure(XIII) was ruled out.

Ziegler and his coworkers have also reported the formation of some heterocyclic compounds from malonyl chloride and substituted malonyl chlorides.

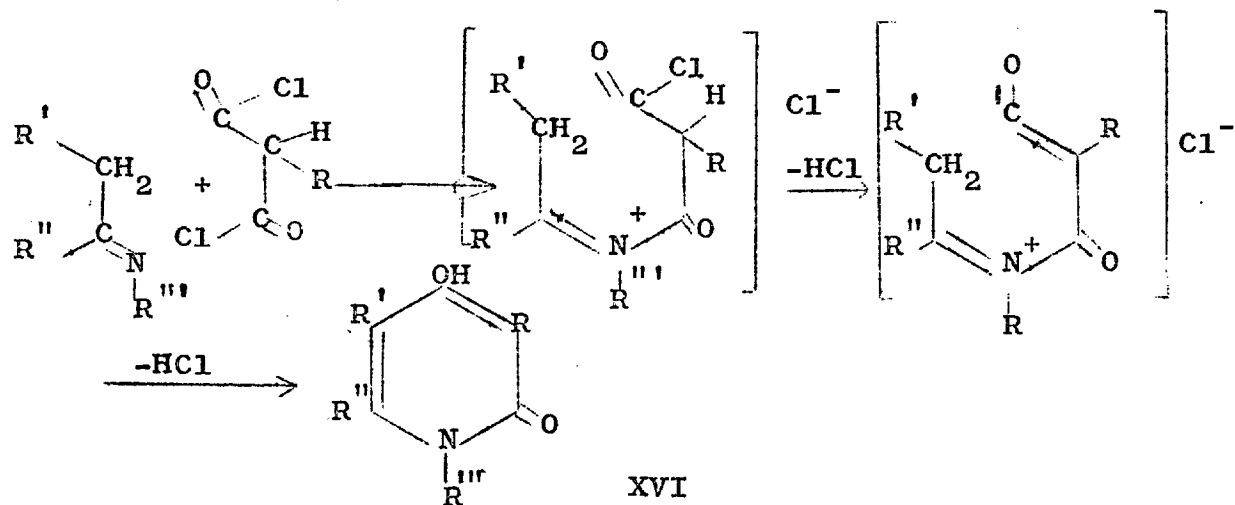
Ziegler et al¹¹ reported the formation of derivatives of 4-hydroxy-2-pyridone(XIV) by the action of malonyl chloride on primary and secondary ~~enamines~~ amines obtained from β -ketoesters and β -diketones. They found that ~~enamines~~ amines also reacted with malonic acid in acetic anhydride yielding the same derivatives of 4-hydroxy-2-pyridone.



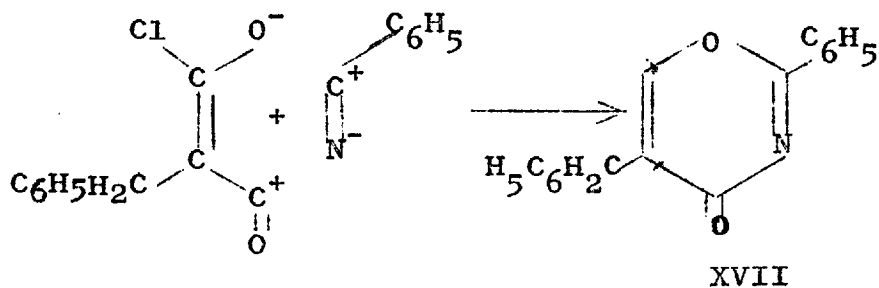
Kleineberg and Ziegler¹² also studied the reaction of malonyl chloride and monosubstituted malonyl chlorides with carbodiimides. From these reactions they obtained the derivatives of 6-chloro-2-imino-3,4-dihydro-2H-(1,3)-oxazine-4-one(XV). These oxazines in aqueous solution were shown to be rearranged to 1,3-disubstituted barbituric acid.



Ziegler and Kleineberg¹³ also showed that anils with a methyl or methylene group in α -position to the C=N bond reacted with malonyl chloride yielding N-aryl-4-hydroxy-2-pyridones(XVI). They suggested the following mechanism for the reaction

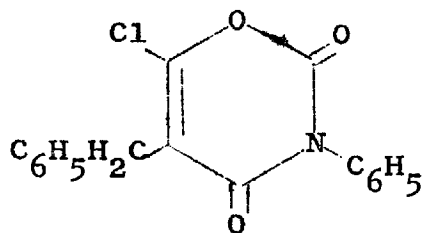


In their further investigation Ziegler, Kleineberg and Meindl¹⁴ studied the reaction of substituted malonyl chloride with nitriles and isocyanates. Benzonitrile and substituted benzonitriles reacted with benzyl malonyl chloride yielding 6-chloro-5-benzyl-2-phenyl-1,3-oxazines (XVII)



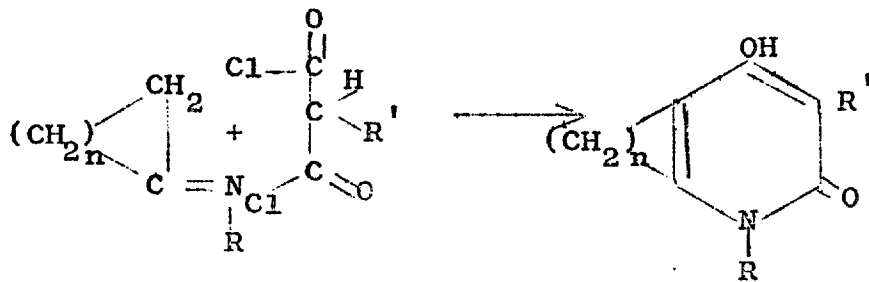
They also showed that these oxazines could be easily converted into dihydroxy pyrimidines by the action of ammonia.

Similarly phenyl isocyanates and their substituted derivatives reacted with malonyl chloride producing 6-chloro-5-benzyl-3-phenyl-2,4-dioxo-dihydro-1,3-oxazines (XVIII).



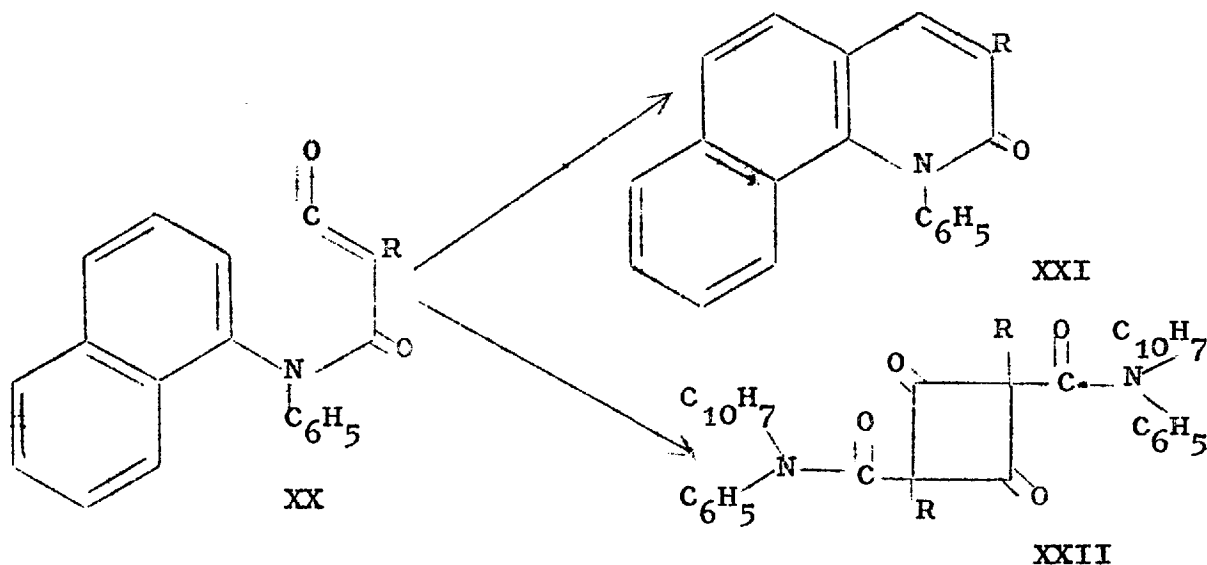
XVIII

Ziegler et al.¹⁵ also obtained N-aryl-4-hydroxy-5,6-polymethylene-pyrid-2-ones (XIX) from the reaction of cyclic ketone anils and substituted malonyl chloride



XIX

Similarly Ziegler and his coworkers¹⁶ have also reported that benzyl malonyl chloride reacted with α -tetralon-anil and gave a mixture of 5,6-dihydro-7,8-benzo-4-hydroxy carbostyryl (XXI) and compound (XXII). According to these workers the formation of compound (XXII) took place by the dimerization of the intermediate ketene acid anilide (XX).



Purpose of the Present Investigation:-

Earlier work revealed that acetonitrile and its monosubstituted nitriles condensed with malonyl chloride at room temperature to yield 3-substituted-2-chloro-4,6-dihydroxy-pyridines. Therefore, this work was thought to be capable of further extension to the preparation of a variety of 3-substituted pyridones. Of special interest was the preparation of 3-halogeno-2-chloro-4,6-dihydroxy-pyridines by condensing halogeno acetonitriles with malonyl chloride. Stoll¹⁷ condensed fluoroacetonitrile with malonyl chloride in order to get 2-chloro-3-fluoro-4,6-dihydroxy-pyridine, but the product could not be identified. Therefore, it was thought proper to study the condensation of nitriles especially halogeno nitriles with malonyl chloride in some detail. The investigation in this field gave some interesting results which are reported.

CHAPTER 2.

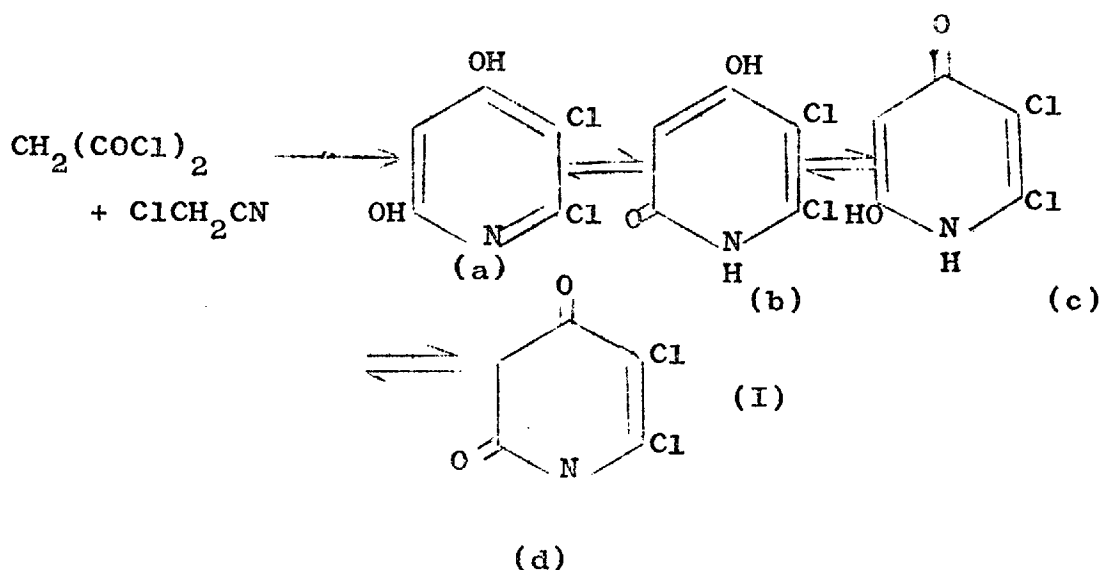
The reaction of chloroacetonitrile and malonyl chloride:-

The mixture of chloroacetonitrile and malonyl chloride was kept at room temperature for three days. The product after trituration with a mixture of ether and dioxan was crystallized from ethyl alcohol. The colourless crystalline product was seen under the microscope of the Kofler hot stage melting point apparatus to consist of a mixture of two types of crystals which melted at 173° and $273-274^{\circ}$ respectively. The low melting component was found to be soluble in chloroform whilst the high melting component was completely insoluble, enabling a separation to be achieved. From their molecular weights and elemental compositions, the molecular formulae of the chloroform insoluble and soluble components were found to be $C_5H_3NCl_2O_2$ and $C_5H_4N_2Cl_2O$ respectively.

Compound $C_5H_3Cl_2NO_2$:-

The mass spectrum showed its molecular weight was 179, indicating the presence of an odd number of nitrogen atoms. In its mass spectrum the relative intensities of the $P + 2$ and $P + 4$ peaks with respect to the parent peak were 65 and 10% respectively. These values are very close to those calculated¹⁸ for a compound containing two chlorine atoms. The parent peak

was the base peak which indicated that the compound was aromatic. The compound gave a faint pink colour (phenolic test) with ferric chloride. The nuclear magnetic resonance spectrum of the compound gave a broad band for two OH or NH groups and a singlet corresponding to one aromatic proton. In its infrared spectrum there were bands assignable to an aromatic ring. Its ultraviolet absorption spectrum also supported the aromatic nature of the compound. These various observations and its molecular formula suggested that the compound was 2,3-dichloro-4,6-dihydroxy-pyridine(I). This had been expected by analogy with products obtained in the previous work of Davis, Elvidge and Foster (loc. cit.). This compound can perhaps exist in four tautomeric forms, (a) - (d) :-



However, form (d), could be ruled out on the basis of its nuclear magnetic resonance spectrum which did not show any signal for a methylene group flanked by carbonyls.

Infrared spectroscopic results for compound(I) are given in Table 1.

TABLE 1.

cm^{-1}	Assignment
* 3279 - 2223	(broad and complex) Chelation or associated NH.
1887, 1786	"substitution pattern"
1656	C=O stretching
1595 ⁻)	ring stretching
)	
1548)	
)	
1488)	
)	C-O stretching or O-H
1435)	
)	
1351)	deformation
)	
1323)	ring vibration or hydrogen deformation.
1246	

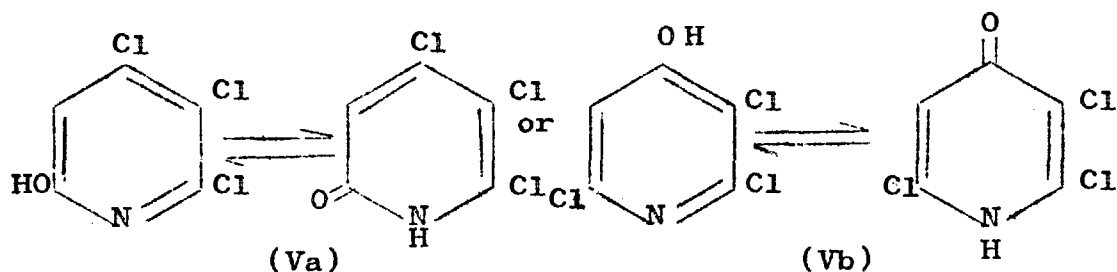
* KBr disc

The band at 1656 and four bands in the ring stretching region at 1595, 1548, 1488 and 1435 cm^{-1} agree with Katritzky and Jones's¹⁹ data for 2-pyridones. den Hertog and Buurman²⁰ had studied the ultraviolet spectra of O- and N- methyl

derivatives of 2,4-dihydroxy pyridine and they found that the three tautomeric forms had distinct ultraviolet light spectra. They concluded that 2,4-dihydroxy pyridine was best regarded as 4-hydroxy-2-pyridone. Therefore, it might be suggested that compound(I) probably exists as 2,3-dichloro-4-hydroxy-2-pyridone.

2,3-Dichloro-4-hydroxy-2-pyridone has one free β -position and there are also nucleus activating groups. Therefore, some electrophilic substitution reactions could be expected to take place easily and this was found to be true. The compound(I) on bromination yielded 5-bromo-2,3-dichloro-4,6-dihydroxy pyridine(II). Compound(I) was also easily nitrated to yield 2,3-dichloro-4,6-dihydroxy-5-nitro pyridine(III). In order to further establish the structure of compound(I) the compound was treated with phosphorus oxychloride at about 180° . This reaction yielded 2,3,4,6-tetrachloropyridine(IV) m.p. 38° in a very good yield, a compound earlier described by den Hertog and Schogt²¹. Thus this last reaction confirmed chemically the structure of compound(I). With phosphorus oxy chloride at refluxing temperature, compound(I) yielded a product in a very low yield with the molecular formula $C_5H_2Cl_3NO$. From its mass spectrum and proton magnetic resonance spectrum it appeared that one of the two hydroxy

groups of compound(I) had been replaced by chlorine and thus the product might have one of the following structures or their tautomers:-

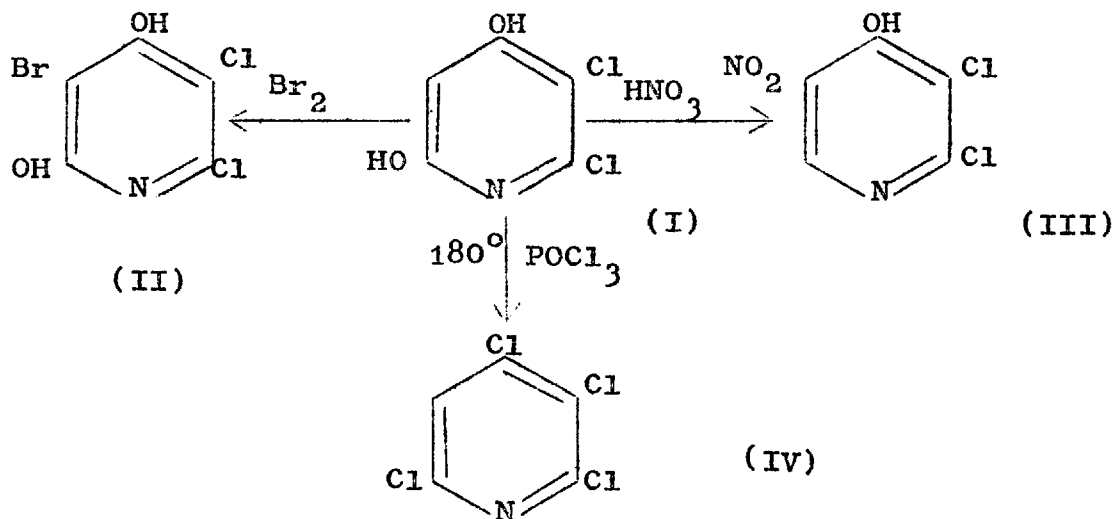


Neither of these two compounds are known. Infrared spectra of this compound were taken in carbontetrachloride as well as in nujol mull but neither showed any absorption in the region of $1600-1700\text{ cm}^{-1}$, a characteristic region for pyridones. This clearly showed the absence of a carbonyl group in the compound whether in solution or in the solid state. There are many reports in the literature mentioning that 2-hydroxy as well as 4-hydroxy pyridines prefer to exist in their corresponding pyridone forms. If structure (Vb) is assumed for this compound then it can be argued that due to intramolecular hydrogen bonding with the chlorine substituent at the β -position the compound does not exist in its pyridone form but preferentially in the chelated hydroxyform. The absence of carbonyl absorption militates against structure (Va),

for which there is no reason for presuming assumption of the hydroxy form. Therefore, on the basis of its infrared spectrum (Table 2), the compound appeared to be 2,3,6-trichloro-4-hydroxy pyridine (Vb).

TABLE 2

cm ⁻¹	Assignment
3200-2200	Chelation
1592 (Sh.)	C=C and C=N vibration
1570 (S)	
1540 (Sh.)	
1460 (S)	
1351	C-O stretching or O-H deformation
1220	ring vibration and hydrogen deformation
1150	
S=strong	Sh = shoulder



Ultraviolet light absorptions of compound(I) and its derivatives are given in Table 3

<u>TABLE 3.</u>		
Compound	Max. (m μ)(in EtOH)	ϵ
(I)	225 Sh.	4700
	275	3300
(II)	245 Sh.	3900
	282	3550
	312 Sh.	650
(III)	245 Sh.	5000
	283	3150
	355 Sh.	1700
(IV)	232	6300
	27 $\frac{1}{2}$ Sh.	2100
	282	3350
	289	3100
(V)	231	3900
	293	3400

Sh = Shoulder.

Nuclear magnetic resonance spectroscopic results of compounds (I) and (IV) are given in Table 4.

TABLE 4

Compound	τ	Intensity	Multiplicity	Assignment
(I)	3.08	2	broad	OH and/or NH
(in DMSO)	3.63	1	singlet	aromatic H
(IV)	2.63	-	singlet	aromatic H
(in CCl ₄)		-	singlet	aromatic H

The chemical shift of the β -aromatic proton in 2,3,4,6- tetrachloro - pyridine is lower than the value (3.01) for the β - protons of the unsubstituted pyridine. This shows that in this tetrachloropyridine the inductive effect of chlorine atoms is more pronounced than their mesomeric effect.

Compound C₅H₄Cl₂N₂O :-

From the mass spectrum of this compound its molecular weight was found to be 178 which according to the nitrogen rule established the presence of an even number of nitrogen atoms. The parent peak in its mass spectrum was the base peak, indicating the aromatic nature of the compound. The percentages of the intensities of (P+2) and (P+4) peaks with respect to the parent peak were 64.9 and 10.2 respectively. These relative abundances of (P+2) and (P+4) are very close to the calculated values (65.3, 10.6%) for the compound containing two chlorine atoms. The compound also gave a

faint phenolic test with ferric chloride. The nuclear magnetic resonance spectrum of this compound showed a broad band at a low field for one OH or NH, a singlet corresponding to one aromatic proton and another singlet corresponding to two protons. The chemical shift ($\tau=5.62$) for the last suggested a chloromethyl group attached to an aromatic ring. The presence of a side chain CH_2Cl substituent was also indicated from the mass spectrum of the compound, as there was a quite intense peak (49%) at $m/e = 129$. The infrared (Table 5) and ultraviolet absorptions of the compound also indicated the aromatic nature of the compound. The presence of a chloromethyl side-chain ruled out the possibility of a pyridine ring. Therefore, the compound was considered to be a pyrimidine one bearing a chloromethyl, one chlorine substituent, and one hydroxy group. The chemical shift of the aromatic proton ($\tau, 3.46$) indicated that this proton must be at the meta position to nitrogen atoms. Thus, this compound appeared to be 2-chloromethyl-4-chloro-6-hydroxypyrimidine or its tautomer(VI).

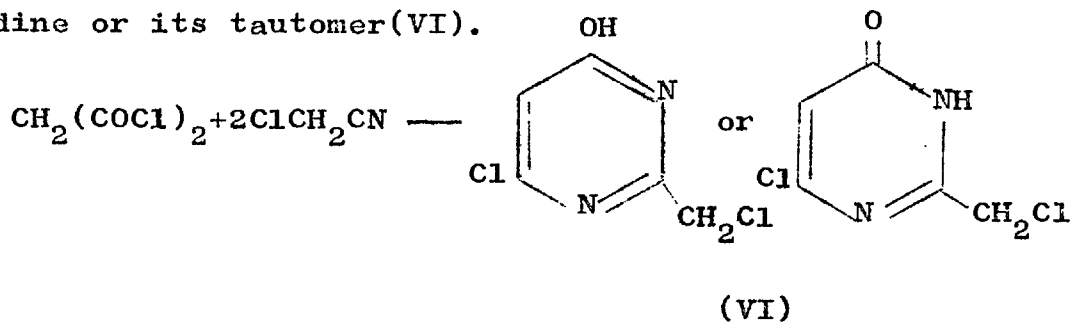


TABLE 5

cm^{-1}	Assignment
* 3226 - 2220	(very broad and complex) chelated OH or associated NH
1681 (S)	C = O stretching
1653 (S)	C = N stretching
1595 (S)]	ring stretching
1563 (S)]	
1471]	skeletal vibration of nucleus and CH ₂ deformation
1437]	

* KBr disc, S = strong

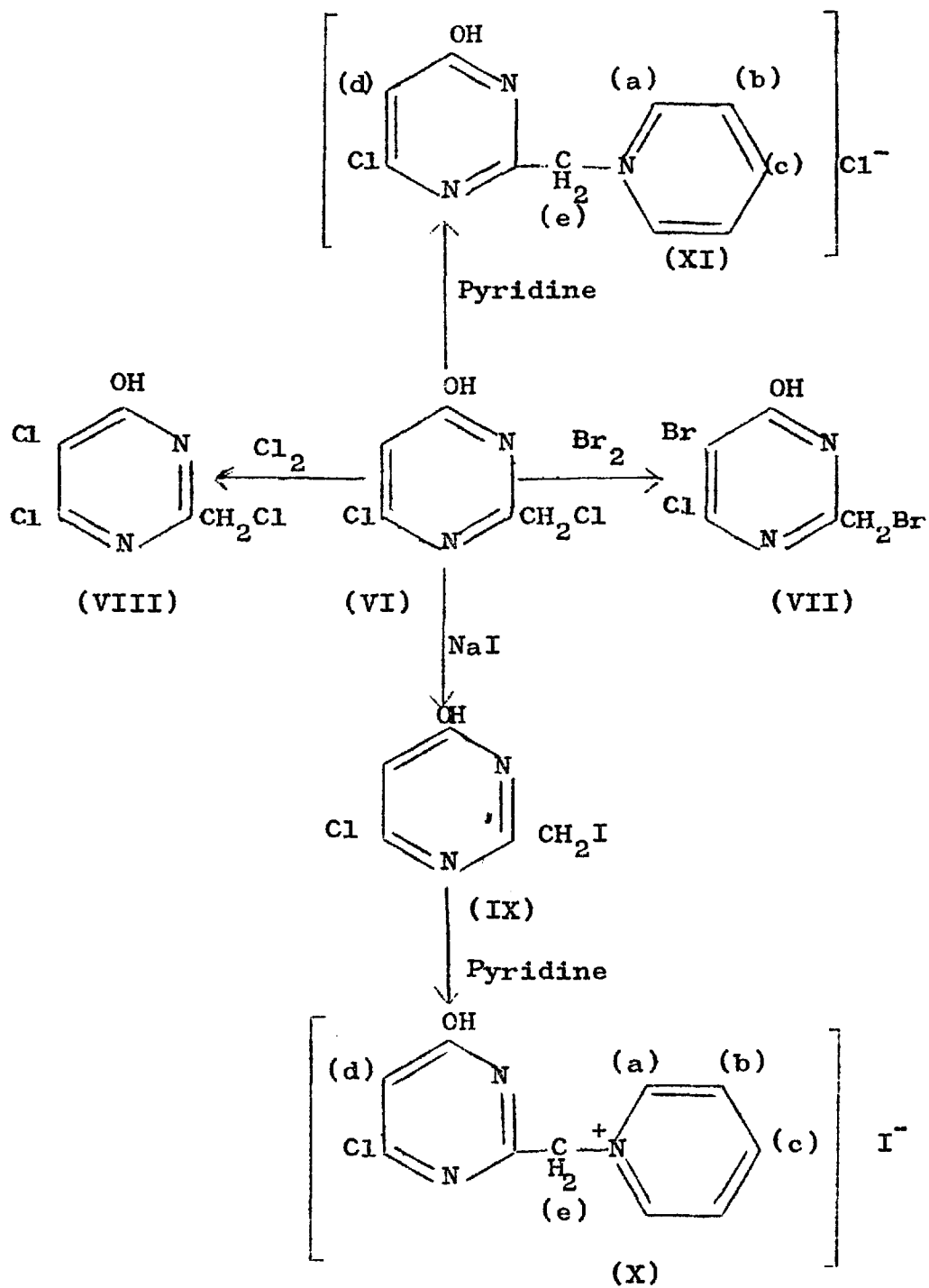
The most important bands in this spectrum are at 1681 and 1653 cm^{-1} . Absorptions at these high frequencies can hardly be attributed to ring vibration because the derivatives of pyrimidine without amino or hydroxy groups do not show bands in this region.²² In the present investigation also 2-chloromethyl-4,6-dichloropyrimidine(XII) did not show any band at such a high frequency. However, Short and Thompson (loc. cit.) found a doublet at 1620 - 1650 for hydroxy pyrimidines and they assigned the band at higher frequency to carbonyl stretching and the band at lower frequency to C = N stretching. Therefore, it appeared from

its infrared spectrum that the compound(VI) exists in its keto form.

To prove the assigned structure for the compound (VI) a series of chemical reactions was carried out. This pyrimidine derivative has a 5- position free, which is further activated by the presence of hydroxy and chlorine substituents on the adjacent carbon atoms, substitution was indeed readily effected. Thus, on chlorination of compound (VI), 2-chloromethyl-4,5-dichloro-6-hydroxypyrimidine(VIII) was obtained. The molecular weight from its mass spectrum was 212 with the expected relative intensities of P, (P + 2), (P + 4) peaks for a compound containing three chlorine atoms. Bromination of the compound (VI) however gave a product containing a higher percentage of bromine and a lower percentage of chlorine than that calculated for the corresponding bromo derivative of compound (VI). The nuclear magnetic resonance spectrum of the brominated product showed two singlets in the methylene region and no signal for an aromatic proton. These results indicated that during bromination, in addition to substitution at C₅ partial replacement of the side chain chlorine substituent by bromine took place. Therefore, for complete replacement of the side chain chlorine substituent by bromine the product was treated with hydrobromic acid in acetic acid, which yielded a single compound, 2-bromomethyl-5-

bromo-4-chloro-6-hydroxypyrimidine(VII). The mass spectrum molecular weight of this was 300, and the percentages of (P + 2), (P + 4), (P + 6) with respect to the parent peak were 232, 168, and 31.2% respectively, in agreement with the calculated percentages of these peaks for a compound containing two bromine atoms and one chlorine atom, viz. 228, 159 and 31.2 respectively (loc. cit.).

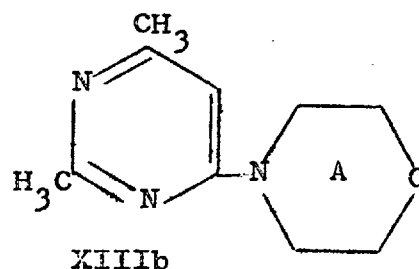
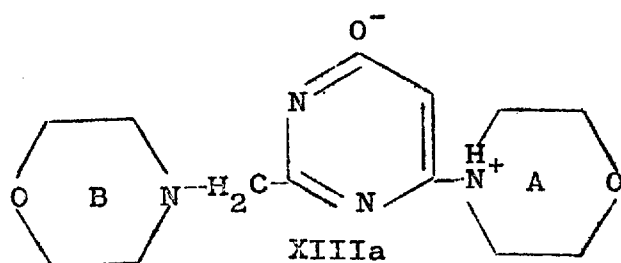
When compound (VI) in acetone was treated with sodium iodide the side chain chlorine substituent was replaced by iodine, producing 4-chloro-6-hydroxy-2-iodomethyl pyrimidine(IX) in a very good yield. This iodo compound on treatment with pyridine gave a crystalline salt, N-(4-chloro-6-hydroxy-pyrimidyl-2-methyl)-pyridinium iodide(X). Compound (VI), also with pyridine yielded the corresponding salt (XI). In both these pyridinium halides the chemical shifts of the methylene groups are at very low δ field due to the positive charge on the adjacent nitrogen atom.



With phosphorus oxychloride at refluxing temperature compound(VI) yielded 2-chloromethyl-4,6-dichloro pyrimidine (XII) which had low melting point 40° . As expected, the chemical shift of the aromatic proton in compound (XII) is at lower field (τ , 2.66) than that of the parent compound (τ , 3.46).

On treating the compound (VI) with morpholine both of the chlorine atoms were replaced by morpholine groups producing 4-hydroxy-2-morpholinomethyl-6-morpholino pyrimidine (XIII). The nuclear magnetic resonance spectrum of this morpholino derivative showed that the aromatic proton had a chemical shift at a considerably higher field (τ , 4.72) than that of the parent compound (VI) (τ = 3.46). The chemical shift of the four protons adjacent to the nitrogen atom of the morpholine ring (A) were at $\tau \approx 6.3$ as compared with 7.13 for the same protons in morpholine itself. At first therefore it was thought that the compound (XIII) might exist in the zwitterionic form (XIIIa). To clarify this point 2,4-dimethyl-6-morpholinopyrimidine (XIIIb) was prepared. Its n.m.r. spectrum showed one singlet

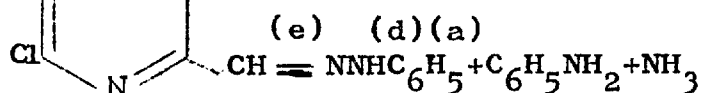
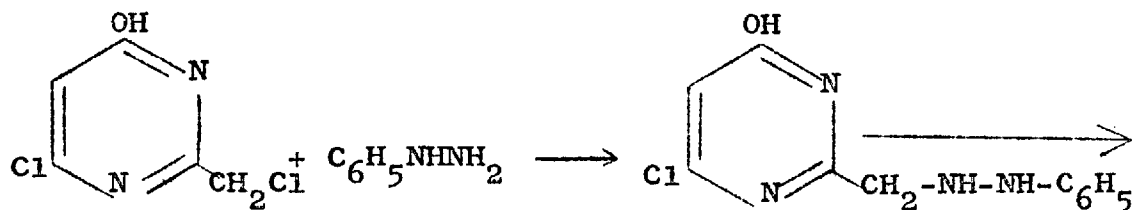
at τ 4.0 for one aromatic proton, one complex signal (τ = 6.45) from eight proton of the morpholine ring and two singlets (τ = 7.65, 7.80) for two methyl groups. Therefore, it was concluded that the differences in the proton chemical shifts between compounds (XIII) and (VIb) were merely due to the direct attachment of the morpholine ring (A) to the nucleus of the pyrimidine.



Since in compound (VI) the side chain chlorine substituent could be replaced by bromine, iodine and morpholine groups treatment of the compound (VI) with phenyl hydrazine was examined in the hope of replacing the side chain chlorine substituent and possibly the ring chlorine substituent also by phenyl hydrazine groups. The nuclear magnetic resonance spectrum of the yellow crystalline product showed that only the side chain chlorine has been substituted. The most

interesting feature of this spectrum was that there was no band for the methylene group. There were two broad bands at lower field corresponding to the two "enolic" protons. There was a singlet at τ 3.65 from the pyrimidine ring proton and a complex six-proton signal in the normal aromatic region at 2.7. Moreover the molecular weight of this compound from its mass spectrum was 248 instead of 250 calculated for the phenyl hydrazine derivative (XIV). Therefore, on the basis of its nuclear magnetic resonance spectrum and its mass spectrum it was concluded that the compound from the reaction of compound(VI) and phenyl hydrazine was 4-chloro-6-hydroxy-2-phenyl hydrazono methyl pyrimidine(XV) instead of (XIV). For the formation of this hydrazone it can be suggested that in the first step of the reaction 2-chloromethyl-4-chloro-6-hydroxy-pyrimidine reacted with one molecule of phenyl hydrazine producing 4-chloro-6-hydroxy-2-phenyl hydrazine methyl-pyrimidine(XIV). Then in the second step another molecule of phenyl hydrazine as hydrogen acceptor reacted with compound (XIV) oxidizing the latter into its hydrazone(XV). This oxidizing property of phenyl hydrazine is commonly experienced toward groups which can be easily dehydrogenated. This structure is further supported by its ultraviolet spectrum which showed absorption at a wave length of 395 m μ (ϵ = 19000) in addition to other

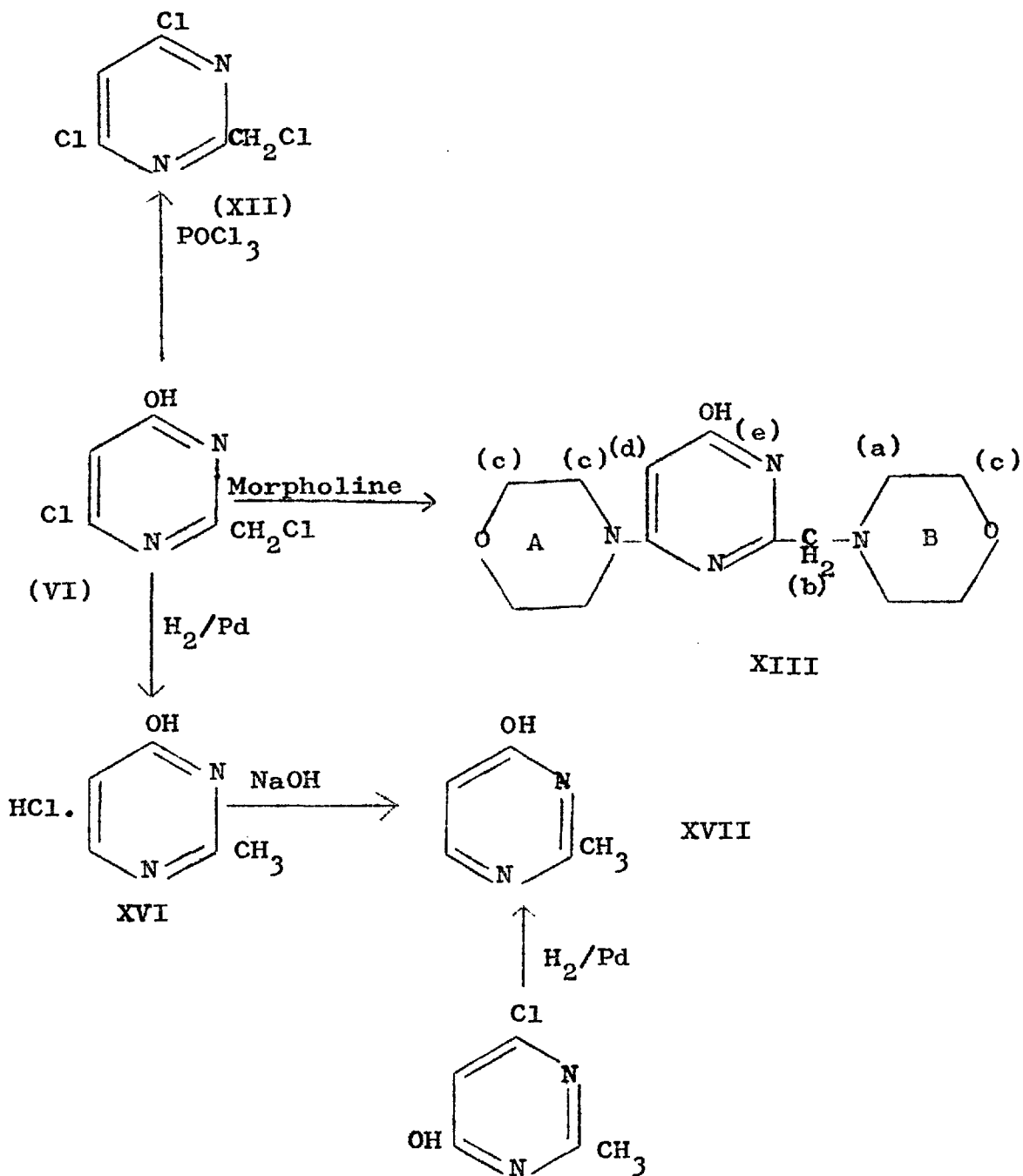
absorptions at lower wave lengths. This long wave length absorption is due to the extension of conjugation.



Finally to confirm the structure of compound (VI) it was decided to convert it into some known compound. For this purpose the compound (VI) was hydrogenated at atmospheric pressure and at room temperature in the presence of 10% Pd on charcoal to get a known compound 4-chloro-6-hydroxy-2-methyl-pyrimidine. But one molecule of compound (VI) consumed two mols. of hydrogen to yield 4-hydroxy-2-methyl-pyrimidine hydrochloride(XVI). The free base from this hydrochloride was a known compound. Therefore, this hydrochloride(XVI) was neutralized by 10% sodium hydroxide

and after acidifying with acetic acid the free base 4-hydroxy-2-methyl-pyrimidine(XVII) was extracted with chloroform. The nuclear magnetic resonance spectrum of this compound (XVII) showed two doublets for two aromatic protons and one singlet for a methyl group. The mass spectrum showed its molecular weight to be 110.

Akiva Takamizawa²³ reported this compound as melting at 214° which agreed with the observed melting point of $213.7 - 214.5^{\circ}$. 4-Hydroxy-2-methyl pyrimidine was also obtained by the reductive dehalogenation of 4-chloro-6-hydroxy-2-methyl pyrimidine obtained from a known route. The mixed melting point was undepressed and the infrared spectra of these two samples were identical. Thus, this last reaction finally confirmed that one of the two products obtained from chloroacetonitrile and malonyl chloride is 2-chloromethyl-4-chloro-6-hydroxy-pyrimidine(VI).



The nuclear magnetic resonance results for the compounds(VI) to XVII are given in Table 6.

TABLE 6

Compound	τ	Intensity	Multiplicity	Assignment
VI	0.69	1	broad	OH or NH
(in CDCl_3)	3.46	1	singlet	aromatic H
	5.52	2	singlet	$-\text{CH}_2-$
VII	5.60		singlet	$-\text{CH}_2-$
(in DMSO)				
VIII	5.48		singlet	$-\text{CH}_2-$
(in DMSO)				
IX	3.58	1	singlet	aromatic H
(in DMSO)	5.82	2	singlet	$-\text{CH}_2-$
X	0.8	2	complex	a
(in DMSO)	1.27	1	complex	c
	1.70	2	complex	b
	3.41	1	singlet	d
	3.95	2	singlet	e

Compound	τ	Intensity	Multiplicity	Assignment
XI	0.85	2	complex	a
(in DMSO)	1.25	1	complex	c
	1.70	2	complex	b
	3.41	1	singlet	d
	4.10	2	singlet	e
XII	2.66	1	singlet	aromatic H
(in CCl_4)	5.39	2	singlet	$-\text{CH}_2-$
XIII	0.34	1	broad	e
(in CDCl_3)	4.72	1	singlet	d
	~6.3	12	complex	c
	6.57	2	singlet	b
	7.42	4	triplet	a
XV	2.70	6	complex	a & e
(in DMSO)	3.65	1	singlet	b
	1.90	1	broad	c & d
	0.6	1	broad	

Compound	τ	Intensity	Multiplicity	Assignment
XVI	1.95	1	doublet	aromatic H
(in D ₂ O+t.BuOH)			J = 8C/sec.	at C ₄
	3.29	1	doublet	aromatic H
			J = 8C/sec.	at C ₅
	7.21	3	singlet	-CH ₃
XVII	2.0	1	doublet	aromatic H
(in D ₂ O+t.BuOH)			(J = 8C/sec.)	at C ₄
	3.55	1	doublet	aromatic H
			(J = 8C/sec.)	at C ₅
	7.5	3	singlet	-CH ₃

The chemical shift for the proton at C₅ in unsubstituted pyrimidine is 2.63 but in compound (VI) the found value is 3.55. This diamagnetic shift is to be expected because of a hydroxy group at the ortho position. The chemical shift of this aromatic proton in all the derivatives of compound (VI) containing the hydroxy group, except for compound (XIII), is not much altered. But the chemical shift of the aromatic proton in compound (XII) is 2.66 τ which is very close to the value (τ 2.63) for the same proton in unsubstituted pyrimidine. This shows that the chlorine atoms in compound (VI) and its derivatives have no significant effect on the electron

distribution in the pyrimidine ring which may be due to a balance of inductive and mesomeric effects of chlorine.

Ultra-violet spectroscopic results for compound(VI) and its derivatives are given in Table 7.

TABLE 7

Compound	Max. mμ	ε
VI	228	4500
	282	3500
VII	243	4600
	298	8800
VIII	240	3200
	290	3100
IX	240	5300
	295	6100
X	257 Sh.	3900
	261	4100
	268 Sh.	3400
XI	258 Sh.	6200
	261	6400
	267	5100
XII	252 Sh.	3300
	257	3550
	263 Sh.	2800

TABLE 7 (Continued)

Compound	Max. μ	ϵ
XIII	234	21600
	270	8800
XIV	239	7700
	246	7200
	258	5100
XV	275	3700
	293	2600
	302	2000
	395	1900
XVI	223	6050
	268	3000
XVII	220	8000
	275	4800

Solvent Ethanol

Sh. Shoulder.

It is interesting to mention here that this new synthesis of pyrimidine derivatives from malonyl chloride and chloroacetonitrile is the first direct synthesis of chloropyrimidines in which the halogen is in an active position. D.J. Brown²⁴ had mentioned, "Halogens in the active positions

can not be introduced in the course of a direct synthesis nor can they be introduced by halogenation of a preformed pyrimidine" The only methods previously available for the preparation of pyrimidines containing halogen in an active position involved the action of phosphorus halides on the corresponding hydroxy or mercapto derivatives of pyrimidine.

Attempted reactions of malonyl chloride
and chloroacetonitrile at different temperatures:-

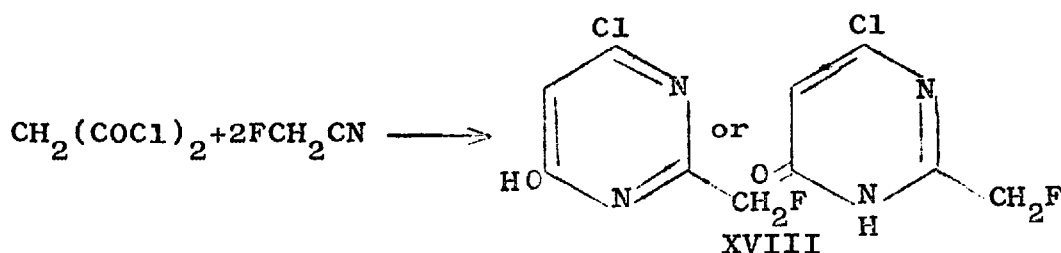
It has been mentioned earlier that Davis and Elvidge had found that malonyl chloride and some nitriles at 100° produced bicyclic heterocycles. Therefore, the mixture of malonyl chloride and chloroacetonitrile was heated at 100° for one hour. In the end a completely charred material was obtained from which nothing could be isolated.

The mixture of malonyl chloride and chloroacetonitrile was also kept at 0° for seven days. But the foregoing two products i.e. 2,3-dichloro-4,6-dihydroxy-pyridine and 2-chloromethyl-4-chloro-6-hydroxy-pyrimidine were isolated. The reaction between malonyl chloride and chloroacetonitrile was also carried out in the presence of nitromethane as solvent but the products were the same as obtained in the absence of nitromethane.

The reaction of malonyl chloride with fluoroacetonitrile:-

Malonyl chloride and fluoroacetonitrile when kept at room temperature yielded a crystalline product in about 24 hours. The product was purified by crystallization and sublimation to a colourless compound melting sharply at 193° . This compound gave twice the percentage of nitrogen expected for a pyridine derivative. The molecular weight of this compound, determined by mass spectrometry, was 162 instead of 163 for the corresponding fluoropyridine. The even mass number of the compound also confirmed the presence of two nitrogen atoms. The relative intensity of (P+2) peak (31.8%) with respect to parent peak showed the presence of one chlorine atom. Parent peak in the mass spectrum was the base peak indicating the aromatic nature of the compound, On the basis of its microanalysis and molecular weight its molecular formula appeared to be $C_5H_4ClFN_2O$. The nuclear magnetic resonance spectrum of this compound showed a broad band at a low field for one OH or NH proton, one sharp singlet corresponding to one aromatic proton and a doublet at $\tau=4.75$ with a coupling constant of 46 c/sec. and the intensity of this doublet was equivalent to two protons. Therefore, this doublet clearly indicated the presence of a methylene group attached to a

fluorine atom, which is responsible for its splitting into a doublet, and to one aromatic ring. The aromatic nature of the compound is also indicated from its infrared and ultraviolet light spectra. The infrared spectrum of this compound resembled in its general features to that of 2-chloromethyl-4-chloro-6-hydroxy pyrimidine. Therefore, it can be easily concluded that the product obtained from fluoroacetonitrile and malonyl chloride is 4-chloro-2-fluoromethyl-6-hydroxy-pyrimidine(XVIII) or its tautomer.



This reaction of malonyl chloride and fluoroacetonitrile completed in a shorter period than that of malonyl chloride and chloroacetonitrile and moreover, the reaction product was cleaner also. The nuclear magnetic resonance spectrum of the crude product was taken to detect the presence of the corresponding pyridine derivative if there was any, but no trace of the pyridine derivative could be detected. It seems that this reaction produced exclusively the pyrimidine derivative.

Important features of infrared spectrographic results of compound(XVIII) are shown in Table 8.

TABLE 8

cm ⁻¹	Assignment
* 3120 - 2418(very broad)	chelated OH or associated NH
1916, 1826	"substitution pattern"
1683 - 1641 (s)(broad band)	C=O and C=N stretching
1597 - 1558 (s)	ring stretching
1493	skeletal vibration of nucleus
1452	CH ₂ deformation
1022 - 1008 (s)	skeletal vibration of substituted pyrimidine

(s) = strong

* KBr disc.

The broad band at 1683-1641 appears to be a doublet. In the infrared spectrum of its bromo derivative this band splits clearly into two bands, one at 1675 and the other at 1650 cm.⁻¹ The band at such a high frequency could not be explained without assuming the keto form of the compound. In one of its derivatives 4,6-dichloro-2-fluoromethyl(XX) there was only one single band in this region at 1550 cm.⁻¹ Therefore, most probably the band at higher frequency is due

to the lactam C=O group. Thus, the infrared spectrum of the compound(XVIII) supported the oxo form.

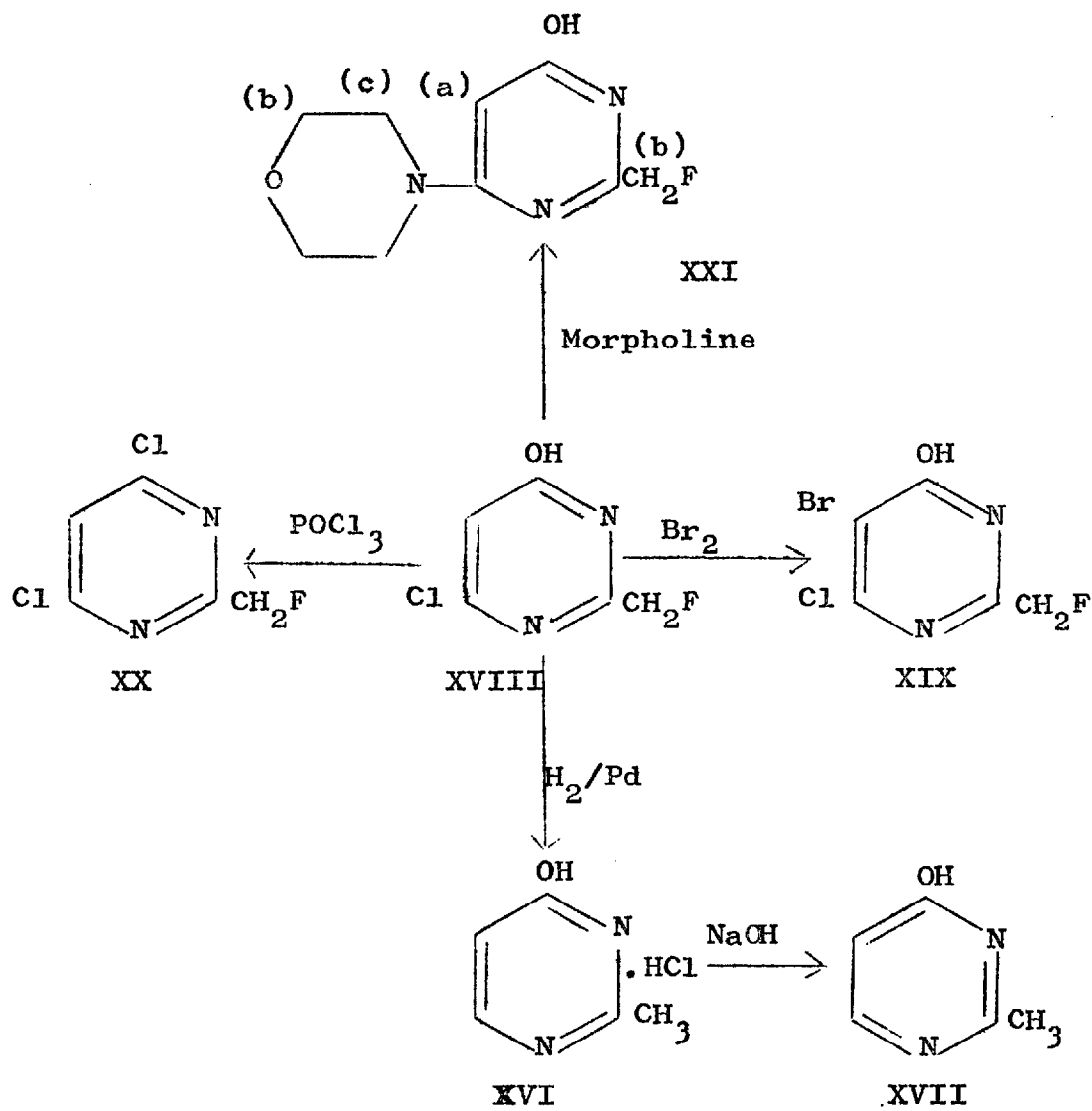
A series of chemical reactions was carried out to establish the structure of compound (XVIII). Its free β -position is susceptible to electrophilic substitution. On bromination compound (XVIII) gave 5-bromo-4-chloro-2-fluoromethyl-6-hydroxy-pyrimidine(XIX). The molecular weight of this bromo derivative from its mass spectrum was 240. The percentages of (P+2) and (P+4) peaks with respect to parent peak were 131 and 33.5 respectively, and these values are very close to the calculated values for a compound containing one chlorine and one bromine atom.

With phosphorus oxychloride at refluxing temperature compound (XVIII) gave 4,6-dichloro-2-fluoromethyl-pyrimidine(XX).

4-Chloro-2-fluoromethyl-6-hydroxy-pyrimidine was hydrogenated at atmospheric pressure and room temperature. This reductive dehalogenation yielded the hydrochloride of 4-hydroxy-2-methyl pyrimidine(XVI) which on neutralization with sodium hydroxide gave 4-hydroxy-2-methyl-pyrimidine(XVII, m.p. 214°), the same compound as obtained from the hydrogenation of 2-chloromethyl-4-chloro-6-hydroxy-pyrimidine. The mixed melting point was undepressed. The infrared and nuclear

magnetic resonance spectra of these two samples of 4-hydroxy-2-methyl pyridine were identical. Thus the formation of 4-hydroxy-2-methyl-pyrimidine substantiated the structure(XVIII) of the compound obtained from fluoroacetonitrile and malonyl chloride.

4-Chloro-2-fluoromethyl-6-hydroxy-pyrimidine reacted with only one mol. of morpholine yielding 2-fluoromethyl-6-hydroxy-4-morpholino-pyrimidine(XXI). The fluorine substituent unlike the side chain chlorine of compound(VI) was unreactive towards morpholine. In this morpholine derivative(XXI) also the chemical shift of the aromatic proton was found to be $\tau=4.62$ comparable to the chemical shift of the same proton in morpholine derivative(XIII).



The condensation of fluoroacetonitrile and malonyl chloride was also carried out in the presence of nitromethane. The reaction yielded the same compound (XVIII) in the same yield as it was obtained in the absence of nitromethane. This reaction of malonyl chloride and fluoroacetonitrile was also attempted at 100°. After heating the mixture of malonyl chloride and fluoroacetonitrile at 100° for about twenty minutes a dark red solid product was obtained. This product was found to be 4-chloro-2-fluoromethyl-6-hydroxypyrimidine (51%), the compound obtained from the reaction carried out at room temperature. However, it was found that the best yield (65%) of the compound (XVIII) was obtained from one mol. of malonyl chloride and two mols. of fluoroacetonitrile kept at room temperature for twenty-four hours.

Nuclear magnetic resonance results of compound (XVIII) and its derivatives are given in Table 9.

TABLE 9

Compound		Intensity	Multiplicity	Assignment
XVIII (in dioxan)	1.50	1	broad	OH or NH
	3.55	1	singlet	aromatic H
	4.75	2	doublet (J=46 c/sec.)	-CH ₂ -F
XIX (in dioxan)	1.16	1	broad	OH or NH
	4.74	2	doublet (J=46 c/sec.)	-CH ₂ -F
XX (in CDCl ₃)	2.60	1	singlet	aromatic H
	4.52	2	doublet (J=46.5 c/sec.)	-CH ₂ -F
XXI (in CDCl ₃)	4.64	1	singlet	aromatic H
	4.81	2	doublet	-CH ₂ -F
			(J=46.5 c/sec.)	
	6.34	4	complex)	b and c
	6.42	4	complex)	

Ultraviolet spectroscopic results of compounds

XVIII to XXI are shown in Table 10.

TABLE 10

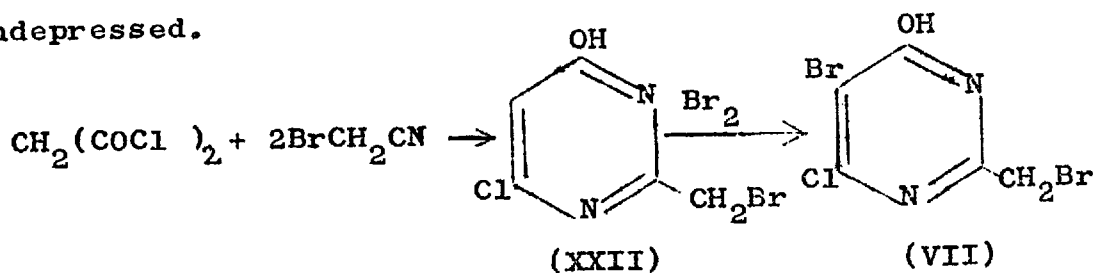
Compound	Max. μ	ϵ
XVIII	228	5500
	281	4200
XIX	241	2600
	292	3400
XX	209	5800
	256	4600
XXI	239	10650
	269	7050

Solvent-Ethanol.

The reaction between bromoacetonitrile and malonyl chloride:-

A mixture of malonyl chloride and bromoacetonitrile, when kept at room temperature for two days, gave a red crystalline product. This, on crystallization from methanol yielded colourless fine needles. The molecular weight, from the mass spectrum, was 222 showing the presence of an even number of nitrogen atoms. The percentages of the intensities of the (P+2) and (P+4) peaks (131.5 and 32.8% respectively) with respect to the parent peak showed the presence of one chlorine atom and one bromine atom. The molecular formula of this compound calculated from the microanalytical results and mass spectrum was $C_5H_4BrClN_2O$. The proton magnetic resonance spectrum showed a singlet for an aromatic proton and a singlet for a methylene group. Its infrared and ultra violet spectra resembled those of pyrimidine derivatives. Therefore, it was concluded that this new compound was 2-bromomethyl-4-chloro-6-hydroxy pyrimidine(XXII). This was confirmed by bromination which yielded 5-bromo-2-bromomethyl-4-chloro-6-hydroxy-pyrimidine(VII). The infrared and nuclear magnetic resonance spectra of the product were identical with those of compound(VII) obtained by the bromination of compound(VI), and the mixed melting point was

undepressed.



Important absorptions in the infrared spectrum of compound (XXII) are given in Table 11.

TABLE 11.

* cm^{-1}	Assignment
2700 - 2000 (very broad)	Chelation or associated NH
1920, 1840	"substitution pattern"
1665 (s)	C=O stretching
1630 (sh.)	C=N stretching
1590]	ring stretching
1550]	
1440 (sh.)	CH_2 deformation
965	ring vibration

* Nujol mull

s = strong

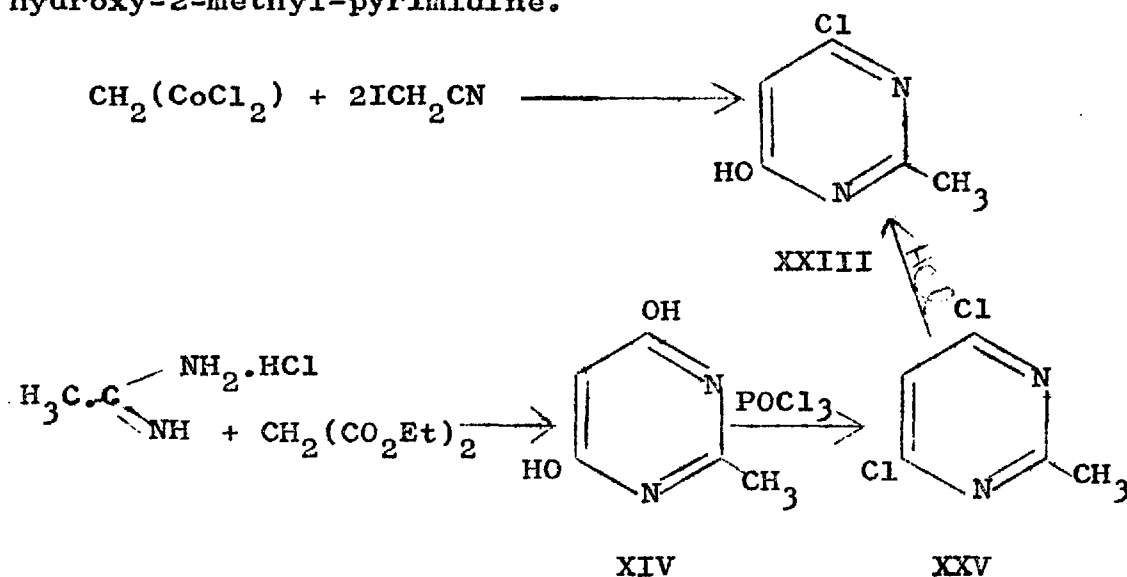
sh. = shoulder

All efforts to detect the presence of a bromo-derivative of pyridine failed. Thus the reaction of bromoacetonitrile and malonyl chloride appeared to yield exclusively the pyrimidine derivative. This difference from the behaviour of chloroacetonitrile remains unexplained.

The reaction of iodoacetonitrile with malonyl chloride:-

This reaction yielded a very dirty product which contained some free iodine. However, after being washed and triturated with different solvents the product was obtained as a brown substance which on crystallization from ethanol gave colourless fine needles (m.p. $233-234^{\circ}$). The molecular weight of this product from its mass spectrum unexpectedly appeared to be 144 and the parent peak in the mass spectrum was the base peak. Thus from its mass spectrum it appeared that the compound was an aromatic, containing one chlorine atom but without iodine. Its molecular formula from its mass spectrum and microanalysis was $C_5H_5ClN_2O$. The proton magnetic resonance spectrum showed a singlet corresponding to an aromatic proton and another singlet ($\tau = 7.52$) corresponding to three protons indicating the presence of a methyl group attached to an aromatic ring. The infrared and ultraviolet spectra of this compound in their general features resembled

those of pyrimidine derivatives. Therefore, from its molecular formula and from its spectroscopic properties the compound appeared to be 4-chloro-6-hydroxy-2-methyl-pyrimidine (XXIII). This was a known compound and its melting point had variously been reported as 233° ^{25,26} and $231.5-232^{\circ}$ ²⁷. This compound was therefore prepared by the known route, 4,6-dihydroxy-2-methyl pyrimidine(XXIV) was obtained²⁶ from acetamide hydrochloride and diethyl malonate, and then treated with phosphorus oxychloride to yield 4,6-dichloro-2-methyl-pyrimidine(XXV).²⁵ Hydrolysis of the last gave 4-chloro-6-hydroxy-2-methyl-pyrimidine.

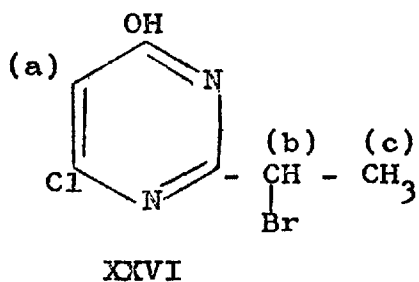


The mixed melting point was undepressed and infrared spectra of the two samples were identical. Therefore, it is quite evident that in the reaction of iodoacetonitrile and malonyl chloride reductive deiodination took place at some stage producing compound (XXIII). It has been found in this investigation that 4-chloro-6-hydroxy-2-iodomethyl-pyrimidine (VIII) is a quite stable compound. Therefore, it is not likely that the reductive deiodination took place after the formation of compound (VIII) but at some stage before that. Such reductive deiodination is not uncommon in the literature of iodo compounds.

Reaction of α -bromo-propionitrile with malonyl chloride:-

A mixture of malonyl chloride and α -bromo-propionitrile gave a yellow crystalline product which on crystallization yielded colourless needles. The molecular formula of this compound from its molecular weight and microanalysis appeared to be $C_6H_6BrClN_2O$. The nuclear magnetic resonance spectrum gave one singlet for one aromatic proton, one quartet corresponding to one proton and one doublet corresponding to three protons. The chemical shift of the quartet suggested that the proton was attached to a carbon atom bonded to (1) an aromatic ring, (2) one halogen atom and (3) one methyl

group. Thus the nuclear magnetic resonance spectrum indicated the presence of one aromatic proton and a side chain $-\text{CH}(\text{Br})\text{CH}_3$. In the mass spectrum the parent peak corresponded to a mass number of 236 confirming the presence of an even number of nitrogen atoms. The presence of one chlorine and one bromine atom was also confirmed from the relative intensities of the (P+2) and (P+4) peaks with respect to the parent peak. Its infrared and ultraviolet spectra also indicated that the compound was a pyrimidine derivative. Therefore it was concluded that the compound was 2-(α -bromoethyl)-4-chloro-6-hydroxy pyrimidine (XXVI). The formation of this pyrimidine derivative from α -bromopropionitrile and malonyl chloride showed that the reaction does not require the presence of a cyanomethylene group in the nitrile component.



The reaction of dibromoacetonitrile with malonyl chloride:-

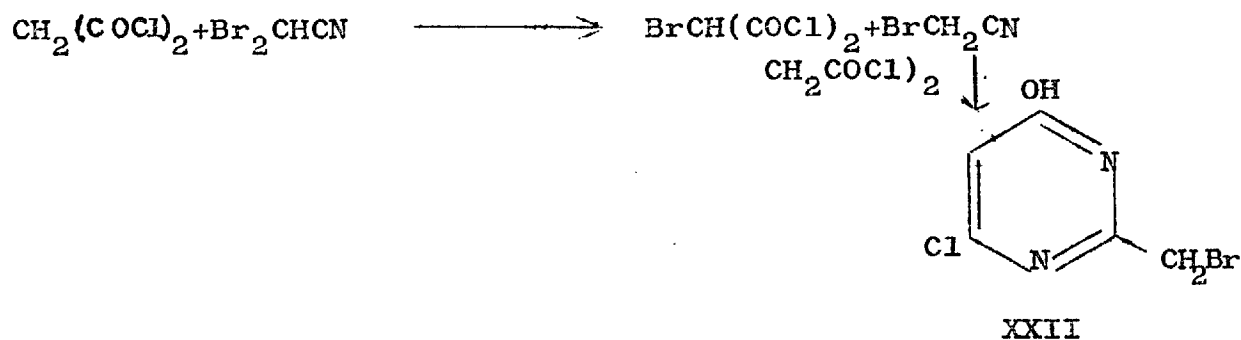
This reaction gave a reddish brown solid product which on crystallization from ethyl alcohol yielded colourless fine needles (m.p. $194 - 195^{\circ}$). Its molecular weight from its mass spectrum was found to be 222 instead of 300 calculated for the expected 2-dibromomethyl-4-chloro-6-hydroxy-pyrimidine. Moreover, the relative intensities of the (P+2) and (P+4) peaks with respect to the parent peak were 132 and 32.5% respectively showing the presence of one chlorine atom and only one bromine atom. From the micro-analysis and mass spectrum the molecular formula appeared to be $C_5H_4BrClN_2O$. The nuclear magnetic resonance spectrum of this compound showed a singlet for one aromatic proton and a singlet corresponding to two protons from a bromomethyl substituent. The chemical shifts of the aromatic proton and methylene protons were exactly the same as those found for 2-bromomethyl-4-chloro-6-hydroxy-pyrimidine (XXII), obtained from bromoacetonitrile and malonyl chloride. The infrared spectrum of this compound and that of compound (XXII) were exactly the same. The mixed melting point was undepressed. Therefore, it was concluded that the compound obtained from dibromoacetonitrile and malonyl chloride was

2-bromomethyl-4-chloro-6-hydroxy-pyrimidine. This reaction was repeated several times but each time the same compound (XXII) was obtained. Since the product obtained was quite unexpected, therefore, it was considered necessary to check the purity of the dibromoacetonitrile employed. The nuclear magnetic resonance spectrum of this nitrile showed only one singlet with a chemical shift of $\tau^{4.15}$, quite different from that of the methylene protons of bromoacetonitrile ($\tau = 6.2$). Microanalytical results upon the dibromoacetonitrile were the final proof of its purity. Therefore, it is quite obvious that at some stage reductive debromination took place. Malonyl chloride has a very reactive methylene group which is susceptible to easy halogenation. On this basis it can be suggested that dibromoacetonitrile might have brominated malonyl chloride into bromomalonyl chloride, dibromoacetonitrile being itself reduced to bromoacetonitrile. Bromoacetonitrile, thus produced, reacted with the unreacted malonyl chloride producing compound (XXII). In the present investigation it has been found that the reaction of bromomalonyl chloride with the nitriles producing pyrimidine derivatives was very slow in comparison to that of malonyl chloride with nitriles. Therefore, the bromomalonyl chloride

thus formed, had very little chance of reacting with the bromoacetonitrile. Again, it might be assumed that the bromination of malonyl chloride and the reaction of malonyl chloride with bromoacetonitrile took place simultaneously and the rates of these two reactions are comparable. Moreover, it has been found that if the malonyl chloride was taken in excess a better yield of pyrimidine resulted. This suggested that some of the malonyl chloride was being consumed in some side reaction. If this suggestion of bromination of malonyl chloride was correct, then the presence of bromo malonyl chloride in the reaction product should be capable of demonstration. Therefore, it was decided to subject the product to gas liquid chromatography. For this purpose some methanol was added to the reaction product to convert the acid chlorides into their methyl esters. The resulting sample when injected onto a column of 10% carbowax 1000 in the Pye-Argon Chromatograph at 125°, gave a chromatogram showing five peaks. Four of these peaks were sharp but the fifth was a broad. An authentic sample of methyl bromomalonate also gave a broad peak corresponding to the fifth broad peak in the chromatogram of the reaction product. But the shapes of these two broad peaks

were not satisfactory. Usually compounds having electro-negative groups give such trouble in the Pye-Argon Chromatograph. Hence the Flame Ionization Chromatograph was employed using a 10% carbowax 1000 column at 145° . The chromatogram of the reaction product then showed six peaks (four sharp and two broad). Four of these six peaks corresponded to the four sharp peaks of the previous chromatogram. But the fifth broad peak in the chromatogram from the Pye-Argon Chromatograph seemed to split into two broad bands in the chromatogram obtained from the Flame Ionization Chromatograph, Chromatograms of authentic methyl bromomalonate also showed two broad bands. But it was found that the chromatograms with respect to these two broad bands were not consistent. These two broad bands differed in their relative intensities and in relative retention times in different chromatograms taken on the same Flame Ionization Chromatograph under similar conditions. Therefore, it was concluded that methyl bromomalonate was undergoing some chemical changes in the presence of the hydrogen at such a high temperature. Lastly the Gas Density Balance Chromatograph was found to be the best one for this purpose. Again a 10% carbowax 1000 column at 140° was used. The chromatogram of the product showed

five very sharp peaks. All these corresponded in their relative intensities and relative retention times to those of the chromatograms obtained from the Pye-Argon Chromatograph. The chromatograms of authentic methyl bromomalonate showed only one sharp peak which exactly corresponded in its retention time to the fifth peak of the chromatogram of the reaction product. Then a small amount of authentic methyl bromomalonate was mixed with the reaction product. In the chromatogram of this mixture the relative intensity of the fifth peak was almost double that in the original chromatogram in its shape and retention time being unaltered. In the same way two more peaks were also identified. The second peak was due to methyl bromoacetate and the third one to dimethyl malonate. Authentic methyl dibromomalonate was also injected but it decomposed on the column giving a broad band. Thus, gas liquid chromatography proved the presence of bromomalonyl chloride in the reaction product. Therefore, the suggestion that dibromoacetonitrile had brominated the malonyl chloride seemed a sound one.



Reaction of malonyl chloride with dichloroacetonitrile and trichloro acetonitrile:-

The mixture of malonyl chloride and dichloroacetonitrile was kept for several days. A dark red thick syrupy mass was obtained from which no solid material could be isolated.

Similarly no pyrimidine was isolated from trichloroacetonitrile and malonyl chloride.

The reaction of β -chloropropionitrile with malonyl chloride:-

The mixture of β -chloropropionitrile and malonyl chloride when kept at room temperature for five days gave a dirty red crystalline product. This was crystallized from ethanol to give colourless crystals. The nuclear magnetic resonance spectrum of this compound showed a singlet for one aromatic proton, a singlet corresponding to two protons, a quartet for two protons and a triplet corresponding to three protons. The chemical shifts of the quartet and triplet suggested the presence of an ethoxy group. The chemical shift of the singlet corresponding to two protons suggested that it might be a methylene group linked on one side with an aromatic ring and on the other side with an oxygen atom.

In the corresponding pyrimidine derivative which can be expected from this reaction, there must be a side chain of $\text{CH}_2\text{CH}_2\text{Cl}$ which must give two triplets for the two methylene groups, but instead of that the presence of a singlet corresponding to a methylene group suggested that the compound was a pyridine derivative. The empirical formula of this compound was found to be $\text{C}_8\text{H}_{10}\text{ClNO}_3$ which ruled out the possibility of a pyrimidine derivative. Its infrared spectrum resembled in general features those of pyridine derivatives. Thus from its molecular formula and its nuclear magnetic resonance spectrum it was concluded that the primary product from malonyl chloride and β -chloropropionitrile was 2-chloro-3-chloromethyl-4,6-dihydroxy pyridine(XXVII), but that during crystallization it had evidently reacted with ethyl alcohol. The side chain chlorine substituent was thereby replaced by an ethoxy group, to give 2-chloro-3-ethoxy methyl-4,6-dihydroxy pyridine(XXVIII). The reaction of β -chloropropionitrile and malonyl chloride was therefore repeated and this time the product was crystallized from acetone. The nuclear magnetic resonance spectrum of the crystalline product in DMSO showed a singlet for an aromatic proton and a singlet for two protons of a methylene group

indicating that the compound had structure (XXVII). To make sure that in its nuclear magnetic resonance spectrum there were no signals at higher field, the spectrum was also taken in pyridine solution. But surprisingly this spectrum showed only one singlet for an aromatic proton and there was no signal from the protons of a methylene group.

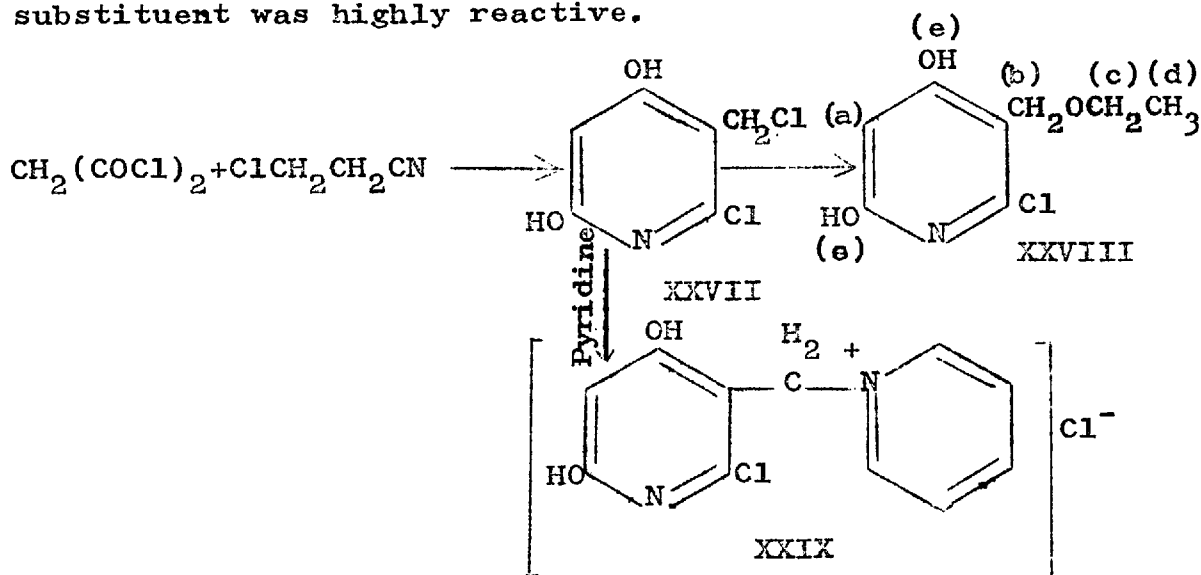
Therefore, with pyridine, salt-formation was suspected.

Pyridine was removed completely under reduced pressure and the solid residue was crystallized from ethanol. The nuclear magnetic resonance spectrum of this compound in DMSO showed the presence of a pyridine ring and a singlet corresponding to one proton. In the pyridine region the integration showed the presence of seven protons. Therefore, it seems that the chemical shift of the two protons of the methylene group being adjacent to a positively charged nitrogen atom, is comparable to that of the pyridine protons. The empirical formula of this compound was found to be

$C_{11}H_{10}Cl_2N_2O_2$. This compound gave a positive test for chloride ion. Therefore, this salt appeared to be

N-(2-chloro-4,6-dihydroxypyridyl-3-methyl)pyridinium chloride (XXIX). An analytically pure sample of compound (XXVII) could not be obtained probably because the side chain chlorine

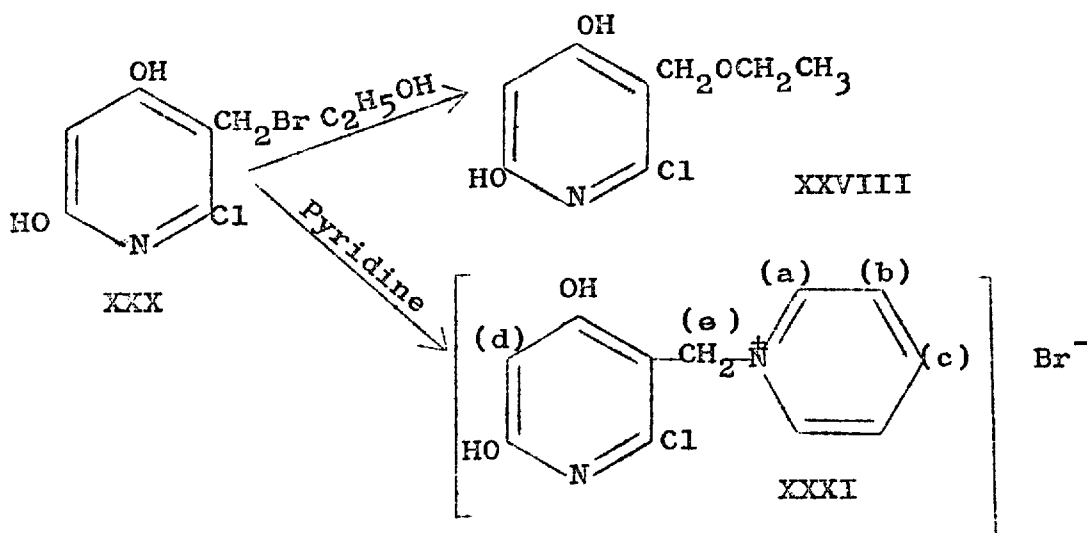
substituent was highly reactive.



The reaction of malonyl chloride with β -bromopropionitrile:-

The product obtained from this reaction was crystallized from acetone. The nuclear magnetic resonance spectrum of this product showed the presence of one aromatic proton and a bromomethylene group. The main features of the infrared spectrum resembled that of compound(XXVII). This compound also reacted with ethanol yielding the same compound (XXVIII) as obtained by the action of ethanol on compound (XXVII). Both the samples of compound (XXVII) gave identical infrared and nuclear magnetic resonance spectra and the mixed melting-point was undepressed. The compound also reacted with pyridine yielding the corresponding pyridinium bromide(XXXI).

The nuclear magnetic resonance spectrum of this pyridinium bromide showed three complex bands for five protons of an unsubstituted pyridine ring. Due to a positive charge on the nitrogen atom the chemical shifts of the protons of the unsubstituted pyridine ring were at very low fields as compared to those of pyridine itself. The spectrum also showed one singlet for the aromatic proton of the substituted pyridine ring and a singlet for two protons of the methylene group at an unusually low field ($\tau = 3.95$). Thus, though the product from β -bromopropionitrile could not be obtained in analytically pure form, the spectroscopic results and the formation of the two derivatives (XXVIII) and (XXXI) were quite strong indications that the compound was 3-bromomethyl-2-chloro-4,6-dihydropyridine (XXX).



In both the reactions of malonyl chloride with β -chloropropionitrile and β -bromopropionitrile the presence of pyrimidine derivatives could not be traced. Therefore, apparently both these reactions produced exclusively pyridine derivatives.

The infrared spectral characteristics of compound (XXX) are given in Table 12.

TABLE 12

* cm^{-1}	Assignment
2800-2000	Chelation and/or associated NH
1640 (s)	C=O stretching
1600 (s)	C=C and C=N vibration
1562 (w)	
1482	
1430	
1220 (s) 1030	Ring vibration and hydrogen deformation
* Nujol mull	
(s)=strong, (w)=weak.	

Nuclear magnetic resonance data for compounds XXII, XXIII, XXVI-XXVIII, XXX and XXXI are given in Table 13.

TABLE 13

Compound	τ	Intensity	Multiplicity	Assignment
XXII	3.46	1	singlet	aromatic H
(in DMSO)	5.63	2	singlet	-CH ₂ -Br
XXIII	-4	1	broad	OH or NH
(in CDCl ₃)	3.61	1	singlet	aromatic H
	7.50	3	singlet	-CH ₃
XXVI	3.5	1	singlet	aromatic H
(in CDCl ₃)	5.08	1	quartet	(b)
			(J=7 c/sec.)	
	7.95	3	doublet	(c)
			(J=7c/sec.)	
XXVII	3.8	1	singlet	aromatic H
(in DMSO)	5.31	2	singlet	-CH ₂ -Cl
XXVIII	-3.57	2	broad	(e)
(in pyridine)	3.47	1	singlet	(a)
	5.13	2	singlet	(b)
	6.32	2	quartet	(c)
			(J=7c/sec.)	
	8.77	3	triplet	(d)
			(J=7c./sec.)	

TABLE 13 (Continued)

Compound		Intensity	Multiplicity	Assignment
XXIX	-3.1	2	singlet	OH or/and NH
(in DMSO)	1-3.0	7	complex	unsubstituted pyridine protons + CH ₂ protons
	3.75	1	singlet	substituted pyridine proton
XXX	3.88	1	singlet	aromatic H
(in DMSO)	5.30	2	singlet	-CH ₂ Br
XXXI	0.75	2	complex	(a)
(in DMSO)	1.27	1	complex	(c)
	1.65	2	complex	(b)
	3.65	1	singlet	(d)
	4.15	2	singlet	(e)

Ultraviolet absorptions of compounds XXII , XXIII, XXVI, XXVII and XXX are given in Table 14.

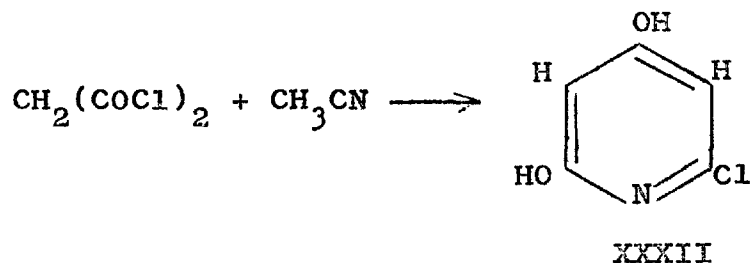
TABLE 14

Compound	λ max. (m μ)	ϵ
XXII	232	5300
(in ethanol)	288	4500
XXIII	226	6300
(in ethanol)	279	5000
XXVI	232	3400
(in ethanol)	288	3000
XVII	244	-
(in dioxan)	268	-
XXX	245	-
(in dioxan)	270	-

CHAPTER 3

The reaction of malonyl chloride with acetonitrile:-

Davis et. al.⁹ had reported that the reaction of malonyl chloride with acetonitrile yielded a compound melting at 233°. They also reported its molecular weight to be 146, the chlorine content as 24.45% and the molecular formula $C_5H_4ClNO_2$. They concluded that this compound was 2-chloro-4,6-dihydroxypyridine(XXXII).

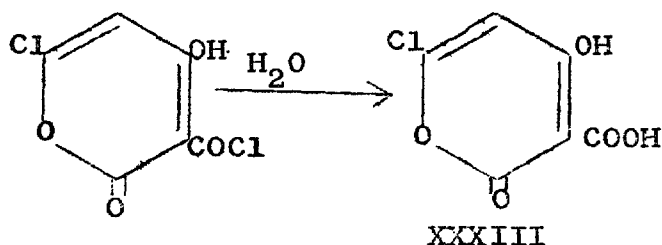


In support of this structure they had mentioned that Schroeder and Finck²⁸ had earlier reported this compound as melting at 233°. No nuclear magnetic resonance spectrum was reported, this work having been completed before the advent of that technique. In the present investigation it was found that some substituted acetonitriles condensed with malonyl chloride to yield pyrimidine derivatives as well as pyridines. Therefore on the basis of these newer results it became possible that the product from acetonitrile and malonyl chloride might be 4-chloro-6-hydroxy-2-methylpyrimidine. This pyrimidine derivative had also been reported in the literature and has been obtained in the present investigation from the reaction of iodoacetonitrile and malonyl chloride. This pyrimidine derivative melts at 233°, its molecular weight is 145 and the percentage of chlorine is 24.5. Consequently it can be concluded that the data about this product given by Davis et al. was insufficient to decide whether the product obtained from this reaction was actually 2-chloro-4,6-dihydroxypyridine as reported or was it 4-chloro-6-hydroxy-2-methylpyrimidine. Therefore, it was decided to reinvestigate the reaction. The mixture of malonyl chloride and acetonitrile yielded, after 3 days, a product which on fractional sublimation gave two compounds melting at 135° and 233° respectively.

The molecular weight of high melting compound was found to be 144 from its mass spectrum which showed the presence of an even number of nitrogen atoms. The relative intensity of the (P+2) peak with respect to the parent peak indicated the presence of one chlorine atom. Its molecular formula calculated from the analytical results and mass spectrum was $C_5H_5ClN_2O$. Its nuclear magnetic resonance spectrum showed one singlet for an aromatic proton and one singlet corresponding to three protons indicating the presence of one methyl group. The infrared spectrum of this compound and that of authentic 4-chloro-6-hydroxy-2-methyl-pyrimidine were exactly the same. The mixed melting point was undepressed. Thus the product obtained from acetonitrile and malonyl chloride appeared to be 4-chloro-6-hydroxy-2-methyl-pyrimidine instead of 2-chloro-4,6-dihydroxy-pyridine.

The empirical formula of the low melting compound was found to be $C_6H_3ClO_5$ and its nuclear magnetic resonance spectrum showed a very broad band at a very low field ($\tau = -4$) and a singlet $\tau = 3.58$ for one proton. The infrared spectrum of this compound showed absorptions for C=O groups. Therefore the compound appeared to be 6-chloro-4-hydroxy-2-oxopyran-3-carboxylic acid(XXXIII). This compound is a known one:

comparison of the observed light absorption spectrum with that reported in the literature (loc. cit.) indicated that the compounds were the same. Evidently, acetonitrile, being a weakly basic compound, induced self condensation of malonyl chloride to the pyrone acid chloride which hydrolysed to the pyrone acid (XXXIII) during work-up. Elvidge, Davis and Foster (loc. cit.) also had reported the isolation of this pyrone acid from the reaction of α -dinitriles with malonyl chloride.



Davis and Elvidge (loc. cit.) had earlier reported that acetonitrile and malonyl chloride at 100° yielded chloropyranooxazines through the formation of the pyrone acid chloride as intermediate. It seems that at room temperature in this reaction the self condensation of malonyl chloride into pyrone acid chloride, and the reaction of malonyl chloride with acetonitrile producing the pyrimidine derivative take place simultaneously. But the second step in the formation of a pyranooxazine either does not take place at all or is

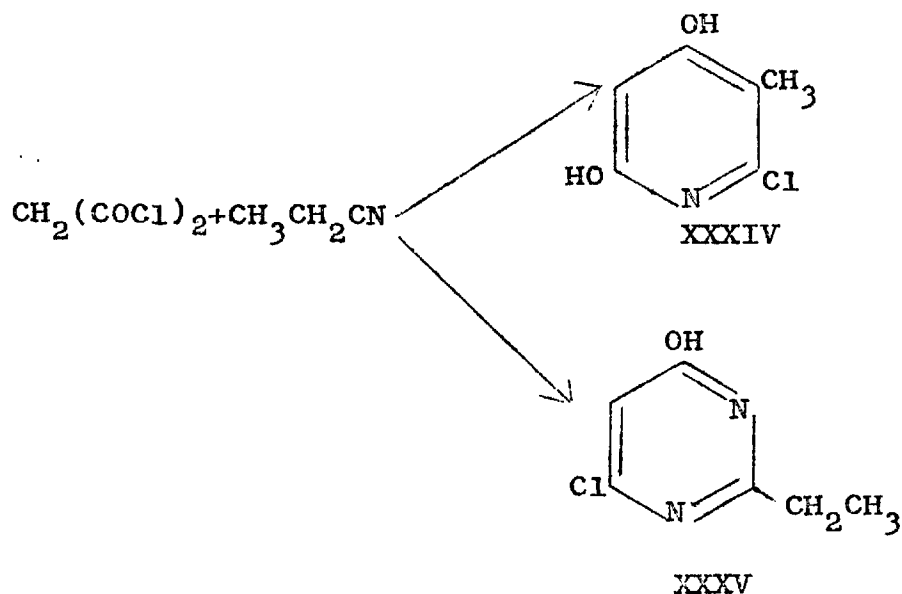
very slow in comparison to the rate of reaction of malonyl chloride with acetonitrile leading to the formation of the pyrimidine derivative.

The reaction between malonyl chloride and propionitrile:-

Davis et. al. (loc. cit.) had reported that propionitrile reacted with malonyl chloride and produced 2-chloro-4,6-dihydroxy-3-methyl pyridine(XXXIV). The structure of this pyridine derivative was proved with the aid of chemical transformations. After getting the pyrimidine derivative from acetonitrile in this investigation it was considered proper to reinvestigate this reaction of propionitrile with malonyl chloride in order to obtain the corresponding pyrimidine derivative, if it was present. The product obtained from this reaction gave a small amount of a sublimate at 140° - 150° /10m.m. The main bulk of the product which remained unsublimed, on crystallization from methanol yielded 2-chloro-4,6-dihydroxy-3-methyl pyridine as reported by Davis et. al. The structure of this pyridine derivative was further confirmed by its mass spectrum and nuclear magnetic resonance spectrum. Its molecular weight from the mass spectrum was 159, confirming the presence of one nitrogen atom. The relative intensity of the (P+2) peak (32%) with respect to the parent peak showed

the presence of one chlorine atom. Its nuclear magnetic resonance spectrum showed a broad band for two OH or NH protons, one singlet for one aromatic proton and a singlet at $\tau=8.07$ corresponding to three protons, showing the presence of a methyl group. Thus its nuclear magnetic resonance and mass spectrum fully supported the reported structure for this compound.

The sublimate crystallized from ethanol as fine colourless crystals. Its molecular weight from the mass spectrum was 158, indicating the presence of an even number of nitrogen atoms. On the basis of its microanalysis and its mass spectrum its molecular formula appeared to be $C_6H_7ClN_2O$. The nuclear magnetic resonance spectrum showed a singlet for an aromatic proton, one quartet corresponding to two protons and one triplet from three protons. The presence of a quartet and a triplet, and their chemical shifts, clearly indicated the presence of an ethyl substituent. The infrared spectrum showed the main absorptions at 1690, 1650, 1590 and 1550 cm^{-1} resembling those of pyrimidine derivatives. Therefore, on the basis of its microanalytical results and spectroscopic studies this compound appeared to be 4-chloro-2-ethyl-6-hydroxypyrimidine(XXXV).



Thus this reaction yielded a mixture of pyridine and pyrimidine derivatives but the main bulk of the product was the previously reported pyridine derivative.

The reaction of butyronitrile with malonylchloride:-

Davis et. al. (loc. cit.) had reported the reaction of γ -chlorobutyronitrile with malonyl chloride yielding 2-chloro-3-2'-chloroethyl-4,6-dihydroxypyridine, but the reaction with the unsubstituted butyronitrile was not examined by these workers. Therefore, to complete this series the reaction of malonyl chloride with butyronitrile was investigated. The product obtained from this reaction

appeared to be a mixture of at least two compounds. By repeated fractional crystallization from ethanol two compounds were isolated, one of them (in a small quantity) was low melting (171°) and the other which constituted the main bulk of the product, was high melting ($>300^{\circ}$). The composition of the low melting compound appeared to be $C_6H_9ClN_2O$ and the composition of the high melting compound was calculated as $C_7H_8ClNO_2$.

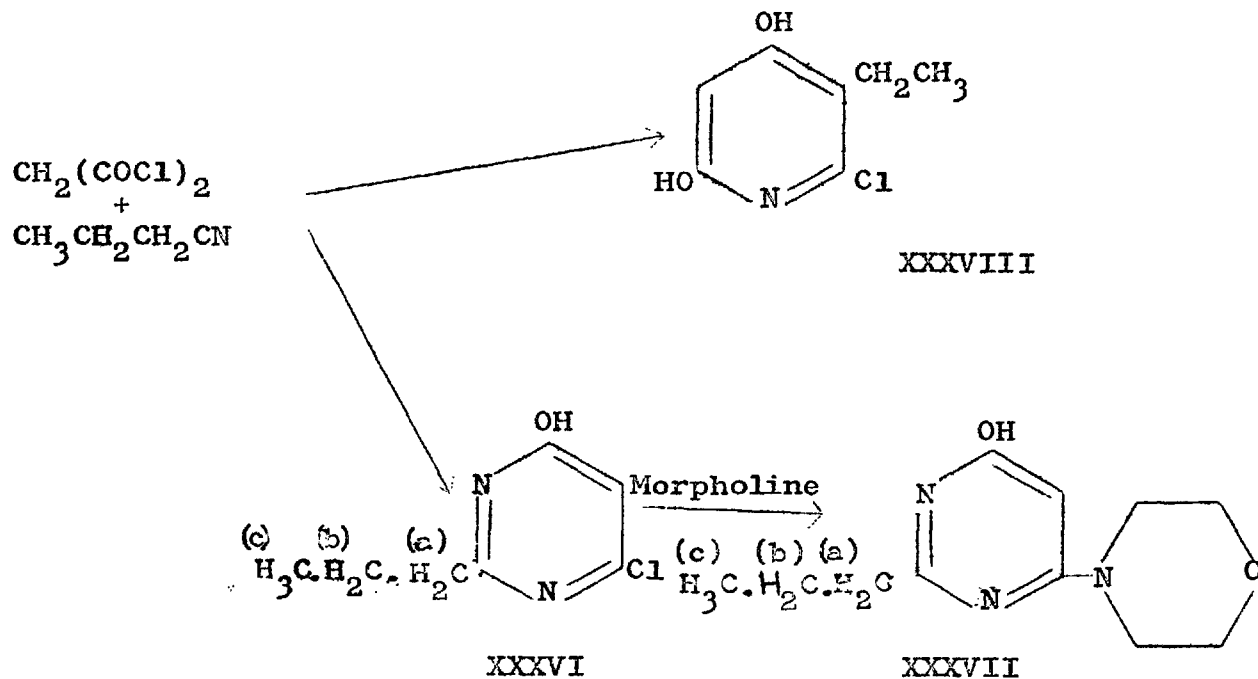
Compound $C_7H_9ClN_2O$:-

The nuclear magnetic resonance spectrum of this compound showed a very broad band for one OH or NH proton, a singlet for an aromatic proton, a triplet corresponding to two protons, a sextet equivalent to two protons and one triplet for three protons. The splitting and the chemical shifts of the last three signals showed the presence of a n propyl substituent. The aromatic nature of the compound was also indicated from its infrared and ultraviolet spectra. This compound was quite stable towards alcohols and water which excluded the possibility of a bicyclic pyrano oxazine structure. Thus, this compound appeared to be 4-chloro-6-hydroxy-2-propylpyrimidine(XXXVI). In order further to establish the structure of this compound it was treated with

morpholine which yielded 6-hydroxy-4-morpholine-2-propyl-Pyrimidine (XXVII), established by spectroscopic studies.

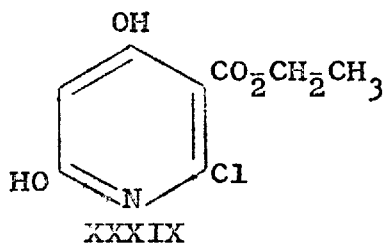
Compound $C_7H_8ClNO_2$:-

Its nuclear magnetic resonance spectrum showed the presence of two protons of OH and/or NH groups and one aromatic proton. In addition to these two signals there was one quartet and one triplet corresponding to two and three protons respectively showing the presence of an ethyl group. The infrared spectrum of this compound resembled those of pyridine derivatives. Thus the compound appeared to be 2-chloro-3-ethyl-4,6-dihydroxypyridine (XXXVIII).



The reaction of malonyl chloride with ethylcyano-acetate:-

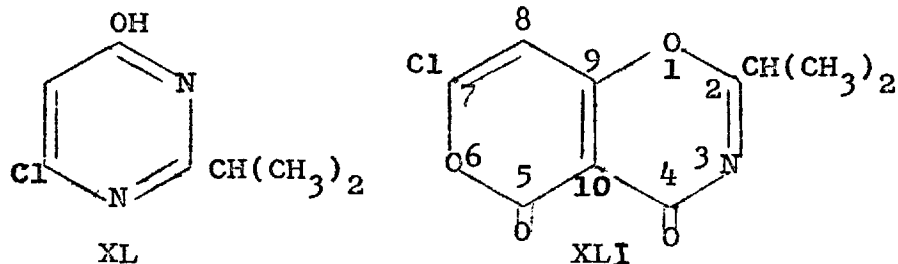
This reaction has also been reported by Davis et. al. (loc. cit.) to yield 2-chloro-3-ethoxy carbonyl-4,6-dihydroxy pyridine(XXXIX). The structure of this compound had been confirmed by its chemical transformation. This reaction was also reinvestigated and a search made for the corresponding pyrimidine derivative. The product on crystallization yielded a single compound (m.p.219^o) which was found to be the same pyridine derivative as reported by Davis et. al. However, this structure was further confirmed by its nuclear magnetic resonance spectrum (Table 16), not reported earlier.



The reaction of malonyl chloride with isobutyronitrile:-

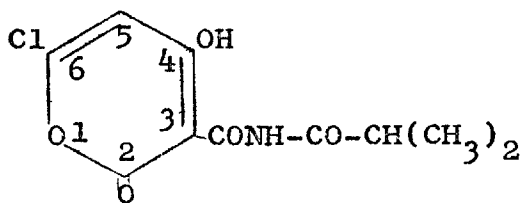
The mixture of isobutyronitrile and malonyl chloride when kept at room temperature did not produce any solid product during several days, but on heating the mixture at 60^o it yielded a very dirty solid. On repeated crystallization from ethyl acetate this afforded fine light yellow needles.

The nuclear magnetic resonance spectrum (in DMSO) showed a singlet for an aromatic proton and a doublet corresponding to six protons. This doublet is obviously due to the two methyl groups of an isopropyl substituent. The signal due to the single proton of the substituent could not be observed because of the strong signal from the solvent and the side bands. There were two possible products from this reaction, either a pyrimidine derivative(XL) or the pyrano oxazine(XLI).



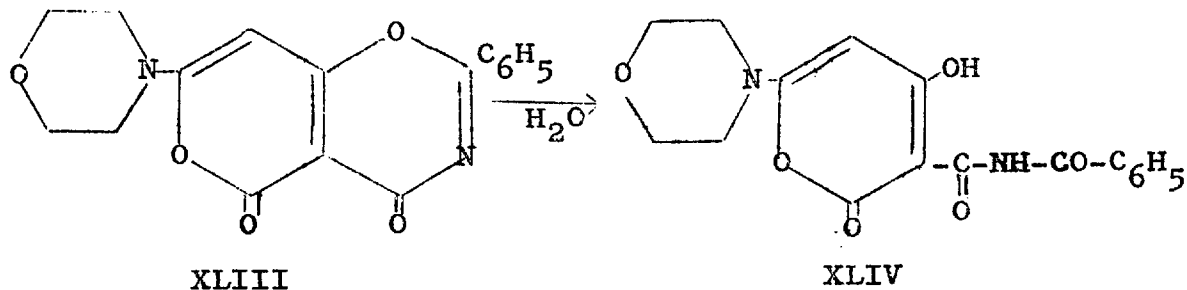
However, nuclear magnetic resonance could not distinguish easily between these two structures. The infrared spectrum showed bands at 3300, 1715 cm.⁻¹ The ultra violet light spectrum showed maximum absorptions at 225, 278 and 333 mμ. In their infrared spectra, hydroxy pyrimidines usually show absorptions at about 1680 cm.⁻¹ for carbonyl stretching and in the ultra violet absorb at about 280 mμ. Thus, the light absorption spectra of this compound did not favour the pyrimidine structure. Davis and Elvidge (loc. cit.) had

found that in the infrared pyranooxazines showed absorptions at about $1770-1780\text{ cm}^{-1}$. Therefore, on this basis structure (XLI) was ruled out. Moreover, from the microanalysis, the empirical formula was calculated to be $\text{C}_{10}\text{H}_{10}\text{ClNO}_5$ which did not fit with either of these two structures (XL) and (XLI). Therefore, it was concluded that most probably the original product of the reaction was 2-isopropyl-7-chloro-4,5-dioxopyrano-oxazine(XLI) and that atmospheric moisture or moisture in the solvent had hydrolysed the oxopyranooxazine at the 1,9-bond yielding 3-isopropylamido-carbonyl-4-hydroxy-6-chloro-2-oxopyran(XLII)



XLII.

Davis and Elvidge (loc. cit.) had reported such a hydrolysis of 7-morpholino-2-phenyl-oxopyrano-oxazine(XLIII) into 3-benzamidocarbonyl-hydroxy-6-morpholino-2-oxopyran(XLIV)



Infrared absorptions of compound (XLII) shown in Table 15 and its ultraviolet light absorptions are comparable to those of compound (XLI V) reported by Davis and Elvidge (loc. cit.).

TABLE 15

* cm^{-1}	Assignment
3300 Sharp	Bonded N-H
2800-2400	Bonded O-H
1720 (s)	C=O (2,hydrogen bonded)
1690 (s)	C=O (attached to isopropyl group)
1640 (sh)	C=O (at 3-position, bonded
1590 (s)	C=C
1540 (sh.)	
1525	

* Nujol mull. s=strong, sh=shoulder.

The nuclear magnetic resonance results for some compounds are given in Table 16.

TABLE 16

Compound (solvent)		Intensity	Multiplicity	Assignment
XXXIV (DMSO)	-0.8	2	broad	OH and NH
	4.0	1	singlet	aromatic H
	8.07	3	singlet	-CH ₃
XXXV (CDCl ₃)	3.60	1	singlet	aromatic H
	7.26	2	quartet (J=6.8 c/sec.)	-CH ₂ -
	8.66	3	triplet (J=6.8 c/sec.)	-CH ₃
XXXVI (pyridine)	-1.5	1	broad	OH or NH
	3.41	1	singlet	aromatic H
	7.33	2	triplet (J=7.6 c/sec.)	(a)
	8.25	2	sextet (J=7.6 c/sec.)	(b)
	9.14	3	triplet (J=7.6 c/sec.)	(c)
XXXVII (CDCl ₃)	-3.25	1	broad	OH or NH
	4.65	1	singlet	aromatic H
	6.35	8	complex	morpholine ring protons.
	7.37	2	triplet (J=7.6 c/sec.)	(a)
	8.20	2	sextet (J=7.6 c/sec.)	(b)
	9.05	3	triplet (J=7.6 c/sec.)	(c)

TABLE 16 (Continued)

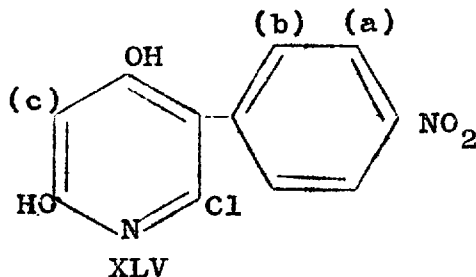
Compound (solvent)	τ	Intensity	Multiplicity	Assignment
XXXVIII (pyridine)	-2	2	broad	OH or/and NH
	3.50	1	singlet	aromatic H
	7.06	2	quartet (J=7.6 c/sec.)	-CH ₂ -
	8.70	3	triplet (J=7.6 c/sec)	-CH ₃
XXXIX (DMSO)	-1.5	2	broad	OH
	3.51	1	singlet	aromatic H
	5.64	2	quartet (J=7.6 c/sec.)	-CH ₂ -
	8.71	3	triplet (J=7.6c/sec.)	-CH ₃
XLII (DMSO)	3.70	1	singlet	-CH=
	8.95	6	doublet (J=7.3 c/sec.)	(CH ₃) ₂

CHAPTER 4

Reaction between malonyl chloride and p-nitrobenzyl cyanide:-

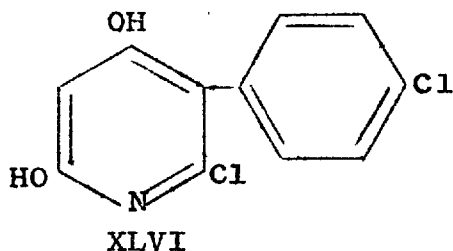
Earlier, the reaction of malonyl chloride with benzyl cyanide had been reported by Davis et. al. (loc. cit.) to yield 2-chloro-4,6-dihydroxy-3-phenyl pyridine. It was thought proper to study the effect of electron withdrawing and electron donating substituent in the benzene ring on the nature of the products of these reactions. For this purpose the reaction of p-nitrobenzyl cyanide was first examined. Since p-nitrobenzyl cyanide was insoluble in cold malonyl chloride, the mixture of the two was heated at 60°. The product, on crystallization, yielded bright yellow needles. Its molecular weight was found to be 266 from its mass spectrum. The molecular formula of this compound appeared to be $C_{11}H_7ClN_2O_4$. The nuclear magnetic resonance spectrum of this compound showed a broad band for two protons of OH and/or NH groups, two doublets for four protons of a para disubstituted benzene ring and a singlet for one β -proton of a pyridine nucleus. The infrared and ultraviolet spectra resembled those of

pyridine derivatives. Therefore, this compound appeared to be 2-chloro-4,6-dihydroxy-3-(p-nitrophenyl)-pyridine(XLV).



Reaction between malonyl chloride and p-chloro benzyl cyanide:

The reaction product afforded a colourless crystalline compound which from the microanalysis had the composition $C_{11}H_7Cl_2NO_2$. Its nuclear magnetic resonance spectrum showed a broad signal for two protons of OH and/or NH groups, a complex band for four protons of a benzene ring and one singlet for the β -proton of a pyridine ring. The structure of this compound therefore appeared to be 2-chloro-3-(p-chlorophenyl)-4,6-dihydroxy pyridine(XLVI).

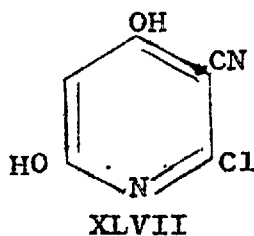


In both these reactions of substituted benzyl cyanides with malonyl chloride the corresponding pyrimidine derivatives could not be detected. Thus both these nitriles appeared to produce only the pyridine derivatives like benzyl cyanide. Thus it seemed that the presence of substituents did not play any obvious part in directing the course of the reaction with malonyl chloride.

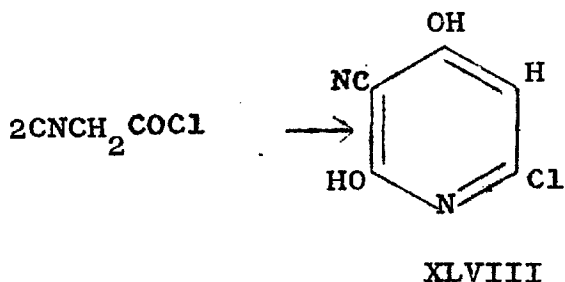
The reaction of malonyl chloride with malanonitrile:-

Davis et. al. (loc.cit.) had studied the reaction of malonyl chloride with succino- and glutaronitriles. They could not find any pyridine derivative from these two reactions but they isolated the pyrone acid(XXXIII). They concluded that these nitriles were sufficiently basic to induce the self condensation of malonylchloride to the pyrone acid chloride, which on hydrolysis gave the pyrone acid. In the present investigation malanonitrile reacted vigorously with malonyl chloride producing a charred product. This was extracted with dioxan to yield a yellow crystalline solid in a very small amount. The product, further purified by

crystallization and sublimation, formed colourless crystals. The same reaction performed at 0° yielded the same product after seven days but in a better yield. The molecular weight of this compound from its mass spectrum was 170, indicating the presence of an even number of nitrogen atoms. The percentage intensity of the (P+2) peak with respect to the parent peak was 33%, which showed the presence of one chlorine atom. As the parent peak in the spectrum was the base peak, it was evident that the compound was aromatic. There was an intense peak (55%) corresponding to mass number 142 which is most probably due to elimination of carbon monoxide, a characteristic of phenols. There was also an intense peak (45%) at 135 which is perhaps due to cleavage of a chlorine atom. The molecular formula of this compound from its microanalysis and mass spectrum was $C_6H_3ClN_2O_2$. Its infrared spectrum showed a strong absorption for a $C\equiv N$ group, and on the whole, the spectrum resembled those of pyridines. The nuclear magnetic resonance spectrum of this compound showed only one singlet for an aromatic proton. Therefore it was concluded to be 2-chloro-3-cyano-4,6-dihydroxy pyridine (XLVII).



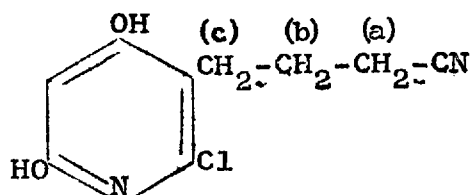
Schroeter and Seidler²⁹ had earlier obtained 2-chloro-5-cyano-4,6-dihydroxy pyridine(XLVIII) from the self condensation of cyanoacetyl chloride, but later it was found ³⁰ that mono-substituted cyanoacetyl chlorides gave different products of higher molecular weights.



This compound (XLVIII) is the positional isomer of (XLVII) obtained from malononitrile and malonyl chloride. Compound (XLVIII) was also prepared by the self condensation of cyanoacetyl chloride for comparison. The infrared spectra of these two compounds were quite different from one another, and the mixed melting point was depressed considerably. The chemical shifts of the aromatic protons in the isomers were different.

The reaction of adiponitrile with malonyl chloride:-

This reaction yielded a dirty black semi solid product which after trituration with acetone was crystallized from methyl alcohol as colourless crystals. Its molecular weight from the mass spectrum was 212, indicating the presence of an even number of nitrogen atoms. The mass spectrum also confirmed the presence of one chlorine atom showing a P+2 peak with 32.4% of the intensity of the parent peak. From its microanalysis and mass spectrum its molecular formula was $C_9H_9ClN_2O_2$. The base peak in its mass spectrum appeared at m/e 158. The infrared spectrum of this compound showed a sharp band for a $C\equiv N$ group, and the absorptions in the region of 6-7 μ showed the aromatic nature of the compound. Its nuclear magnetic resonance spectrum showed one singlet for one aromatic proton, and two triplets and one quintuplet each corresponding to two protons. Thus, the presence of a $-CH_2CH_2CH_2-$ group was established. The ultraviolet light absorption also supported its aromatic nature. Therefore, on the basis of all this information it could be concluded that the compound was 2-chloro-3-3'-cyanopropyl-4,6-dihydroxypyridine XLIX. The presence of the corresponding pyrimidine could not be detected.



XLIX

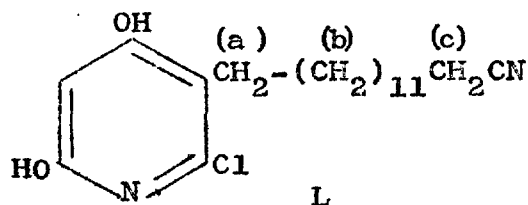
The appearance of the base peak in the mass spectrum, at 158 (m/e), indicated the cleavage at the beta bond to the pyridine ring, giving the fragment $C_6H_5ClNO_2$. This type of cleavage is characteristic of alkyl substituted aromatic compounds.

In the malonyl chloride reaction it could be expected that both the cyanide groups of adiponitrile might take part in the formation of pyridine rings, producing a bis-pyridine compound, but in actual fact this did not happen. The reason might be that the compound (XLIX) is insoluble in malonyl chloride, its separation from the solution preventing further reaction.

Reaction of malonyl chloride with 1,14-dicyano-tetradecane:-

The empirical formula of the compound obtained from this reaction appeared to be $C_{19}H_{29}ClN_2O_2$. The infrared spectrum showed a weak absorption at 2240 cm^{-1} for the $C\equiv N$ group.

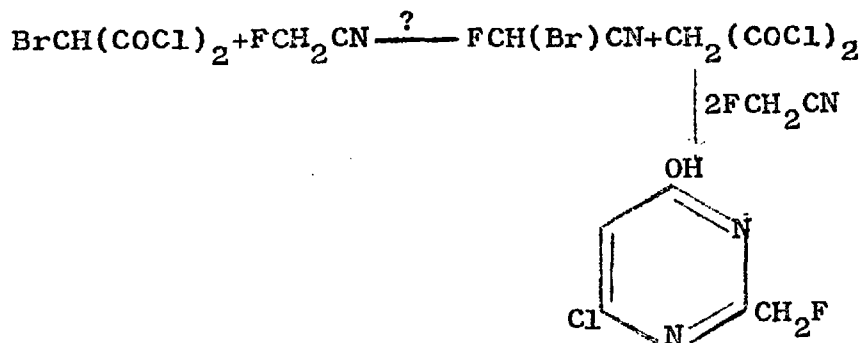
The nuclear magnetic resonance spectrum showed a singlet for one aromatic proton, two triplets for two methylene groups and a complex band for twenty two protons. Its infrared and ultra violet light absorption indicated that the compound was aromatic. Thus, the compound appeared to be 2-chloro-4,6-dihydroxy-3- (13'-cyanotridecanyl)-pyridine(L).



The reaction of bromomalonyl chloride with fluoroacetonitrile:-

Davis, Elvidge and Foster (loc. cit.) had reported that the reaction of bromomalonyl chloride with cyanoethyl acetate produced 5-bromo-2-chloro-3-ethoxycarbonyl-4,6-dihydroxy-pyridine. They had also reported the failure of the reaction of methyl malonyl chloride with propionitrile. In the present investigation bromomalonyl chloride with fluoroacetonitrile produced a dark red gelatinous mass. This product on crystallization yielded fine leaflets (m.p. 193°). The molecular weight from its mass spectrum was found to be 162. The relative intensity of the (P+2) peak with respect to the parent peak was 32% showing the presence of one chlorine atom and the absence of bromine atoms. Its nuclear magnetic

resonance spectrum showed one singlet for one aromatic proton and one wide doublet for two protons indicative of the presence of a $-\text{CH}_2\text{F}$ group. The infrared spectrum was found to be identical with that of 4-chloro-2-fluoromethyl-6-hydroxy pyrimidine obtained from the reaction of malonyl chloride and fluoroacetonitrile. The melting point of a mixture was undepressed. Therefore, it was concluded that the product from this reaction was 4-chloro-2-fluoromethyl-6-hydroxy-pyrimidine instead of the expected 5-bromo derivative of this compound. The formation of the solid product in this reaction was slower than in the reaction of malonyl chloride with fluoroacetonitrile but it is very difficult to give the exact reason for the formation of unbrominated product. However, it can be suggested that bromomalonyl chloride might have brominated the fluoroacetonitrile to bromo-fluoroacetonitrile and it was itself reduced to malonyl chloride. The malonyl chloride thus produced reacted with the unbrominated fluoroacetonitrile producing the unbrominated pyrimidine. The only observation which could support this suggestion to some extent was that a higher proportion of fluoroacetonitrile increased the yield of the product.

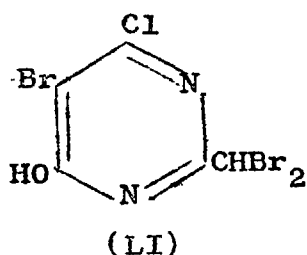


The reaction of bromomalonyl chloride with dibromoacetonitrile:

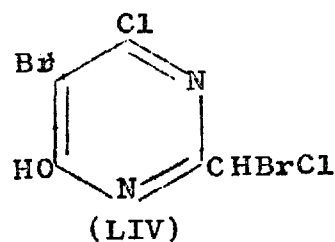
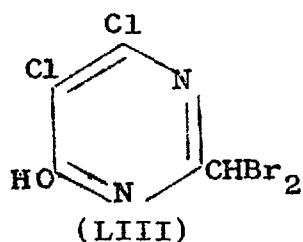
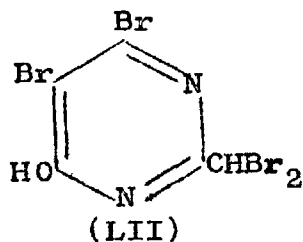
A mixture of bromomalonyl chloride and dibromoacetonitrile after about two months produced a black gelatinous mass, trituration of which with acetone yielded colourless crystals. The mass spectrum gave its molecular weight as 378, showing an even number of nitrogen atoms. There were five intense peaks at m/e 378, 380, 382, 384 and 386 corresponding to (P), (P+2), (P+4), (P+6) and (P+8) respectively. The percentage intensities of the (P+2), (P+4), (P+6) and (P+8) peaks with respect to the parent peak were 310, 400, 190, and 32% respectively. These relative intensities were very close to those calculated for a compound containing three bromine atoms and one chlorine atom. In addition to these five intense peaks there was also a series of five less intense peaks at mass numbers 422, 424, 426, 428, and 430. The relative intensities of these five peaks (1:4:5.5:3.4:.8 respectively), showed the presence of four bromine atoms in

the ion responsible for these peaks. There was also a series of four peaks at mass number 343, 345, 347, and 349, and their relative intensities (1:2.85:2.82:0.90 respectively) suggested the presence of three bromine atoms in this ion. This ion could be derived by loss of either one chlorine atom from the molecule of mass number 378 or one bromine atom from a molecule of mass number 422. Again there ~~were~~ four peaks at mass numbers 334, 336, 338 and 340 in the ratio of 1:2.4:2.2:0.8 respectively. The relative intensities of these peaks suggested the presence of two chlorine atoms and two bromine atoms in the particular ion. There was also a series of four intense peaks at mass numbers 299, 301, 303, and 305 in the ratio of 1:2.17:1.52:0.32 respectively. These relative intensities were very close to those calculated for (P), (P+2), (P+4) and (P+6) peaks of an ion containing one chlorine atom and two bromine atoms. Such an ion was obviously produced by the removal of one bromine atom from the molecule of mass number 378 and/or by the removal of one chlorine atom from the molecule of mass number 334. From the microanalysis and molecular weight (378) the molecular formula of the compound appeared to be $C_5H_2Br_3ClN_2O$. Its nuclear magnetic resonance spectrum showed one singlet ($\tau=3.63$)

and nothing at higher field. The chemical shift of this singlet suggested that it might be due to a proton attached to carbon bonded to two bromine atoms and one aromatic ring. Its infrared and ultra violet light absorptions supported its aromatic nature. Therefore, this compound appeared to be 5-bromo-2-dibromomethyl-4-chloro-6-hydroxy-pyrimidine (LI).



The appearance of the series of five peaks in the region of mass number 422 may be due to traces of 4,5-dibromo-2-dibromomethyl-6-hydroxy pyrimidine (LII). This might have been formed due to some exchange of chlorine of malonyl chloride with bromine. Similarly the four peaks starting with mass number 334 may be due to traces of 4,5-dichloro-2-dibromomethyl-6-hydroxy pyrimidine (LIII) or its isomer (LIV). These compounds might also be formed by mutual halogen exchange at some stage in the reactions



The reaction of chloromalonyl chloride with fluoroacetonitrile:-

After five days the reaction afforded a product as colourless crystals. From its mass spectrum its molecular weight was found to be 196 indicating the presence of an even number of nitrogen atoms. The parent peak was the base peak, showing the aromatic nature of the compound. The relative intensities of the (P+2) and (P+4) peaks with respect to the parent peak were 64.1 and 10.3% respectively, indicating the presence of two chlorine atoms in the compound. The molecular formula of the compound was $C_5H_3Cl_2FN_2O$. Its nuclear magnetic resonance spectrum showed one doublet ($\tau = 4.65$) with a coupling constant of 46 c/sec. showing the presence of a $-CH_2F$ group. Thus its nuclear magnetic resonance spectrum showed the absence of any free aromatic proton. In its infrared spectrum the main absorptions (Table 17) resembled those of 4-chloro-2-fluoromethyl-6-hydroxy-pyrimidine. Similarly its ultraviolet absorption also indicated the aromatic nature of the compound. Therefore, the compound appeared to be 4,5-dichloro-2-fluoromethyl-6-hydroxy-pyrimidine (LV).

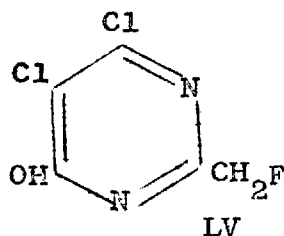


TABLE 17

* cm^{-1}	Assignment
2800-2200 (broad)	Chelation
1680 (s)	C=O
1660 (s)	C=N
1585 (s)	ring stretching
1550 (s)	
1445 (s)	CH_2 deformation
1310	skeletal vibration
1010	tetrasubstituted pyrimidine ring vibration

* Nujol mull s = strong.

The reaction of chloromalonyl chloride with
chloroacetonitrile:-

The reaction product on repeated crystallization yielded a colourless crystalline compound with molecular formula $\text{C}_5\text{H}_3\text{Cl}_3\text{N}_2\text{O}$. The nuclear magnetic resonance spectrum of this compound showed one singlet corresponding to methylene protons. The infrared spectrum was identical with that of 4,5-dichloro-2-chloromethyl-6-hydroxy pyrimidine obtained by the chlorination of 4-chloro-2-chloromethyl-6-hydroxy pyrimidine. The melting point of a mixture was also undepressed.

Thus the compound obtained from chloromalonyl chloride and chloroacetonitrile was 4,5-dichloro-2-chloromethyl-6-hydroxy-pyrimidine. The purification of this compound was achieved with some difficulty by repeated crystallization, and so this may be due to the presence of some corresponding pyridine derivative (2,3,5-trichloro-4,6-dihydroxy-pyridine) in the reaction product. However, this pyridine derivative could not be isolated.

Thus, halogenomalonyl chlorides also condensed with some nitriles yielding fully substituted pyrimidines, but these reactions were slower than those of unsubstituted malonyl chloride with nitriles.

The proton magnetic resonance measurements of compounds (XLV) to (L) are given in Table 18.

TABLE 18

Compound (Solvent)	τ	Intensity	Multiplicity	Assignment
(XLV)	-1.1	2	broad	OH and/or NH
(DMSO)	1.74	2	doublet (J=8.9 c/sec.)	(a)
	2.43	2	doublet (J=8.9 c/sec.)	(b)
	3.81	1	singlet	(c)
(XLVI)	-0.9	2	broad	OH and/or NH
(DMSO)	2.66	4	multiplet	benzene-protons
	3.85	1	singlet	pyridine-proton

TABLE 18 (Continued)

Compound	τ	Intensity	Multiplicity	Assignment
(XLVII) (DMSO)	3.86	1	singlet	aromatic H
(XLVIII) (DMSO)	3.66	1	singlet	aromatic H
(XLIX)	3.11	1	singlet	aromatic H
(trifluoro acetic acid)	6.92	2	triplet (J=7.5 c/sec.)	(c)
	7.32	2	triplet (J=7.4 c/sec.)	(a)
	7.85	2	quintuplet	(b)
(L) (pyridine)	3.45	1	singlet	aromatic H
	7.01	2	triplet (J=7.5 c/sec.)	(a)
	~7.8	2	triplet	(c)
	~8.75	22	multiplet	(b)

Ultra violet light absorptions of compounds (XLV) to (XLVII), (XLIX) and (L) are given in Table 19.

TABLE 19

Compound	max. (m μ)	ϵ
(XLV)	273	5200
	293	5300
(XLVI)	239	9700
	293	2000
(XLVII)	248	4100
(XLIX)	230	2700
	276	2100
	287	2100
(L)	230	3200
	280	2800
	290	3000
(LI)	240	5600
	295	5100
(LV)	232	4000
	289	4900
	300	3900

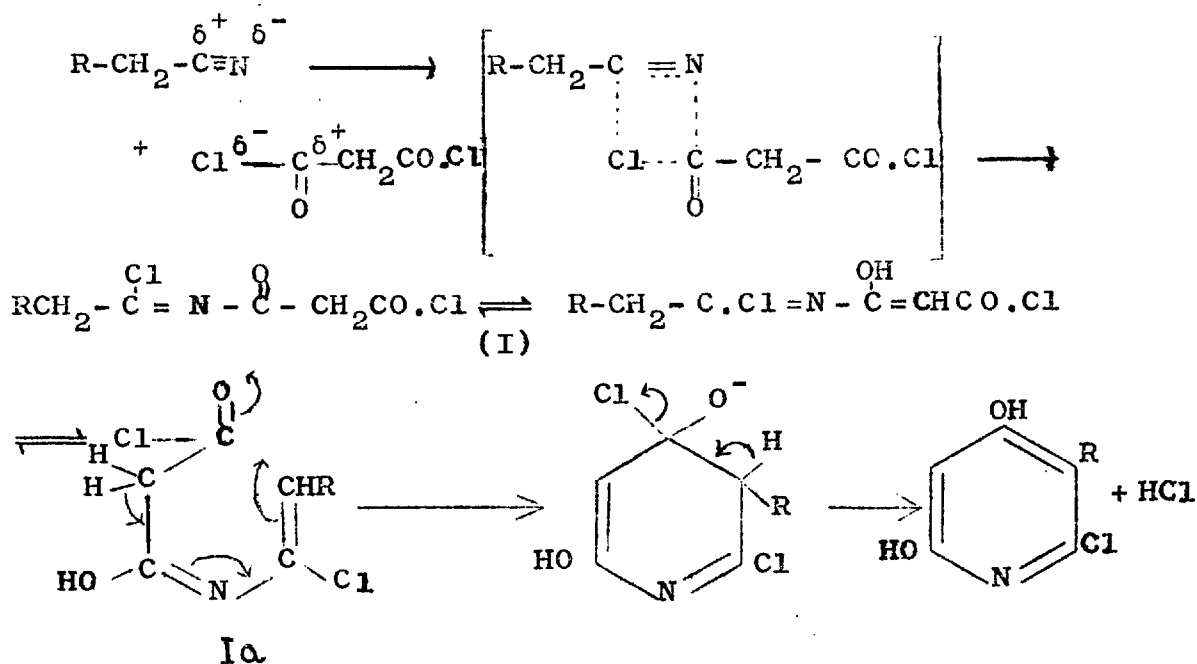
Solvent-ethanol

CHAPTER 5

Mechanism of the formation of pyridines:-

The earlier work by Davis, Elvidge and Foster (loc. cit.) as well as the present investigation revealed that malonyl chloride and some nitriles reacted together in the molar ratio of 1:1 yielding 3-substituted-2-chloro-4,6-dihydroxy pyridines. The α -substituent of the nitrile appeared as a 3-substituent of the pyridine nucleus. This showed that the β -carbon of the pyridine nucleus was the α -carbon of the nitrile. It also followed that the cyanomethylene ($-\text{CH}_2\text{CN}$) group was necessary for the formation of a pyridine nucleus in this reaction. The formation of a fully substituted 5-bromopyridine from bromomalonyl chloride and cyanoethyl acetate showed that C-5 in the pyridine nucleus was C-2 of malonyl chloride. Davis, Elvidge and Foster (loc. cit.) followed the reaction of malonyl chloride and propionitrile spectrophotometrically. It was found that during the first two hours the reaction mixture showed an increasing absorption at about 257 m μ . At the end of this time the evolution of hydrogen chloride was readily detectable and absorption at 269 m μ was observed. This absorption was the characteristic absorption of 2-chloro-3-methyl-4,6-dihydroxy-pyridine. In the final reaction solution there was also an absorption band

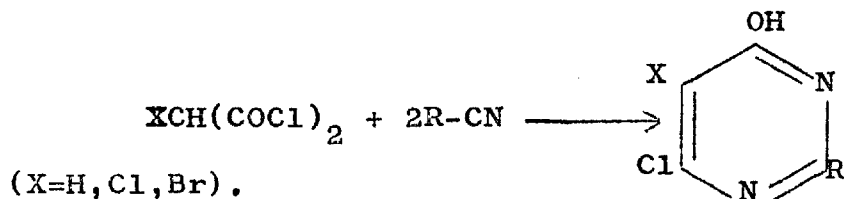
at 305 mμ which was due to the formation of chloro-hydroxy-pyrone acid chloride. This indicated that self condensation of malonyl chloride was occurring as a side reaction. The reaction was also studied in the presence of an excess of bromide ion (lithium bromide) but the reaction still produced the same chloro-hydroxy-pyridine. From these observations they concluded that the formation of pyridine derivatives in these reactions proceeded in two steps. In the first step the nitrogen of the nitrile was acylated by malonyl chloride producing a linear intermediate(I). This intermediate being enolic showed enhanced diene absorption at 257 mμ (cf. sorbic acid). In the second step the cyclization of this intermediate in the tautomeric form (Ia) evidently took place to produce the pyridine derivative with the evolution of hydrogen chloride.



There are two main points in this mechanism. Firstly, the acid chloride must have a powerful electron withdrawing substituent and, secondly, the nitrile must contain a cyanomethylene group. In the present investigation the experiments with labelled malonyl chloride (to be discussed later) confirmed that all the three carbon atoms of malonyl chloride appear in the nucleus of the pyrimidine product.

Proposed mechanism of the formation of pyrimidines.

It was found that malonyl chloride or a substituted malonyl chloride reacted with some nitriles in the molar ratio of 1:2 to produce chloro-hydroxy-pyrimidines:-

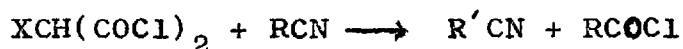


The formation of pyrimidines from the reactions of α -bromopropionitrile and dibromoacetonitrile with malonyl chloride and bromomalonyl chloride severally showed that the presence of a cyanomethylene group in one reactant was not essential. The appearance of the substituent of a substituted malonyl chloride at C-5 of pyrimidine showed that this carbon atom in the pyrimidine ring is C-2 of malonyl chloride.

Similarly, the appearance of R at C - 2 of the pyrimidine suggested that this carbon is that of the cyanide group.

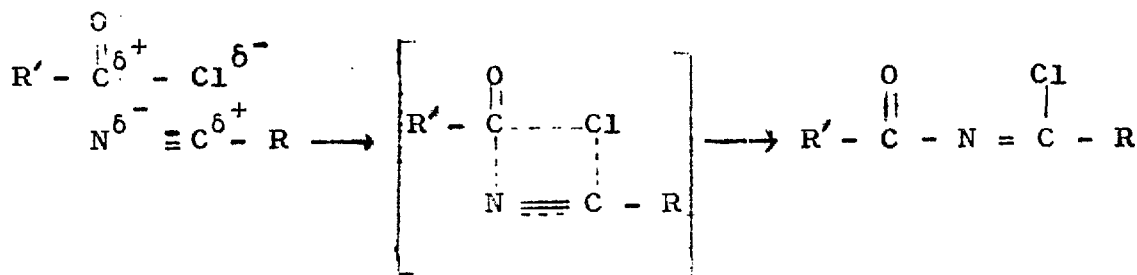
A few chloro pyrimidines have been reported from cyclisation effected with phosphorus halides, but in these the introduction of the halogen is a secondary process resulting from the replacement of enolic oxygen. Therefore, it was thought that in the reaction of malonyl chloride and nitriles the primary product might be 2-substituted-4,6-dihydroxy-pyrimidine. This dihydroxy pyrimidine might have reacted with malonyl chloride with the result of replacement of one enolic oxygen of dihydroxy pyrimidine by chlorine producing the corresponding 4-chloro-6-hydroxypyrimidine. Therefore, an authentic sample of 4,6 dihydroxy-2-methyl-pyrimidine was mixed with the excess of malonyl chloride. After several days the starting dihydroxy pyrimidine was recovered from the reaction mixture and no corresponding chloro-hydroxypyrimidine could be obtained. Thus, unlike phosphorus halide, malonyl chloride has no action upon dihydroxy pyrimidine. So the chlorine substituent in the malonyl chloride products is a direct result of the new ring-synthesis.

At first the following mechanism was proposed. In the first stage the malonyl chloride was supposed to react with one molecule of the nitrile producing cyanoacetyl chloride or a substituted cyanoacetyl chloride as the case might be:-



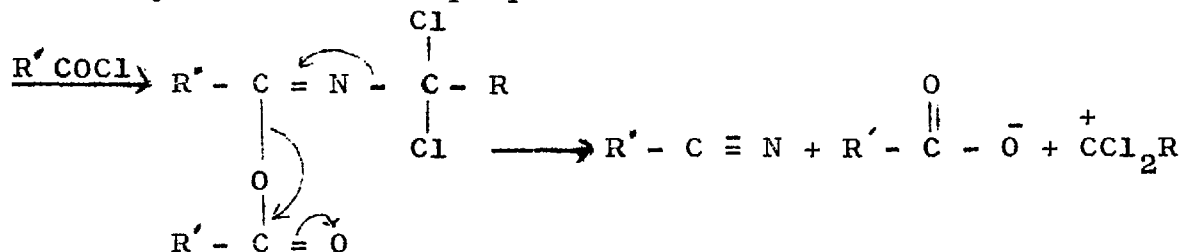
The following detailed mechanism can be suggested for this:

1 (a) N-acylation of the nitrile

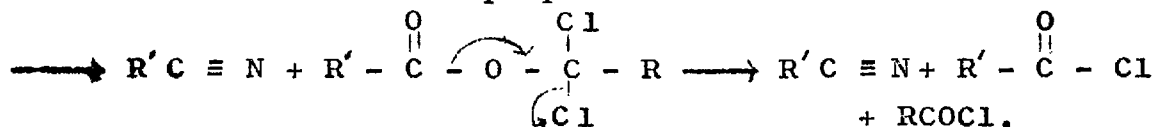


(b)

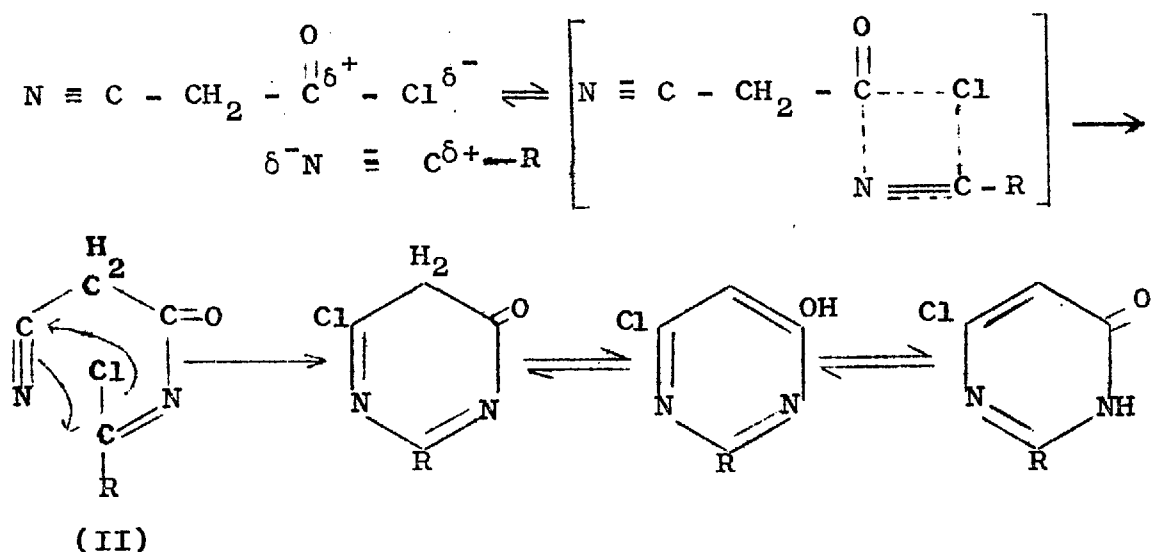
O-acylation and disproportionation



(c) Recombination and disproportionation



In the second stage it was proposed that N-acylation of the nitrile was effected by the cyanoacetyl chloride to give the linear intermediate(II). In the third stage the latter cyclizes to produce the pyrimidine derivative.



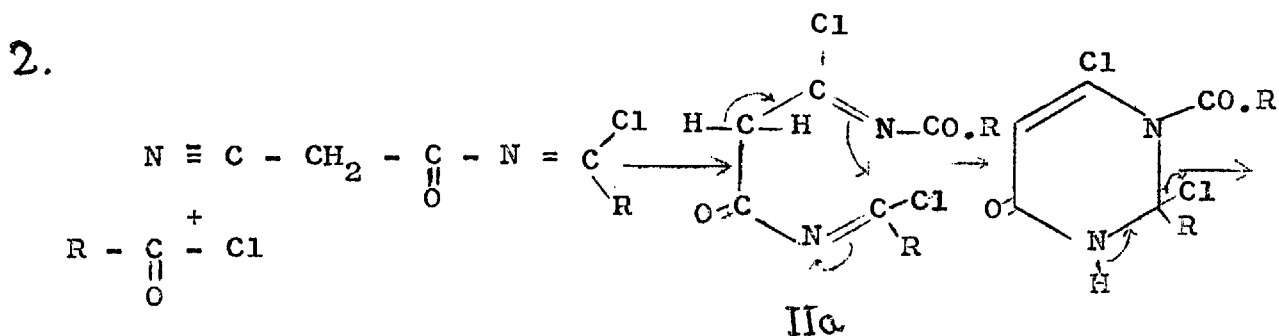
According to the above proposals there must be RCOCl present also in the reaction products. To establish the presence of chloroacetyl chloride, the nuclear magnetic resonance spectrum (in CDCl_3) of a crude filtrate of the reaction product of chloroacetonitrile and malonyl chloride was obtained. In this spectrum there were two distinct signals at 5.41τ and 5.82τ . The chemical shifts of the methylene protons of malonyl chloride, chloroacetonitrile and chloroacetyl chloride (in CDCl_3) were found to be

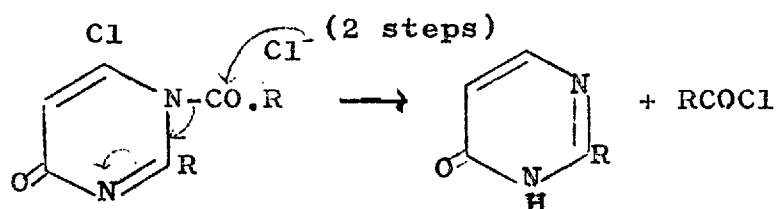
5.60 τ , 5.85 τ and 5.40 τ respectively. Therefore, the two bands in the spectrum of the filtrate closely corresponded to chloroacetyl chloride and some unreacted chloroacetonitrile. To check if there was any change of chemical shifts of chloroacetyl chloride and chloroacetonitrile in the presence of each other, the spectrum was run for a mixture of both these compounds in CDCl_3 , but no change was found in the chemical shifts. Thus, this spectrographic study indicated the presence of chloroacetyl chloride in the reaction products. To prove chemically, the presence of chloroacetyl chloride, the filtrate of the reaction product was treated with aniline. Thus chloroacetanilide was obtained. Chloroacetanilide was also prepared from an authentic sample of chloroacetyl chloride. The infrared and nuclear magnetic resonance spectra of these two samples were exactly the same and the melting point of a mixture was undepressed. Thus, the presence of chloroacetyl chloride among the reaction products was established. Moreover, in the reaction products of dibromoacetonitrile and malonyl chloride the presence of bromoacetyl chloride was established with the help of gas liquid chromatography (discussed in Chapter 2.). It must be noted here that Schroeter and Seidler (loc. cit.) had reported

the self condensation of cyanoacetyl chloride to produce 2-chloro-5-cyano-4,6-dihydroxy-pyridine. But it was thought that in the reaction of malonyl chloride with nitriles the rate of reaction of cyanoacetyl chloride (if indeed it was formed) might be more rapid than the self condensation of cyanoacetyl chloride.

If the above proposed mechanism was correct, preformed cyanoacetyl chloride should also react with nitriles to produce pyrimidines. Therefore, authentic cyanoacetyl chloride was prepared and mixed with fluoroacetonitrile. The reaction mixture did not produce any solid product on keeping for several days. Similarly a mixture of cyanoacetyl chloride and chloroacetonitrile did not yield any pyrimidine derivative. Therefore, the above proposed mechanism was not a likely one.

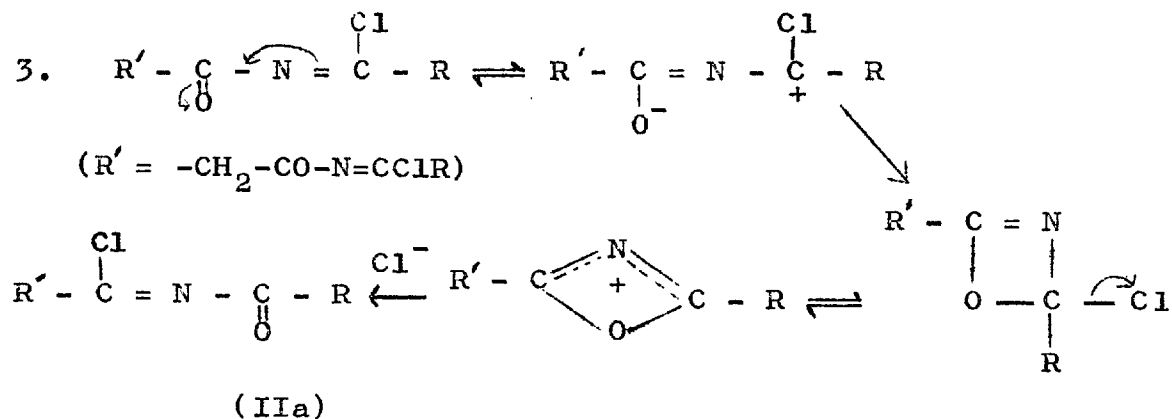
Then it was considered that the nitrogen of the cyanide group of (II) might be acylated by RCOCl produced in the reaction forming the intermediate (IIa). The intermediate (IIa) could then cyclize into a pyrimidine in the following way:



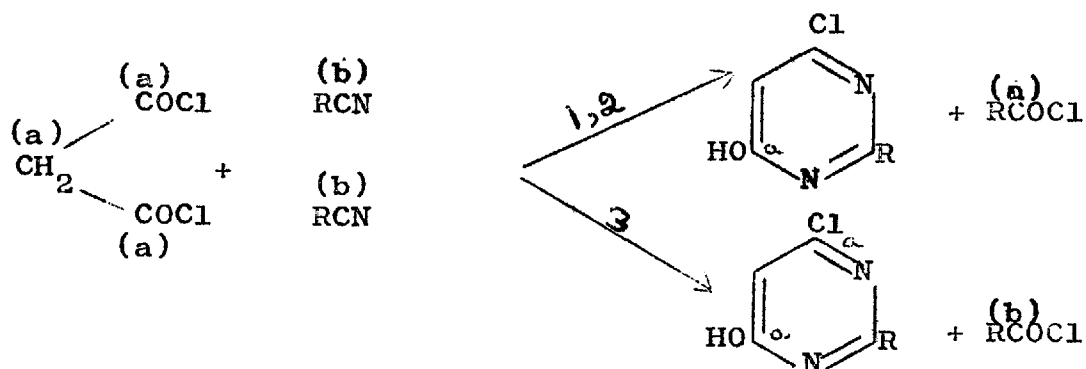


According to this mechanism a mixture of RCN, cyanoacetyl chloride and RCOCl should produce the corresponding pyrimidine derivative. Therefore, preformed cyanoacetyl chloride was mixed with fluoroacetyl chloride and fluoroacetonitrile, but the reaction did not produce any pyrimidine derivative. Similarly a mixture of chloroacetyl chloride, cyanoacetyl chloride and chloroacetonitrile did not yield any pyrimidine.

However, it appeared that formation of intermediate (IIa) could also be achieved through a rearrangement, e.g. via a four-membered ring, without involving the formation of cyanoacetyl chloride.



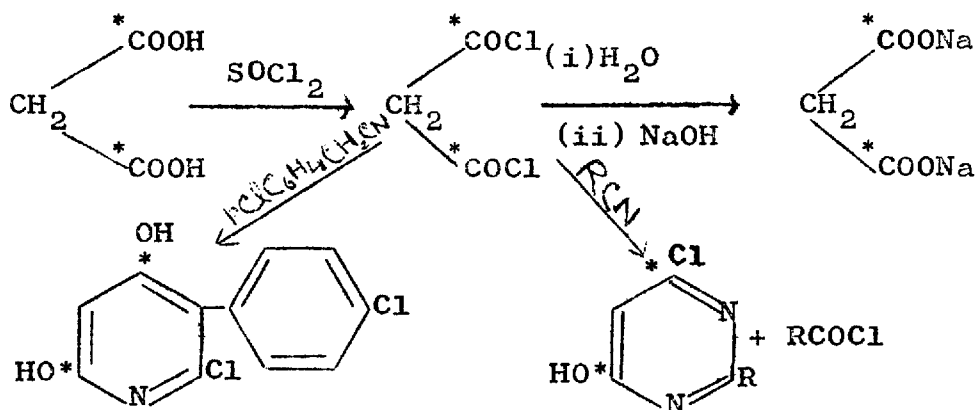
The intermediate (IIa) then could be cyclized into a pyrimidine ring as previously indicated in mechanism 2. There are two important points to note in this third mechanism. Firstly it does not involve the intermediate cyanoacetyl chloride and the second point is that all the three carbon atoms of malonyl chloride appear in the nucleus of the pyrimidine whilst in the first two mechanisms only two carbon atoms of malonyl chloride appear in the nucleus of the pyrimidine. Similarly in the first two mechanisms the carbonyl chloride group of RCOCl is the carbonyl chloride of malonyl chloride, but in the third mechanism the carbon of the carbonyl chloride group of RCOCl is the carbon of the original cyanide group of nitrile. Thus these two types of mechanisms can be represented as follows:-



Therefore, to distinguish between these possibilities it was decided to start the reaction with labelled malonyl chloride and to compare the radioactivity in the pyrimidine derivative with that of the starting malonyl chloride. For this purpose

sodium 1,1 -di[¹⁴C]-malonate was employed. This labelled sodium malonate (0.05 mc.) was diluted with ordinary malonic acid and then was converted into malonyl chloride. The labelled malonyl chloride was mixed with fluoroacetonitrile and with p-chloro-benzyl cyanide to get the corresponding pyrimidine and pyridine derivatives respectively. A portion of the same malonyl chloride was hydrolysed into malonic acid which was converted into sodium malonate for counting (as starting material). The radioactivity of the labelled samples (as solids on planchets) was measured with an end-window Geiger counter. The specific activity of the sodium malonate was found to be 6729C/100 seconds. The specific activity of the derived 4-chloro-2-fluoromethyl-6-hydroxy-pyrimidine was found to be 5982C/100 seconds. According to mechanism No. 3, the calculated specific activity of 4-chloro-2-fluoromethyl-6-hydroxy pyrimidine should be 6147C/100 secs., while according to mechanisms Numbers 1 and 2, the activity of this compound should be 3073C/100 secs. The specific activity of 2-chloro-3-(p-chlorophenyl)-4,6-dihydroxy pyridine was found to be 3758C/100 secs., while its activity calculated on the basis of the given mechanism was found to be 3889C/100 secs.

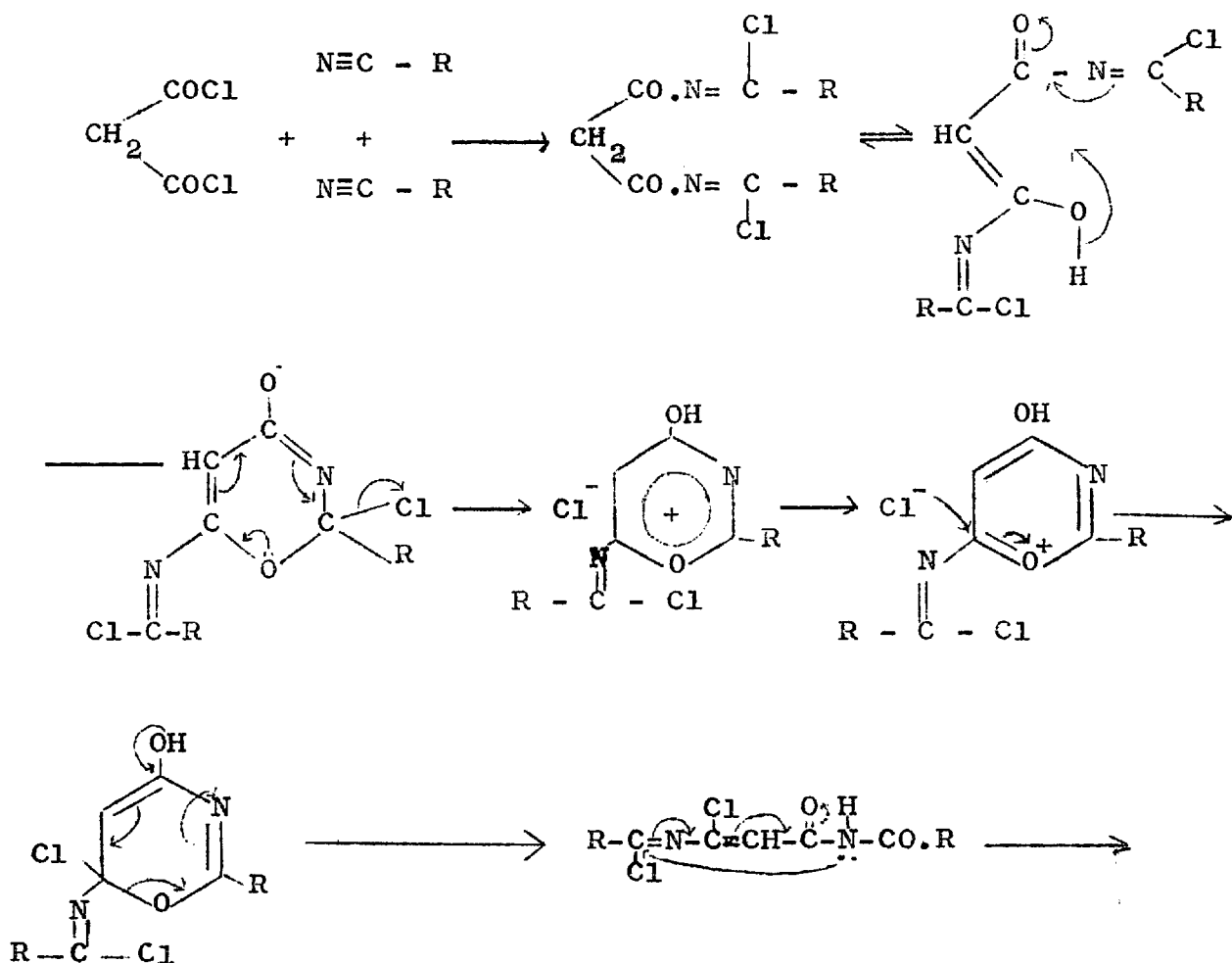
In another experiment the sample of sodium malonate gave 3072C/1000 secs. The specific activity of 4-chloro-2-fluoromethyl-6-hydroxy-pyrimidine was measured as 2757C/1000 seconds, while the calculated counts on the basis of third mechanism were 2806C/1000 secs. The chloroacetanilide obtained from the reaction of malonyl chloride and chloro acetonitrile did not show any radioactivity.

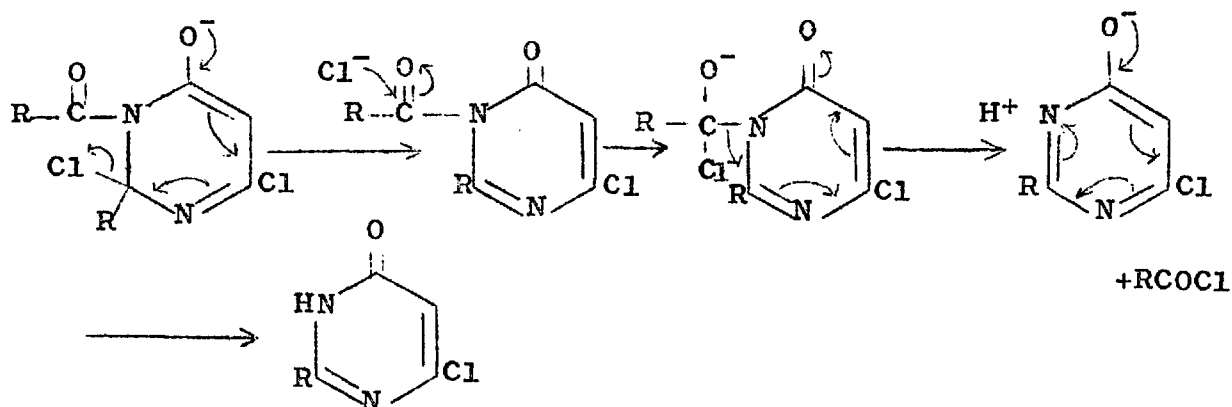


Thus, these experiments with labelled malonyl chloride together with those using bromomalonyl chloride clearly showed that all the three carbon atoms of malonyl chloride appeared in the pyrimidine nucleus and none of the carbon atoms of malonyl chloride appeared in the second product, RCOCl . Therefore, on the basis of these results the first and second mechanism could be ruled out. The results supported the

third mechanism provided such an exchange of chlorine and oxygen was feasible in some way.

Finally, to account for the proposed rearrangement, the following mechanism is suggested as being in full agreement with the results of the radioactivity experiments. The key intermediate, allowing the rearrangement is probably an azapyrylium salt:-





If external Cl^- participates as indicated above then it would be expected that addition of other halogen ions e.g. I^- would result in the isolation of a 6-iodo-pyrimidine. Attempts to verify this expectation proved, however, extremely difficult. For example, lithium and tetrabutyl ammonium iodides were far too insoluble in the reaction mixture and no way round this experimental difficulty was discovered.

SECTION 'B' EXPERIMENTAL

CHAPTER 1.

Preparation of Malonyl Chloride:-³¹

Finely powdered malonic acid (52 g.) was mixed with thionyl chloride (120 ml.) and heated on a water bath at 45 - 50° for three days. Then the temperature was raised to 60° for about six hours. Finally, the pale yellow malonyl chloride was distilled at reduced pressure (35 g., 50%), b.p. 51°/21 mm. n_D^{20} 1.4582, τ (CDCl₃) 5.60.

Reaction of Chloroacetonitrile and Malonyl Chloride:-

A mixture of malonyl chloride (13.5 g.) and chloroacetonitrile (9.0 g.) was allowed to stand for three days under anhydrous conditions and at room temperature. After three days the red sticky mass was triturated with a mixture of dry dioxan and ether. Yellow crystalline mass was extracted with hot chloroform. Two compounds were obtained, one soluble in chloroform and the other insoluble in chloroform.

The chloroform insoluble compound (2,3-dichloro-4,6-dihydroxypyridine) was recrystallized from aq. ethyl alcohol and finally sublimed to give a perfectly-colourless crystalline 2,3-dichloro-4,6-dihydroxypyridine, m.p. 273 - 274° (Found: C, 33.47; H, 1.75; N, 7.94; Cl, 39.53).

$C_5H_3NCl_2O_2$ requires: C, 33.33; H, 1.66; N, 7.7; Cl, 39.44%).

The chloroform soluble compound was crystallized from aq. methyl alcohol and on sublimation under reduced pressure gave colourless crystalline product -2-chloromethyl,4-chloro-6-hydroxypyrimidine m.p. 173°) (Found: C, 33.8; H, 2.2; N, 15.75. $C_5H_4N_2OCl_2$ requires: C, 33.55; H, 2.2; N, 15.65%).

Preparation of 2,3-dichloro-5-bromo-4,6-dihydroxypyridine:-

2,3-Dichloro-4,6-dihydroxypyridine (0.5 g.) was taken in ethyl alcohol (5 ml.) and bromine (0.3 ml.) was added into it. The mixture was heated under reflux for half an hour. The reaction mixture was cooled and filtered. On recrystallization from aq. ethyl alcohol light yellow needles (0.54 g., 75%) were obtained. Further purification was done by sublimation which yielded colourless needles of compound(II) m.p. 230° (decomp.). Found: C, 23.27; H, 0.48; N, 5.64. required for $C_5H_2NCl_2BrO_2$: C, 23.16; H, 0.77; N, 5.4%).

Preparation of 2,3-dichloro-5-nitro-4,6-dihydroxypyridine:-

2,3-Dichloro-4,6-dihydroxypyridine (0.48 g.) and 50% nitric acid (5 ml.) were heated at 75° on a water bath for about 25 min. The contents of the flask was then poured on crushed ice and the yellow crystalline product (0.46 g., 76%) was collected. On sublimation, bright yellow crystals of

compound(III) were obtained (m.p. 215° decomp.) (Found: C, 27.09; H, 0.88; N, 12.52; Cl, 31.48. $C_5H_2N_2O_4Cl_2$ requires: C, 26.5; H, 0.9; N, 12.5; Cl, 31.5%).

Preparation of 2,3,6-trichloro-4-hydroxypyridine:-

2,3-dichloro-4,6-dihydroxypyridine (0.5 g.) phosphorus oxychloride (8 ml.) and dimethylaniline (0.6 ml.) were refluxed for about 7 hr. Unreacted phosphorus oxychloride was distilled off under reduced pressure. The residue was poured on to ice and the mixture extracted with ether. On evaporating the ether, a sticky solid mass was obtained which was recrystallized from chloroform (0.16 g., 30%)(m.p. $193 - 195^{\circ}$) (Found: C, 30.3; H, 1.29; N, 7.38; Cl, 53.87. $C_5H_2NCl_3O$ requires: C, 30.2; H, 1.1, N, 7.0; Cl, 53.6%).

Preparation of 2,3,4,6-tetrachloropyridine:-

2,3-Dichloro-4,6-dihydroxypyridine (2.0 g.) was heated with phosphorus oxychloride (15 ml.) in a sealed carius tube at 180° for about 24 hr. The reaction mixture was then steam-distilled. In the distillate a white crystalline compound settled down. It was recrystallized from methyl alcohol. The colourless leaflets (1.8 g, 74%) melted at 38° . (Found: C, 27.9; H, 0.7; N, 6.48. Calc. for

C_5HNC1_4 : C, 27.65; H, 0.46; N, 6.45%), ν max (CHCl₃) 1550, 1535 (shoulder), 1390 and 1315 cm⁻¹.

Preparation of 5-Bromo-2-Bromomethyl-4-Chloro-6-hydroxypyrimidine

To a solution of 4-chloro-2-chloromethyl-6-hydroxypyrimidine (0.5 g.) in ethyl alcohol (5 ml.) bromine (0.4 ml.) was added dropwise. The mixture was heated under reflux for about 45 min. After the mixture had been cooled, the crystals were collected on a sintered glass filter. This product was found to be contaminated with 5-bromo-4-chloro-2-chloromethyl-6-hydroxypyrimidine. Therefore, for complete replacement of chlorine the product was heated under reflux with strong hydrobromic acid in glacial acetic acid (2.5 ml.) for about 2 hr. After the mixture had been cooled, the yellowish white crystals (0.67 g., 80%) were collected. On sublimation, the colourless crystalline 5-bromo-2-bromomethyl-4-chloro-6-hydroxy-pyrimidine (m.p. 260 - 261°), was obtained. (Found: C, 19.63; H, 1.0; N, 9.02. $C_5H_3ClBr_2N_2O$ requires C, 19.8; H, 0.99; N, 9.25%), ν max. (Nujol) 2800 - 2000 (broad), 1675, 1660, 1590, 1549 and 1190 cm⁻¹

Preparation of 4,5-dichloro-2-chloromethyl-6-hydroxy-pyrimidine:-³²

A mixture of 2-chloromethyl-4-chloro-6-hydroxypyrimidine (0.53 g.), N-chlorosuccinimide (0.448), benzoyl peroxide (0.18) and chloroform (10 ml.) was refluxed for about twelve hours. The mixture on concentration yielded the crystals of 4,5,dichloro-2-chloromethyl-6-hydroxy-pyrimidine. The crystals were washed with water and recrystallized from chloroform into colourless needles (0.48 g, 80%, m.p. 217-220°). (Found: C, 27.87; H, 1.10; Cl, 50.02; N, 12.91%. Required for C₅H₃Cl₃N₂O: C, 28.10; H, 1.40; Cl, 49.65; N, 13.11%).

Preparation of 4-chloro-6-hydroxy-2-iodomethylpyrimidine:-

2-Chloromethyl-4-chloro-6-hydroxypyrimidine (0.5 g.) in acetone (8 ml.) and sodium iodide (0.5 g.) in acetone (3.5 ml.) were mixed and refluxed on a steam bath for four minutes and filtered. The precipitate was washed with water. By diluting the filtrate with water more precipitate was obtained. On recrystallization from ethanol colourless needles of 4-chloro-6-hydroxy-2-iodomethyl-pyrimidine (0.6 g., 80%) were obtained (m.p. 205-207° with decomposition). (Found: C, 22.19; H, 1.6; N, 10.51; Cl, 13.03; I, 46.8. Required for C₅H₄N₂OClI: C, 22.18; H, 1.48; N, 10.35; Cl, 13.12; I, 46.94%), ν max. (Nujol), 2750-2000(b), 1660, 1630(sh), 1580, 1540 (sh.) and 1120 cm.⁻¹

Formation of N-(4-chloro-6-hydroxy-pyrimidyl-2-methyl)-pyridinium iodide:-

4-Chloro-6-hydroxy-2-iodo-methylpyrimidine (0.2 g.) was heated with pyridine (1 ml.) for one hour on a steam bath. Excess of pyridine was removed under reduced pressure. Solid residue on crystallization from aq. ethanol yielded colourless needles of N-(4-chloro-6-hydroxy-pyrimidyl-2-methyl)pyridinium iodide (0.24 g., 92%) (260°d.).

Found: C, 34.52; H, 2.72; N, 11.91%. $C_{10}H_9N_3OClI$ requires: C, 34.33; H, 2.57; N, 12.01%.

Formation of N-(4-chloro-6-hydroxy-pyrimidyl-2-methyl)-pyridinium chloride:-

2-Chloromethyl-4-chloro-6-hydroxypyrimidine (0.5 g.) was refluxed with pyridine (5 cc.) for two hours. After removing the excess of pyridine under reduced pressure the solid residue was dissolved in ethanol and charcoaled. Recrystallization from aq. ethanol yielded fine needles of the product (0.65 g., 90%, 270°d.). (Found: C, 46.28; H, 4.02; N, 16.06; Cl, 27.24, required for $C_{10}H_9N_3OCl_2$: C, 46.5; H, 3.49; N, 16.28; Cl, 27.51%).

Preparation of 2-chloromethyl-4,6-dichloropyrimidine:-

4-Chloro-2-chloromethyl-6-hydroxypyrimidine (0.5 g.) was refluxed with phosphorus oxychloride (4 ml.) and dimethylaniline (0.3 ml.) for 4 hours. After the unused phosphorus oxychloride had been distilled off under reduced pressure, the contents of the flask were poured over crushed ice and extracted with ether. The extract was dried over anhydrous sodium sulphate. The ether was evaporated to yield a white mass, which crystallized from ethyl alcohol. Colourless needles of compound (XII) were obtained, m.p. 40°. (Found: C, 30.81; H, 1.72; N, 14.53; Cl, 54.18. $C_5H_3N_2Cl_3$ requires: C, 30.42; H, 1.52; N, 14.18; Cl, 53.88%).

Preparation of 4-hydroxy-6-morpholino-2-morpholinomethyl-pyrimidine:-

4-Chloro-2-chloromethyl-6-hydroxypyrimidine (0.4 g.) was stirred with morpholine (4 ml.). After distillation of the excess of morpholine under reduced pressure, a white solid residue (0.47 g., 77%) was obtained which was recrystallized from ethyl alcohol. The product formed leaflet crystals m.p. 182 - 183°. (Found: C, 55.39; H, 7.31; N, 19.61. $C_{13}H_{20}N_4O_3$ requires: C, 55.7; H, 7.14; N, 20.0%)

Reaction of 2-chloromethyl-4-chloro-6-hydroxypyrimidine and phenyl hydrazine hydrate:-

A mixture of 2-chloromethyl-4-chloro-6-hydroxypyrimidine (0.5 g.), hydrazine hydrate (0.5 g.) and ethyl alcohol (5 ml.) was refluxed on a steam bath for two hours. The reaction mixture after cooling was extracted with ether. The solid product after evaporating the ether was crystallized from ethyl alcohol into yellow crystals of 4-chloro-6-hydroxy-2-(phenylhydrazonomethyl)pyrimidine (0.486 g., 70% m.p. 290°d). (Found: C, 53.09; H, 3.77, N, 22.34. Required for $C_{11}H_9ClN_6O$: C, 53.11; H, 3.60; N, 22.53%).

Preparation of 4-hydroxy-2-methyl-pyrimidine:-

4-Chloro-2-chloromethyl-6-hydroxypyrimidine (1.0 g.) in 85% ethyl alcohol (100 ml.) was hydrogenated at atmospheric pressure and room temperature using 10% Pd on charcoal (0.05 g.). The theoretical amount of hydrogen was taken up in about 105 minutes. The filtrate was evaporated to dryness and the solid residue on sublimation gave the colourless hydrochloride of 4-hydroxy-2-methylpyrimidine (0.5 g., 70%, m.p. 259 - 260°d). (Found: C, 40.86; H, 4.93; N, 19.29; Cl, 24.72. $C_5H_7N_2OCl$ requires: C, 40.97; H, 4.78; N, 19.11; Cl, 24.23%).

The above mentioned hydrochloride was taken in 10% sodium hydroxide and then solution was made just acidic with acetic acid. The base (4-hydroxy-2-methylpyrimidine) was extracted with chloroform. The solid residue obtained by the evaporation of the chloroform was sublimed and recrystallized from hot chloroform. The colourless crystals of 4-hydroxy-2-methylpyrimidine had m.p. $213.7 - 214.3^{\circ}$. (Found: C, 54.16; H, 5.36; N, 25.46; calculated for $C_5H_6N_2O$: C, 54.5; H, 5.5; N, 25.43%), ν max. ($CHCl_3$) 1676, 1606, 1557, 1480 and 1320 cm^{-1} .

Reductive dehalogenation of 4-chloro-6-hydroxy-2-methylpyrimidine:-

4-Chloro-6-hydroxy-2-methyl-pyrimidine (0.3 g.) in 80% ethyl alcohol (50 ml.) was hydrogenated in the presence of 10% Pd on charcoal at atmospheric pressure, and room temperature. The reaction mixture was filtered and evaporated to dryness. The sticky solid mass was extracted with hot chloroform. The chloroform extracts on concentration yielded colourless crystalline 4-hydroxy-2-methylpyrimidine (0.131 g. 45% m.p. and mixed m.p. 214°). Its infrared spectrum was identical to that of a sample obtained by the hydrogenation of 4-chloro-2-chloromethyl-6-hydroxypyrimidine.

Attempted reaction of Malonyl Chloride and Chloroacetonitrile at 100°

Malonyl chloride (4.6 ml.) was heated at 100° for 1 hour. with chloroacetonitrile (3.7 ml.) in a flask fitted with a reflux condenser and protected with a drying tube (CaCl₂). The reaction product was found to be completely charred and nothing could be isolated.

Reaction of Malonyl Chloride and Chloroacetonitrile at a low temperature:-

A mixture of malonyl chloride (9.3 ml.) and chloroacetonitrile (7.5 ml.) was placed in a refrigerator (under anhydrous conditions), for about 8 days. The product of reaction was found to be the mixture of the same two compounds as obtained at room temperature.

33

Preparation of fluoroacetonitrile:-

A mixture of fluoroacetamide (20 g.) (dried over concentrated H₂SO₄) and phosphorus pentaoxide (35 g.) was placed in a flask fitted with a water condenser and heated on an oil bath to 110° at which temperature the reaction started. The bath was then kept at 160° until fluoroacetonitrile ceased to distil (9.3 g., 60%). The product was redistilled at 80°/760 mm.

Reaction of Fluoroacetonitrile with Malonyl Chloride:-

Malonyl chloride (6.75 g.) was mixed with fluoroacetonitrile (5.7 g.) and the mixture was kept at room temperature under anhydrous conditions for 24 hrs. The reaction product was washed with a mixture of dry dioxan and dry ether. The yellow crystalline mass (5 g., 65%) was recrystallized from methyl alcohol. On sublimation, colourless crystals (m.p. $192.5 - 193^{\circ}$) of 4-chloro-2-fluoromethyl-6-hydroxypyrimidine were obtained (Found: C, 37.2; H, 2.5; N, 17.28; Cl, 22.26%. $C_5H_4N_2ClO$: requires C, 36.9; H, 2.46; N, 17.24; Cl, 21.81%).

Preparation of 5-bromo-4-chloro-2-fluoromethyl-6-hydroxypyrimidine:-

Bromine (0.6 ml.) was added dropwise to a solution of 2-fluoromethyl-4-chloro-6-hydroxypyrimidine (0.6 g.) in ethanol. Reaction mixture was refluxed for about half an hour. After cooling, yellow crystals of required compound (0.71 g., 80%) were filtered. For further purification the compound was sublimed and colourless crystals of 5-bromo-4-chloro-2-fluoromethyl-6-hydroxypyrimidine were obtained (m.p. 220°). (Found: C, 24.9; H, 1.24; N, 11.24%. $C_5H_3BrClFN_2O$ requires: C, 24.85, H, 1.24; N, 11.6%).

Preparation of 2-fluoromethyl-4-morpholino-6-hydroxypyrimidine:-

4-Chloro-2-fluoromethyl-6-hydroxypyrimidine (0.5 g.) was stirred with morpholine (5 ml.). Unused morpholine was distilled over under reduced pressure. The brown solid residue (0.46 g., 70%) was recrystallized from aq. methyl alcohol. Colourless needles of compound (XXI), m.p. 260° were obtained. (Found: C, 50.89; H, 5.76; N, 19.53; $C_9H_{12}FN_3O_2$ requires: C, 50.7; H, 5.63; N, 19.72%).

Preparation of 2-fluoromethyl-4,6-dichloropyrimidine:-

4-Chloro-2-fluoromethyl-6-hydroxypyrimidine (0.3 g.) was refluxed with phosphorus oxychloride (3 ml.) and dimethylaniline (0.2 ml.) for about 5 hours. Unreacted phosphorus oxychloride was distilled over under reduced pressure. Crushed ice was added to the contents of flask and extracted with ether. The ethereal extracts were washed with sodium carbonate solution and dried over anhydrous sodium sulphate. After evaporating the ether, a brown crystalline compound (XX) (0.1 g., 40%) was obtained which on recrystallization from aq. methyl alcohol and sublimation gave colourless needles, m.p. 56° (Found: C, 32.98; H, 1.85. $C_5H_3NCl_2F$ requires: C, 33.15; H, 1.66%).

Reductive dehalogenation of 4-chloro-2-fluoromethyl-6-hydroxy-pyrimidine:-

The hydrochloride of 4-hydroxy-2-methyl-pyrimidine (0.3 g.) was obtained by reductive dehalogenation of 4-chloro-2-fluoromethyl-6-hydroxy-pyrimidine (0.5 g. in 50 ml. of 85% ethyl alcohol) using the method which has been applied to 4-chloro-2-chloromethyl-6-hydroxypyrimidine. The hydrochloride had m.p. 259° (decomposition). (Found: C, 40.87; H, 4.91; N, 18.71; Cl, 19.53. $C_5H_7N_2OCl$ requires: C, 40.97; H, 4.78; N, 19.11; Cl, 19.72%).

The free base, 4-hydroxy-2-methylpyrimidine, obtained by the neutralization of its hydrochloride had m.p. 214° , and mixed m.p. 214.1° and identical infrared absorptions to that of a specimen described earlier.

Reaction of fluoroacetonitrile with malonyl chloride at 100° :-

A mixture of fluoroacetonitrile (2.4 g.) and malonyl chloride (2.82 g.) was heated under reflux for twenty minutes. A dark red solid product was triturated with a mixture of dry dioxan and dry ether. On recrystallization from ethanol colourless leaflets of 4-chloro-2-fluoromethyl-6-hydroxy-pyrimidine (1.67, 51%) was obtained (m.p. and mixed m.p. $192.5 - 193^{\circ}$).

³⁴
Preparation of bromoacetonitrile:-

³⁵
Bromoacetamide: Ethyl bromoacetate (25 g.) was cooled up to -25° and 10% aq. ammonia (50 ml.) was added with vigorous shaking. Stirring was continued for about 30 minutes. Crystalline bromoacetamide (17 g., 82%, m.p. 90.5°C) was filtered and dried under vacuum.

Dried bromoacetamide (15 g.) was distilled with P_2O_5 (18 g.) under reduced pressure which yielded colourless bromoacetonitrile (8.5 g., 65%, b.p. $60 - 62^{\circ}/24 \text{ m.m.}$), $\tau(\text{CDCl}_3)$ 6.20.

Reaction of bromoacetonitrile and malonyl chloride:-

Bromoacetonitrile (4.8 g.) was mixed with malonyl chloride (2.8 g.) and kept under anhydrous conditions for two days. The solid product after washing with a mixture of dry dioxan and dry ether was recrystallized from methanol into colourless fine needles of 2-bromomethyl-4-chloro-6-hydroxy-pyrimidine (2.3 g., 52%, m.p. $194 - 195^{\circ}$ with decomposition). (Found: C, 26.78; H, 1.82; N, 12.69; Cl, 15.71; Br, 35.69. $\text{C}_5\text{H}_4\text{BrClN}_2\text{O}$ requires: C, 26.9; H, 1.79; N, 12.5; Cl, 15.9; Br, 35.88%).

Bromination of 2-bromomethyl-4-chloro-6-hydroxy-pyrimidine:-

Bromine (0.2 ml.) was added to a solution of 2-bromomethyl-4-chloro-6-hydroxy-pyrimidine (0.5 g.) in ethanol (8 ml.). The mixture was refluxed for about an hour. On cooling and diluting with water yellow crystals of 5-bromo-2-bromomethyl-4-chloro-6-hydroxy-pyrimidine (0.57 g., 84%) were obtained. On sublimation colourless crystals were obtained which had m.p. and mixed m.p. 261° and identical I.R. spectrum to that obtained from the bromination of 2-chloromethyl-4-chloro-6-hydroxy pyrimidine.

36

Preparation of Iodoacetoneitrile:-

Chloroacetoneitrile (22 g.) and methyl alcohol (50 ml.) were refluxed with potassium iodide (75 g.) for three hours. After cooling the solid was filtered off. Bulk of methanol was evaporated on a steam bath. The residue was washed first with water and then with dil. aq. solution of sodium carbonate and dried over anhydrous CaCl_2 . Iodoacetoneitrile (21.5 g., 45%) was distilled under reduced pressure (b.p. $77 - 78^{\circ}/12 \text{ m.m.}$).

Reaction of malonyl chloride with Iodoacetonitrile:-

Iodoacetonitrile (3.3 g.) and malonyl chloride (2.9 g.) were kept together at room temperature (with exclusion of moisture). After two days the product was washed with a mixture of dry dioxan and dry ether. The product was triturated with chloroform. Brownish substance on recrystallization from ethanol gave colourless needles of 4-chloro-6-hydroxy-2-methyl-pyrimidine (0.28 g., 20%, m.p. 233-234 undepressed by authentic sample). (Found: C, 41.47; H, 3.6; N, 19.14; Cl, 24.43. Calc. for $C_5H_5ClN_2O$: C, 41.53; H, 3.46; N, 19.37; Cl, 24.57%), ν max. (Nujol) 1687, 1650, 1600, 1430 and 1128 cm^{-1}

37

Preparation of acetamidine hydrochloride:-

Dry hydrogen chloride gas was passed into a solution of thoroughly dry acetonitrile (100 g.) in absolute ethanol (143 ml.) On keeping the mixture for three days the mass turned to solid acetamide ethyl ether hydrochloride. The paste of this ether in absolute ethanol (100 ml.) was stirred with alcoholic ammonia (29%) for three hours and filtered. Filtrate on concentration and cooling yielded the crystals of acetamidine hydrochloride (180 g. , 78%).

Preparation of 4,6-dihydroxy-2-methyl-pyrimidine:-

Acetamide hydrochloride (9.4 g.) was added into a solution of sodium (6.9 g.) in absolute alcohol (100 ml.). Resulting sodium chloride was filtered. Ethyl malonate (16 g.) was added to the filtrate with vigorous stirring. After keeping the stoppered flask for two days, it was chilled and filtered. Solid was dissolved in water (100 ml.) and 4,6-dihydroxy-2-methyl-pyrimidine was precipitated by adding conc. hydrochloric acid and filtered. To purify, it was redissolved in conc. ammonium hydroxide solution and the ammonia was boiled off till the precipitation of dione occurred (7.7 g., 62%).

Preparation of 4,6-dichloro-2-methyl-pyrimidine:-

4,6-Dihydroxy-2-methyl-pyrimidine (3 g.) and phosphorus oxychloride (21 ml.) were refluxed together for about three hours. Excess of phosphorus oxychloride was removed under reduced pressure. The residue was poured on crushed ice. The solid product was washed with water. On sublimation colourless crystalline 4,6-dichloro-2-methyl-pyrimidine (1.56 g., 40%, m.p. 47.5 - 48°) was obtained.

Preparation of 4-chloro-6-hydroxy-2-methyl-pyrimidine:-

A mixture of 4,6-dichloro-2-methyl-pyrimidine (2.5 g.), water (25 ml.) and conc. hydrochloric acid (10 ml.) was boiled under reflux for 45 minutes. After cooling, the reaction mixture was made alkaline with strong aqueous ammonia and then acidified with acetic acid and kept overnight. The solid product was filtered and washed with water. It was crystallized from ethanol into fine needles of 4-chloro-6-hydroxy-2-methyl-pyrimidine (1.44 g. 62%, m.p. 233°).

Preparation of α -Bromopropionamide:-

Ethyl α -bromopropionate (37.5 g.) was cooled up to -35° . Aqueous ammonia (10%, 65 ml.) was added to the cooled ester with vigorous shaking. The colourless crystals of α -bromopropionamide were filtered and dried under vacuum (20 g., 80%, m.p. 123°).

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Preparation of α -Bromopropionitrile:-

α -Bromopropionamide (18 g., dried over conc. H_2SO_4) was mixed thoroughly with phosphorus pentoxide (27 g.). The mixture was heated on an oil bath from $150 - 200^{\circ}$ under reduced pressure while crude nitrile was distilled over. Redistillation of the crude product gave colourless α -bromopropionitrile (11.2 g., 71%, b.p. $59-60^{\circ}/24 \text{ mm.}$).

Reaction of α -bromopropionitrile and malonyl chloride:-

A mixture of α -bromopropionitrile (3 g.) and malonyl chloride (3.1 g.) was kept in darkness under anhydrous conditions for two days. Crystalline but sticky product was triturated with a mixture of dry dioxan and dry ether. Yellowish product was recrystallized from ethanol into colourless needles of 2-(α -bromoethyl)-4-chloro-6-hydroxypyrimidine (1.6 g., 60.7%, m.p. $178 - 180^{\circ}$). (Found: C, 30.5; H, 2.57; N, 11.63; Cl, 14.93; Br, 33.53. Required for $C_6H_6BrClN_2O$: C, 30.32; H, 2.52; N, 11.8; Cl, 14.95; Br, 33.69%), τ_{max} . (Nujol) 2750 - 2000 (broad), 1675, 1640 (sh.), 1580, 1550 (sh.) and 1130 cm^{-1}

39

Preparation of dibromoacetonitrile:-

Dibromoacetonitrile was prepared by the action of N-bromosuccinimide (67 g.) on the solution of cyanoacetic acid (16 g.) in water (190 ml.). Dibromoacetonitrile (26 g., 70%), was redistilled (b.p. $70 - 72^{\circ}/20\text{ mm}$, n_D^{25} 1.5419). Found: C, 12.07; H, 0.36; N, 6.9; Br, 80.41. Calc. for C_2HBr_2N : C, 12.06; H, 0.5; N, 7.03; Br, 80.4), $\tau(CDCl_3)$ 4.16.

Reaction of dibromoacetonitrile and malonyl chloride:-

Dibromoacetonitrile (4 g.) and malonyl chloride (3.5 g.) were kept together under anhydrous conditions for two days at room temperature. Reddish-brown solid product was triturated with a mixture of dry ether and dry dioxan. Recrystallization from ethanol yielded colourless needles of 2-bromomethyl-4-chloro-6-hydroxy-pyrimidine (1.2 g., 54%, m.p. 194 - 195° undepressed by the sample obtained from malonyl chloride and bromoacetonitrile). (Found: C, 27.12; H, 1.92; N, 12.41; Cl, 15.84; Br, 35.69. Calc. for $C_5H_4BrClN_2O$: C, 26.9; H, 1.79; N, 12.5; Cl, 15.9; Br, 35.88%).

Preparation of dimethyl bromomalonate:-

Freshly distilled dimethyl malonate (33 g.) and carbon tetrachloride (30 ml.) were taken in a three-necked flask fitted with a stirrer, a reflux condenser with calcium chloride tube and a separating funnel. Bromine (41 g.) was added dropwise. In the beginning a large electric bulb was held below the flask to start the reaction. The mixture was then refluxed for one and a half hour. The mixture was cooled and washed four times with 10 ml. portions of 5% sodium carbonate solution. Then it was fractionally distilled using vigreux column under reduced pressure. The fraction

boiling between 107 - 109°/13 mm. was collected. This fraction was redistilled and the fraction boiling at 108 - 108.5°/13 mm. was taken, (CDCl_3) 5.16 (1H) and 6.17 (6H).

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Preparation of dimethyl dibromomalonate:-

Ethyl malonate (10 g.) was taken in three necked flask fitted with a stirrer, separating funnel and a calcium chloride guard tube. A large electric bulb (100 watts) was held below the flask. Bromine (25 g.) was added dropwise. Then the flask was heated on a water bath for one hour. On cooling, crystals of dimethyl dibromomalonate were obtained. Dimethyl dibromomalonate was crystallized from petroleum ether into colourless needles (16 g., 72%, m.p. 66 - 67°), $\tau(\text{CDCl}_3)$ 6.09.

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Preparation of diazomethane:-

Potassium hydroxide (5 g.) in water (8 ml.) and 95% ethyl alcohol (25 ml.) were taken in a hundred ml. distillation flask which was fitted with a dropping funnel and a double walled condenser. The receiving flask placed in a freezing mixture contained 20 ml. of ether and the end of the receiving adapter was dipping below the surface of the

ether. The distillation flask was heated to 65° on a water bath. The solution of N-methyl-N-nitroso-p-toluene sulfonamide (21.5 g.) in ether (200 ml.) was added through the dropping funnel with a rate equal to the rate of distillation. After the addition of this solution another 40 ml. ether was added slowly and distillation was continued until the distillate was colourless.

Preparation of methylbromoacetate:-

Bromoacetic acid (6 g.) was added slowly into the solution of diazomethane. The ether and the excess of diazomethane was evaporated on a water pump. The residue boiled at 144° with decomposition.

Gas-liquid chromatographic analysis of the reaction product of dibromoacetoneitrile and malonyl chloride:-

The mixture of malonyl chloride (2 g.) and dibromoacetoneitrile (2.6 g.) was kept in a two-necked flask under anhydrous conditions for three days. After three days methanol (1.5 ml.) was added dropwise through a dropping funnel with constant shaking and cooling. It was left for four hours with occasional shaking to ensure the complete reaction of methanol with the acid chlorides. The mixture will be referred as reaction product in the following paragraphs.

Methyl alcohol (0.1 μ l) was injected on a column of 10% carbowax 1000 on celite in Pye Argon Chromatograph. The temperature of the column was 125^o, flow rate of argon was 41 ml./minute, voltage 1000 and chart speed was 5"/hour. Methyl alcohol came out immediately after injection. Then the reaction product (0.1 μ l.) was injected on the same column under similar conditions. In addition to the intense peak of methyl alcohol there were five major peaks on the chromatogram with the retention times of 1.9, 6.4, 7.1, 12 and 24 minutes. The fifth peak was broad. The mixture (0.1 μ l) of dimethyl malonate and methanol was also injected. Dimethyl malonate gave a single peak with the retention time of 7.1 minute. Thus, this peak of dimethyl malonate corresponded with the third peak of the reaction product. Then the mixture of reaction product and dimethyl malonate was injected. The chromatogram showed five peaks with the same retention times as in the chromatogram of reaction product; but the relative intensity of the third peak was increased considerably. Similarly dimethyl bromomalonate (0.1 μ l.) was injected and it gave a broad peak which corresponded in its retention time to the fifth peak of the chromatogram of the reaction product. Then the mixture (0.1 μ l) of reaction product and dimethyl bromomalonate was injected. Its chromatogram showed the

same five peaks with the increased relative intensity of the fifth peak. The shapes of the fifth peak in these chromatograms were not satisfactory.

Then the sample of the reaction product (1 μ l) was injected on the same column in Gas Density Balance Chromatograph. The column was at 140^o, carrier gas flow rate was 10 ml./18 sec., and chart speed was 12"/hour. In this chromatogram also there were five peaks in addition to an intense peak of methyl alcohol; but in this chromatogram all the five peaks were sharp. Dimethyl bromomalonate (1 μ l) also showed a sharp peak with the retention time of 5.36 minutes, which was the same as that of the fifth peak of the chromatogram of the reaction product. The mixture (1 μ l) of the reaction product and dimethyl bromomalonate was injected on the same column under similar conditions. The chromatogram showed the same five peaks with the double intensity of the fifth peak. In the same way the sample of dimethyl malonate and methyl bromoacetate and their mixtures with the reaction product were injected. It was found that the second and third peaks in the chromatograms of the reaction product were due to methyl bromoacetate and dimethyl malonate respectively. Dimethyl dibromomalonate was also injected on the same column but it seemed to be decomposed on the column.

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Preparation of β -chloropropionitrile:-

To a well-cooled solution of ethylene cyanhydrin (28 g.) in chloroform (30 c.c) thionyl chloride was added with stirring. After one hour chloroform was evaporated under reduced pressure and the β -chloropropionitrile was distilled on ~~vigreux~~ column (25 g., 70% b.p. $85 - 87^{\circ}/20$ m.m.).

Reaction of β -chloropropionitrile and malonyl chloride:-

β -Chloropropionitrile (6.0 g.) and malonyl chloride (9.4 g.) were kept together under anhydrous conditions for five days. Solid crystalline product was triturated with a mixture of dry dioxan and ether. Crystalline 2-chloro-3-chloromethyl-4,6-dihydroxy-pyridine (5.2 g., 40%) decomposed at 198 without melting.

Preparation of 2-chloro-3-ethoxymethyl-4,6-dihydroxy pyridine:-

2-Chloro-3-chloromethyl-4,6-dihydroxy-pyridine (2 g.) was refluxed with absolute ethanol (10 ml.) for two hours. Reaction mixture was evaporated to dryness under reduced pressure. Solid residue was crystallized from ethanol (1.25 g., 60%, m.p. 210°d.). (Found: C, 46.95; H, 5.39; N, 6.87; Cl, 17.26. Required for $\text{C}_8\text{H}_{10}\text{ClNO}_3$: C, 47.17; H, 4.9; N, 6.8; Cl, 17.4%).

Preparation of N-(2-chloro-4,6-dihydroxy pyridyl-3-methyl)-pyridinium chloride:-

2-Chloro-3-chloromethyl-4,6-dihydroxypyridine (2 g.) was heated with pyridine (5 ml.) on a steam bath for about an hour. Excess of pyridine was removed under reduced pressure. Solid residue was crystallized from aq. ethanol into fine needles of N-(2-chloro-,4,6-dihydroxy-pyridyl-3-methyl)-pyridinium chloride (2.1 g., 74% m.p. $> 300^{\circ}$ d.). (Found: C, 48.12; H, 3.91; N, 9.93; Cl, 25.18. Required for $C_{11}H_{10}Cl_2N_2O_2$: C, 48.35; H, 3.72; N, 10.25; Cl, 25.67%).

Reaction of β -bromopropionitrile and malonyl chloride:-

β -bromopropionitrile (4g.) and malonyl chloride (4.5 g.) were mixed together and kept at room temperature under anhydrous condition for seven days. The product was triturated with dry dioxan. Crystallization from acetone yielded 3-bromomethyl-2-chloro-4,6-dihydroxy-pyridine (2.1 g., 30%, d. 220°).

Preparation of 2-chloro-3-ethoxymethyl-4,6-dihydroxy-pyridine from 3-bromomethyl-2-chloro-4,6-dihydroxy pyrimidine:-

A mixture of 3-bromomethyl-2-chloro-4,6-dihydroxy-pyridine (2 g.) and absolute ethyl alcohol (10 ml.) was refluxed for about two hours. After evaporating the alcohol solid residue was crystallized from ethyl alcohol into colourless crystals of 2-chloro-3-ethoxy methyl-4,6-dihydroxy-pyridine (0.84 g., 50%, m.p. and mixed m.p. 210 d.). (Found: C, 46.87; H, 4.7; N, 6.45%. Required for $C_8H_{10}ClNO_3$: C, 47.17; H, 4.9; N, 6.8%). Infrared spectra of this compound and of the compound obtained by refluxing 2-chloro-3-chloromethyl-4,6-dihydroxy-pyridine with ethanol were identical.

Formation of N-(2-chloro-4,6-dihydroxy-pyridyl-3-methyl)-pyridinium bromide:-

3-Bromomethyl-2-chloro-4,6-dihydroxy-pyridine (1 g.) was dissolved in pyridine (3 ml.) and heated on a steam bath under reflux for two to three hours. Solid residue left after evaporating the excess of pyridine was crystallized from aq. ethanol into fine needles of the product (0.86 g., 65%, m.p. $>300^\circ$). (Found: C, 39.5; H, 2.94; N, 8.48; Cl, 10.7; Br, 24.1. Required for $C_{11}H_{10}BrClN_2O_2$: C, 39.33; H, 3.5; N, 8.3; Cl, 10.6; Br, 23.8%).

Chapter 2.

Reaction of Acetonitrile and Malonyl Chloride

Acetonitrile (4 g.) and malonyl chloride (7 g.) were kept together under anhydrous condition at room temperature for three days. The product was triturated with a mixture of dry dioxan and dry ether. Brownish-yellow product was washed several times with ether, then it was fractionally sublimed. Two fractions were collected, one small fraction at 110-120° and the other major fraction at 200-220°. Major fraction on crystallization from ethanol gave fine needles of 4-chloro-6-hydroxy-2-methylpyrimidine (2.2 g, 32%, m.p. and mixed m.p. 233°). (Found: C, 41.74; H, 3.77; N, 19.12; Cl, 24.32. Calc. for $C_5H_5ClN_2O$: C, 41.53; H, 3.46; N, 19.37; Cl, 24.57%).

Lower fraction of sublimation and the residue from ether extracts were crystallized from petroleum ether (100-120°). Crystalline 6-chloro-4-hydroxy-2-oxopyran-3-carboxylic acid melted at 135-136° (Found: C, 37.89; H, 1.78; Cl, 18.51. Calc. for $C_6H_3ClO_5$: C, 37.88, H, 1.58; Cl, 18.42%).

Reaction of Propionitrile and Malonyl Chloride

Malonyl chloride (7 g.) and propionitrile (2.5 g.) were kept together with exclusion of moisture at room temperature for two days. The product was washed with a mixture of dry dioxan and dry ether. On sublimation at 140-150° a

small amount of colourless sublimate was obtained. The main bulk of residue on crystallization from methanol yielded 2-chloro-4,6-dihydroxy-3-methyl-pyridine (m.p. 304°). The small amount of sublimate on crystallization from ethanol yielded 4-chloro-2-ethyl-6-hydroxy-pyrimidine (m.p. 162°). (Found: C, 45.63; H, 4.63; N, 17.53; Cl, 22.3. Required for $C_6H_7ClN_2O$: C, 45.56; H, 4.43; N, 17.72; Cl, 22.15%), λ_{max} . (Nujol) 2720-2200 (broad), 1695, 1655, 1600, 1550 (sh.) and 1130 cm^{-1}

Reaction of Malonyl Chloride and Butyronitrile:-

A mixture of butyronitrile (4.2 g.) and malonyl chloride (8.4 g.) was kept at room temperature with anhydrous $CaCl_2$ guard tube for three days. The product was filtered and triturated with a mixture of dry ether and dry dioxan. Fractional crystallization of the product (3.65 g.) from ethanol yielded a major fraction of 2-chloro-3-ethyl-4,6-dihydroxy-pyridine and a small fraction of 4-chloro-6-hydroxy-2-propyl-pyrimidine. 2-Chloro-3-ethyl-4,6-dihydroxy pyrimidine (2.45 g.) melted at 285° with decomposition. (Found: C, 48.1; H, 4.8; N, 7.94; Cl, 20.34. $C_7H_8ClNO_2$ requires: C, 48.4; H, 4.61; N, 8.06; Cl, 20.46%). λ_{max} . (Nujol) 2650-2000 (broad), 1660, 1620, 1595 and 1550 cm^{-1}

Fine needles of corresponding pyrimidine derivative (0.5 g.) melted at 171° . (Found: C, 48.59; H, 5.92; N, 16.25; Cl, 20.46%. Required for $C_7H_9ClN_2O$: C, 48.68; H, 5.2; N, 16.2; Cl, 20.6%).

Preparation of 6-hydroxy-4-morpholino-2-propyl-pyrimidine:-

To a solution of 4-chloro-6-hydroxy-2-propyl-pyrimidine (0.5 g.) in chloroform (2.5 ml.) morpholine (1 ml.) was added dropwise. The resulting mixture was washed with a small amount of water. After evaporating the chloroform solid residue was crystallized from ethanol into fine needles of 6-hydroxy-4-morpholino-2-propyl-pyrimidine (0.45, 72%, m.p. $238d.$). (Found: C, 59.36; H, 7.74; N, 18.75. Required for $C_{11}H_{17}N_3O_2$: C, 59.18; H, 7.62; N, 18.83%).

The reaction of malonyl chloride with cyanoethyl acetate:-

A mixture of malonyl chloride (2.5 g.) and cyanoethyl-acetate (2 g.) was kept under anhydrous conditions for six days. The reaction product was triturated with a mixture of dry ether and dioxan. The crystallization of the product from cyanoethyl acetate yielded 2-chloro-3-ethoxy carbonyl-4,6-dihydroxy pyridine (m.p. 219°).

Reaction of malonyl chloride with isobutyronitrile:-

Malonyl chloride (6 g.) and isobutyronitrile (6.5 g.) were heated together at 60° under anhydrous conditions for four hours and left at room temperature overnight. Solid product was washed with ether. On repeated crystallization from ethyl acetate fine yellowish needles of 3-isopropyl-amidocarbonyl-4-hydroxy-6-chloro-2-oxopyran were obtained (m.p. $\approx$ 300d.). (Found: C, 46.13; H, 3.9; N, 5.5; Cl, 13.6. Required for C₁₀H₂₀ClNO₅: C, 46.1; H, 3.8; N, 5.37; Cl, 13.6%). $\nu_{\text{max.}}$ (Nujol) 1715, 1690, 1590 and 1525 cm.⁻¹

CHAPTER 3.

Reaction of malonyl chloride with p-chlorophenyl acetonitrile:-

A mixture of p-chloro-phenyl-acetonitrile (3.4 g.) and malonyl chloride (3.8 g.) was kept at room temperature under anhydrous conditions for two days. The product was filtered and triturated with a mixture of dry ether and dry dioxan. Crystallization of this colourless product from ethanol yielded 2-chloro-3-(p-chlorophenyl)-4,6-dihydroxy-pyridine (1.8 g., 28%, 300° d). (Found: C, 51.47; H, 3.11; N, 5.34; Cl, 27.59. Required for $C_{11}H_7N_1Cl_2O_2$: C, 51.56; H, 2.73; N, 5.47; Cl, 27.77%), γ max(Nujol) 2700 - 2000 (broad), 1640, 1595, 1570, 1540, and 1500.

Reaction of malonyl chloride with p-nitrophenyl-acetonitrile:-

p-Nitrophenyl-acetonitrile (2 g.) and malonyl chloride (4.5 g.) were heated at 60° for four hours with exclusion of moisture. Reddish-yellow solid was filtered and washed with a small amount of a mixture of dry dioxan and dry ether. On crystallization from ethanol bright yellow needles of 2-chloro-4,6-dihydroxy-3-(p-nitrophenyl)-pyridine were obtained (1.3g., 40%, m.p. 300d.). (Found: C, 49.69; H, 2.65; N, 10.54; Cl, 13.32. $C_{11}H_7ClN_2O_4$ requires: C, 49.53; H, 2.62; N, 10.51; Cl, 13.32%), γ max. (Nujol) 2750-2000, 1640, 1600, 1580, 1520 and 1500 cm^{-1}

Reaction of Malanonitrile with Malonyl chloride:-

Malonyl chloride (4.5 g.) and malanonitrile (2.1 g.) were mixed together and kept in a refrigerator under anhydrous conditions for seven days. Highly viscous red liquid was dissolved in a minimum quantity of dry dioxan. To this solution ether was added and filtered. The filtrate was concentrated under reduced pressure. This on keeping in a refrigerator yielded a yellow crystalline mass which was sublimed into colourless crystalline 2-chloro-3-cyano-4,6-dihydroxy pyridine (m.p. 218 - 219°). (Found: C, 41.92; H, 1.83; N, 16.09; Cl, 20.72. Required for $C_6H_3ClN_2O_2$: C, 42.23; H, 1.76; N, 16.43; Cl, 20.81%), γ max. (Nujol) 3450, 3650, 2250, 1610, 1590 and 1500 cm^{-1} . The same experiment was performed at room temperature. Vigorous reaction took place yielding a charred product. This charred product was extracted with dry dioxane. On concentration it yielded a very small amount of 2-chloro-3-cyano-4,6-dihydroxy-pyridine.

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Preparation of cyanoacetyl chloride :-

Cyanoacetyl chloride was prepared by the action of phosphorus pentachloride on the solution of cyanoacetic acid in ether.

Preparation of 2-chloro-5-cyano-4,6-dihydroxy-pyridine:-

Cyanoacetyl chloride (10 g.) was kept at room temperature under anhydrous conditions for one day. After about twenty hours rapid evolution of hydrogen chloride took place and oily liquid converted into a solid mass. This solid mass was extracted from hot water which on concentration yielded a yellowish crystalline compound. This on recrystallization from hot water gave fine needles of 2-chloro-5-cyano-4,6-dihydroxy pyridine (10 g., 60%), m.p. 190° (d),

Reaction of Adiponitrile and Malonyl chloride:-

Adiponitrile (4.3 g.) and malonyl chloride (5.6 g.) were mixed together and were kept under anhydrous conditions for two days. A very dirty reaction product was triturated with acetone. A brownish-yellow product thus obtained was crystallized from methanol which yielded colourless crystalline 2-chloro-3-(α -cyanopropyl)-4,6-dihydroxy pyridine. (1.5 g., 18%, 190° d.). (Found: C, 50.97; H, 4.32; N, 13.02; Cl, 16.5. Required for $C_9H_9ClN_2O_2$: C, 50.84; H, 4.23; N, 13.17; Cl, 16.70%), ν max. (Nujol) 2250, 1650, 1620, 1580 (broad) and 1420 cm^{-1} .

Reaction of tetradecanyl 1,1⁴-dicyanide with malonyl chloride:-

A mixture of tetradecanyl 1,1⁴-dicyanide (2.5 g.) and malonyl chloride (4 g.) was kept at room temperature with the exclusion of moisture for six days. The product was filtered and triturated with a mixture of dry dioxan and dry ether. The yellow product was washed several times with ether. Repeated crystallisation from ethanol yielded crystals of 2-chloro 4,6-dihydroxy-3-(13'-cyanotridecanyl)-pyridine (2.1 g., 21%; d. 250°). (Found: C, 64.35; H, 8.36; N, 7.84; Cl, 10.17%. C₁₉H₂₉ClN₂O₂ requires: C, 64.77; H, 8.23; N, 7.93; Cl, 10.08%). γ_{max} . (Nujol) 2230 (weak) 1675, 1640, 1595 and 1560 cm.⁻¹

Preparation of bromomalonic acid:-⁴⁴

A solution of malonic acid (52 g.) in acetic acid (250 ml.) was taken in a three-necked flask fitted with a stirrer, condenser and a separating funnel. Bromine (80 g.) was added dropwise. After the addition of bromine the bulk of acetic acid was removed on a rotatory evaporator. The material was dried in a vacuum desiccator over sodium hydroxide for six days. Bromomalonic acid was recrystallised from a mixture of acetone and benzene into colourless crystals (56 g., 61% m.p. 112°).

Preparation of bromomalonyl chloride:-

Bromomalonic acid (50g.) and thionyl chloride (65 ml.) were heated together at 50° for two days. After two days the temperature was increased up to 80° and heated further for three days. The reaction mixture was fractionally distilled using small vigreux column under reduced pressure. Bromomalonyl chloride distilled over at 30°/0.35 m.m. (n_D^{21} 1.5478).

Reaction of bromomalonyl chloride with fluoroacetonitrile:-

A mixture of bromomalonyl chloride (4 g.) and fluoroacetonitrile (2 g.) was kept at room temperature for three days. The reaction product was triturated with a mixture of ether and dioxan. The product on crystallization from ethyl alcohol yielded leaflets of 4-chloro-2-fluoromethyl-6-hydroxy-pyrimidine (1.5 g, 50%, m.p. and mixed m.p. 193°).

Reaction of bromomalonyl chloride and dibromoacetonitrile:-

Bromomalonyl chloride (2 g.) and dibromoacetonitrile (3.5 g.) were kept together at room temperature with the exclusion of moisture. After about two months the dirty mass was triturated with acetone. The crystalline mass on recrystallization from ethyl alcohol yielded colourless crystals

of 5-bromo-2-dibromomethyl-4-chloro-6-hydroxy-pyrimidine
(0.950 g., 30%, decomposed above 300°). (Found: C, 15.91;
H, 0.54; Br, 62.81; Cl, 9.46; N, 7.41%. Required for
 $C_5H_2Br_3ClN_2O$: C, 15.74; H; 0.52; Br, 62.99; Cl, 9.34;
N, 7.35%), ν max. (Nujol) 2700 - 2000(broad), 1670, 1630,
1570, 1530, 1350 and 1120 cm^{-1}

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Preparation of chloromalonic acid:-

To a solution of malonic acid (52 g.) in dry ether (500 ml.) sulphuryl chloride (67 g.) was added dropwise with constant stirring. After the addition of sulphuryl chloride stirring was continued for another half an hour. Ether was evaporated under reduced pressure. When there was still some ether the product was dissolved in a small amount of water and extracted with ether. The ether was reduced under reduced pressure. The solid product was dried in vacuum desiccator over $CaCl_2$. The colourless chloromalonic acid (56 g., 80%) was recrystallized from the mixture of acetone and benzene and was dried over paraffin wax. Colourless crystals of chloromalonic acid melted at $130 - 133^{\circ}$.

Preparation of chloromalonyl chloride:-

Chloromalonic acid (25 g.) and thionyl chloride (40 ml.) were heated at 50° for one day. Then the mixture was heated at 70° for five days. Chloromalonyl chloride was distilled at 50°/14 m.m., $\bar{\tau}(\text{CDCl}_3)$ 4.51.

Reaction of chloromalonyl chloride and fluoroacetonitrile:-

A mixture of chloromalonyl chloride (5 g.) and fluoroacetonitrile (3.5 g.) after keeping for five days yielded a crystalline product. This product was triturated with a mixture of dry ether and dry dioxan. On crystallization from ethanol this product gave fine crystals of 4,5-dichloro-2-fluoromethyl-6-hydroxy-pyrimidine (2.48 g., 44% m.p. 195 - 196°). (Found: C, 30.73; H, 1.28, Cl, 35.70; N, 13.83. Required for $\text{C}_5\text{H}_3\text{Cl}_2\text{FN}_2\text{O}$: C, 30.45; H, 1.52; Cl, 36.04, N, 14.21%).

Reaction of chloromalonyl chloride and chloroacetonitrile:-

A mixture of chloromalonyl chloride (4 g.) and chloroacetonitrile (3.3 g.) was kept with the exclusion of moisture for seven days. The product after triturating with dry ether and dry dioxan was repeatedly crystallized from ethyl alcohol into colourless crystals of 4,5-dichloro-2-chloromethyl-6-hydroxy-pyrimidine (1.58, 32%, m.p. and mixed m.p. 216-218°).

Chapter 4.

Attempted reaction of malonyl chloride with 4,6-dihydroxy-2-methyl-pyrimidine:-

A mixture of malonyl chloride (4 ml.) and 4,6-dihydroxy-2-methyl-pyrimidine (1.0 g.) was kept at room temperature for five days. After five days, malonyl chloride was distilled over under-reduced pressure. The residue was triturated with a mixture of dry ether and dry dioxan. The solid material thus obtained on crystallization from ethanol gave the starting compound-4,6-dihydroxy-2-methyl-pyrimidine (0.768 g.).

Attempted reaction of cyanoacetyl chloride and fluoroacetonitrile:

Fluoroacetonitrile (4 g.) was mixed with cyanoacetyl chloride (3 g.). The mixture was kept at room temperature under anhydrous conditions for several days. In the end a very dirty tarry material was obtained from which no solid product could be obtained.

Preparation of fluoroacetyl chloride:-⁴⁶

Fluoroacetyl chloride was obtained by the action of benzotrichloride on fluoroacetic acid in the presence of zinc chloride, b.p. 71 - 72°

Attempted reaction of cyanoacetyl chloride, fluoroacetonitrile and fluoroacetyl chloride:-

A mixture of fluoroacetonitrile (3 g.), cyanoacetyl chloride (2.2 g.) and fluoroacetyl chloride (2.5 g.) was kept under anhydrous conditions for four days, but no solid compound could be obtained from a very dirty product.

Reaction of fluoroacetonitrile and malonyl chloride in the presence of tetrabutyl ammonium iodide:-

Fluoroacetonitrile (3.5 g.), and malonyl chloride (4.2 g.) and tetrabutyl ammonium iodide (5.5 g.) were kept at room temperature for one day. The product was filtered and triturated with a mixture of dry dioxan and dry ether. The solid residue was extracted several times with hot chloroform. The chloroform was evaporated and the residue on crystallization from ethanol yielded 4-chloro-2-fluoromethyl-6-hydroxy-pyrimidine (m.p. 193, undepressed by authentic sample). Chloroform insoluble portion on sublimation at 100° yielded colourless 6-chloro-4-hydroxy-2-oxopyran-3-carboxylic acid (m.p. 135°, undepressed on admixture with authentic sample).

Detection of chloroacetyl chloride in the reaction product of malonyl chloride and chloroacetonitrile:-

The product from the reaction of chloroacetonitrile and malonyl chloride was washed with dry ether. To the cooled ether extracts aniline was added dropwise with stirring. The solid product was filtered and washed with water. It was sublimed at 110 - 120°. The sublimate on crystallization from 50% aq. ethanol yielded colourless needles of chloroacetanilide (m.p. 134 - 135° undepressed by authentic sample). (Found: C, 56.43; H, 4.77; N, 8.18; Cl, 20.8. Calculated for C_8H_8ClNO : C, 56.66; H, 4.71; N, 8.26; Cl, 20.9%), γ max. (Nujol) 3300, 3250, 3150, 1670, 1620, 1560 and 1500 cm^{-1} , $\tau(CDCl_3)$ 1.75 (1H, broad), 2.6 (5H, complex) and 5.85 (2H).

Experiments with sodium 1,1 -di[^{14}C]-malonate

Experiment 1.

Labelled sodium malonate (0.05 m.c.) from the ampoule was extracted with water. Combined water extracts were mixed with the solution of unlabelled malonic acid (5 g.) in water (10 ml.). Water was removed on a rotatory evaporator. The solid mass was dried in a vacuum desiccator over anhydrous calcium chloride for two days. This labelled malonic acid

was mixed thoroughly with another 10 grams of malonic acid. Malonyl chloride was prepared from this malonic acid by the usual method as described earlier.

A portion of this malonyl chloride (1.5 g.) was hydrolysed into malonic acid by the atmospheric moisture. Malonic acid thus obtained was crystallized from a mixture of ether and acetone. Crystalline malonic acid (0.8 g.) was dissolved in methanol and was treated with a solution of sodium hydroxide (0.6 g.) in a minimum amount of aq. methanol. The precipitate of sodium malonate was filtered and washed several times with methanol and dried in a vacuum desiccator over anhydrous calcium chloride. About 250 m.g. of this sodium malonate was transferred to an agate mortar and 2 ml. of ethyl alcohol was added. A fine slurry was made and then the slurry was transferred to a pre-weighed planchet (22 m.m. diameter, flat-type, nickel plated) placed in a glass dish. The slurry was dried to a constant weight under the heat lamp (150 watt spot light reflector). In the same way a duplicate planchet was prepared. Radioactivity of the sample was measured on an end-window counter and scaler (2080 counter, 1805 II scaler,, Isotope Development Ltd., Reading, Berkshire), and the results are shown in Tables 1 and 2.

Working voltage of the counter = 1700 volts.

Mean background counts = $114 \pm 10.6/100$ secs.

Observed count rates of the samples were corrected for background count by the following equation:

$$(A - B) \pm (a^2 + b^2)^{\frac{1}{2}}$$

A = observed count rate of the sample.

a = standard error of the count rate of the sample.

B = count rate of the background.

b = standard error of the background.

Planchet a:- Weight of the sample = 160.2 m.g.

TABLE 1

No. of Reading	Observed Counts (per 100 secs.)	Corrected Counts (per 100 secs.)
1.	6854	6740 ± 83
2.	6817	6703 ± 83
3.	6832	6718 ± 83
4.	6761	6647 ± 83
5.	6726	6612 ± 83
6.	6789	6675 ± 83
7.	6769	6883 ± 83
8.	6706	6592 ± 83
9.	6825	6711 ± 83
10.	6768	6654 ± 83

Mean count rate = $6693 \pm 82/100$ secs.

Standard proportional error = 1.2%

Planchet b:- Weight of the sample = 153.6 m.g.

TABLE 2

No.	Observed Counts (per 100 secs.)	Corrected Counts (per 100 secs.)
1	6858	6744 $\pm$ 83
2.	6826	6712 $\pm$ 83
3.	6851	6737 $\pm$ 83
4.	6867	6753 $\pm$ 83
5.	6959	6845 $\pm$ 84
6.	6846	6732 $\pm$ 83
7.	6930	6816 $\pm$ 84
8.	6950	6836 $\pm$ 84
9.	6937	6823 $\pm$ 84
10.	6784	6670 $\pm$ 83

Mean count rate = 6766 $\pm$ 82/100 secs.

Standard proportional error = 1.2%

Mean count rate of the two planchets = 6729 $\pm$ 82/100 secs.

4-Chloro-2-fluoromethyl-6-hydroxy pyrimidine was prepared from labelled malonyl chloride by the method described in Chapter 1. A Slurry of the sample was made with a mixture of carbon tetrachloride and petroleum ether (60% and 40% respectively). Two planchets of the sample were prepared and counted. Results of these countings are shown in Tables 3 and 4.

Planchet a:- Weight of the sample = 156.6 m.g.

TABLE 3.

No. of Reading	Observed Counts (per 100 secs.)	Corrected Counts (per 100 secs.)
1.	6141	6027 $\pm$ 79
2.	5960	5846 $\pm$ 78
3.	6066	5952 $\pm$ 79
4.	5987	5873 $\pm$ 78
5.	5969	5855 $\pm$ 78
6.	6105	5991 $\pm$ 79
7.	6105	9991 $\pm$ 79
8.	6020	5906 $\pm$ 78
9.	6164	6050 $\pm$ 79
10.	6155	6041 $\pm$ 79

Mean count rate = 5953 $\pm$ 77/100 secs.

Standard proportional error = 1.3%

Planchet b:- Weight of the sample = 137.6 m.g.

TABLE 4.

No. of Reading	Observed Counts (per 100 secs.)	Corrected Counts. (per 100 secs.)
1.	6090	5976 $\pm$ 79
2.	6050	5936 $\pm$ 78
3.	6089	5975 $\pm$ 79
4.	6059	5945 $\pm$ 79
5.	6089	5975 $\pm$ 79
6.	6102	5988 $\pm$ 79
7.	6137	6023 $\pm$ 79
8.	6115	6001 $\pm$ 79
9.	6115	6001 $\pm$ 79
10.	6123	6009 $\pm$ 79

Mean count rate = $5982 \pm 77/100$ secs.

Standard proportional error = 1.3%

Mean count rate of the two planchets = $5967 \pm 77/100$ secs.

Calculated counts = 6147/100 secs.

Discrepancy in the observed counts from calculated counts = -2.9%.

2-Chloro-3-(p-chlorophenyl)-4,6-dihydroxy-pyridine was also prepared from the labelled malonyl chloride by the method described in Chapter 3. The slurry of the sample was made with a mixture of ethanol and petroleum ether (80% and 20% respectively). Two planchets were prepared. The results of counting are given in Tables 5 and 6.

Planchet a:-

TABLE 5.

No. of Reading.	Observed Counts (per 100 secs.)	Corrected Counts (per 100 secs.)
1.	3819	3696 ± 63
2.	3825	3711 ± 63
3.	3845	3731 ± 63
4.	3830	3716 ± 63
5.	3870	3756 ± 63
6.	3832	3718 ± 63
7.	3848	3734 ± 63
8.	3785	3671 ± 62
9.	3865	3751 ± 63
10.	3870	3756 ± 63

Mean count rate = $3724 \pm 61/100$ secs.

Standard proportional error = 1.6%

Planchet b:- Weight of the sample = 133.8 m.g.

TABLE 6.

No. of Reading	Observed Counts (per 100 secs.)	Corrected Counts (per 100 secs.)
1.	3850	3736 $\pm$ 63
2.	3940	3826 $\pm$ 64
3.	3931	3817 $\pm$ 64
4.	3895	3781 $\pm$ 63
5.	3861	3747 $\pm$ 63
6.	3872	3758 $\pm$ 63
7.	3960	3846 $\pm$ 64
8.	3877	3763 $\pm$ 63
9.	3950	3836 $\pm$ 64
10.	3938	3824 $\pm$ 64

Mean count rate = 3793 $\pm$ 62/100 secs.

Standard proportional error = 1.6%

Mean count rate for two planchets = 3758 $\pm$ 61/100 secs.

Calculated count rate = 3889/100 secs.

Discrepancy in the observed counts from the calculated counts = -3.3%.

Experiment 2.

The ampoule containing labelled sodium malonate (0.05m.c.) was extracted with water in the same way as in Experiment 1. Water extracts of sodium malonate were mixed with the solution of malonic acid (5 g.) in water. The resulting solution was dried. 0.8 gram. of this malonic acid was mixed with 49.2 g. of the unlabelled malonic acid. Malonyl chloride was

prepared from this malonic acid. A part of the malonyl chloride was hydrolysed into malonic acid which was converted into its sodium salt as described in Experiment 1. The results of the counting of this sodium malonate are given in Table 7.

Weight of the sample = 129.2 m.g.

TABLE 7.

No. of Reading	Observed Counts (per 1000secs.)	Corrected Counts (per 1000secs.)
1.	4206	3066 $\pm$ 73
2.	4170	3030 $\pm$ 73
3.	4261	3121 $\pm$ 73
4.	4178	3038 $\pm$ 73
5.	4230	3090 $\pm$ 73
6.	4261	3121 $\pm$ 73
7.	4198	3058 $\pm$ 73
8.	4215	3075 $\pm$ 73
9.	4235	3095 $\pm$ 73
10.	4165	3025 $\pm$ 73

Mean count rate = $3072 \pm 55/1000$ secs.

Standard proportional error = 1.8%

Count rates of 4-chloro-2-fluoromethyl-6-hydroxy-pyrimidine obtained from this labelled malonyl chloride are given in Table 8.

Weight of the sample = 146.3 m.g.

TABLE 8.

No. of Reading	Observed Counts (per 1000secs.)	Corrected Counts (per 1000secs.)
1.	3842	2742 $\pm$ 71
2.	3849	2709 $\pm$ 71
3.	3951	2811 $\pm$ 71
4.	3925	2785 $\pm$ 71
5.	3938	2796 $\pm$ 71
6.	3851	2711 $\pm$ 71
7.	3909	2769 $\pm$ 71
8.	3928	2788 $\pm$ 71
9.	3917	2777 $\pm$ 71
10.	3827	2687 $\pm$ 70

Mean count rate = $2757 \pm 52/1000$ secs.

Standard proportional error = 1.9%

Calculated counts = 2806

Discrepancy in the observed counts from the calculated counts = -1.7%.

Labelled malonyl chloride was also treated with chloroacetonitrile and chloroacetanilide was obtained from the filtrate of the reaction product. The slurry of this anilide was made in a mixture of carbon tetrachloride and petroleum ether (40% and 60% respectively), but the sample did not show any radioactivity.

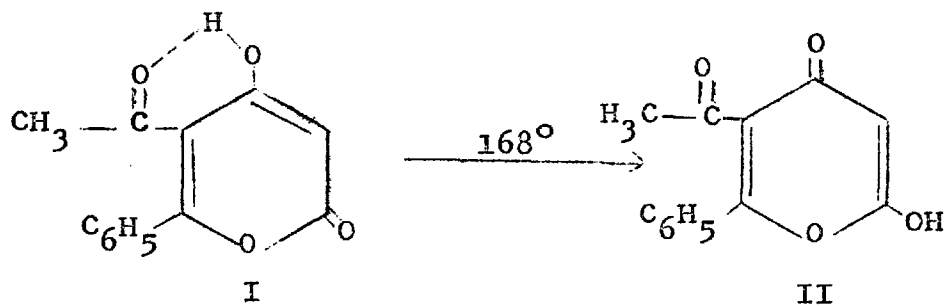
PART II

Reinvestigation of the Reaction of Malonyl
Chloride with Benzoyl Acetone

THEORETICAL

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Butt et. al had reported that malonyl chloride and benzoyl acetone produced 5-acetyl-4-hydroxy-6-phenyl-2-pyrone(I). This compound was found to resolidify after melting at 168° and the second form of this compound melted at 220° . Both these forms had molecular formulae of $C_{13}H_{10}O_4$. But their nuclear magnetic resonance spectra and their light absorption spectra were different from each other. Both forms on deacylation with sulphuric acid yielded 4-hydroxy-6-phenyl-2-pyrone. Similarly with ammonia both forms produced 4-hydroxy-5-acetyl-6-phenyl-2-pyridone. Therefore, Butt et. al concluded that both the forms had identical carbon skeletons and that they were hydroxypyrone tautomerides(I) and (II) respectively.

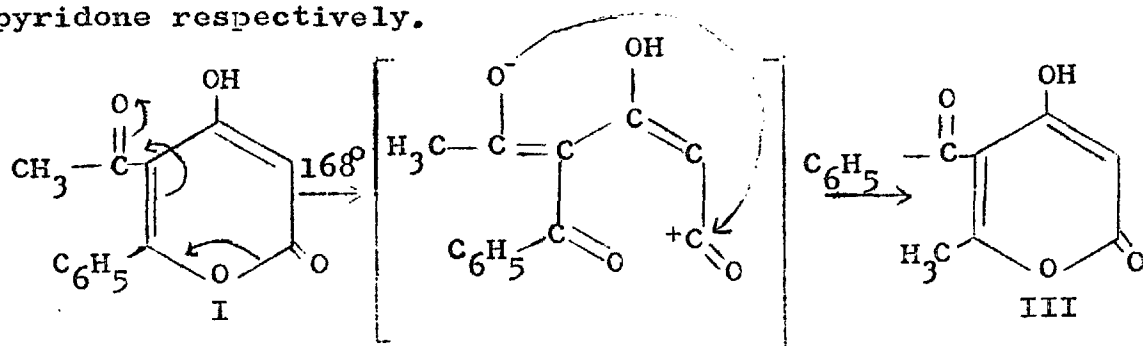


The nuclear magnetic resonance spectrum of compound(I) showed a singlet for the phenyl-protons whilst that of compound(II) showed a complex signal for the phenyl protons.

Butt et. al explained this difference by assuming non-complanarity and complanarity of the phenyl group with the pyrone ring in the tautomerides(I) and (II) respectively.

Ziegler et. al⁴⁸ reinvestigated this reaction and they found that in the crude reaction product both these compounds (m.p. 168°, 220°, respectively) were present. They found that when each of these two compounds was dissolved in sodium hydroxide solution and re-precipitated by hydrochloric acid only one of the forms was obtained. They argued that if these two compounds were the keto-enol tautomers they would have given in alkaline medium the same ions and on reacidification a mixture of the two isomers would have been precipitated. They also studied the ultraviolet light absorption spectra of these two compounds in alkaline methyl alcohol. They found that the two forms showed different absorption maxima (234mμ and 249mμ, respectively). Again they argued that if these two compounds were keto-enol tautomers they would have given the same ultraviolet absorption spectra in alkaline medium. Therefore, on the basis of these results, Ziegler et. al concluded that these two compounds were the positional isomers (I and III, respectively). They suggested that in compound(I) ring opening took place at its melting point giving

a linear intermediate which cyclized to 5-benzoyl-4-hydroxy-6-methyl-2-pyrone(III). Similarly they explained that when these two compounds were treated with sulphuric acid or with ammonia hydrolytic ring opening took place forming similar linear intermediates which cyclized into pyrone and pyridone respectively.

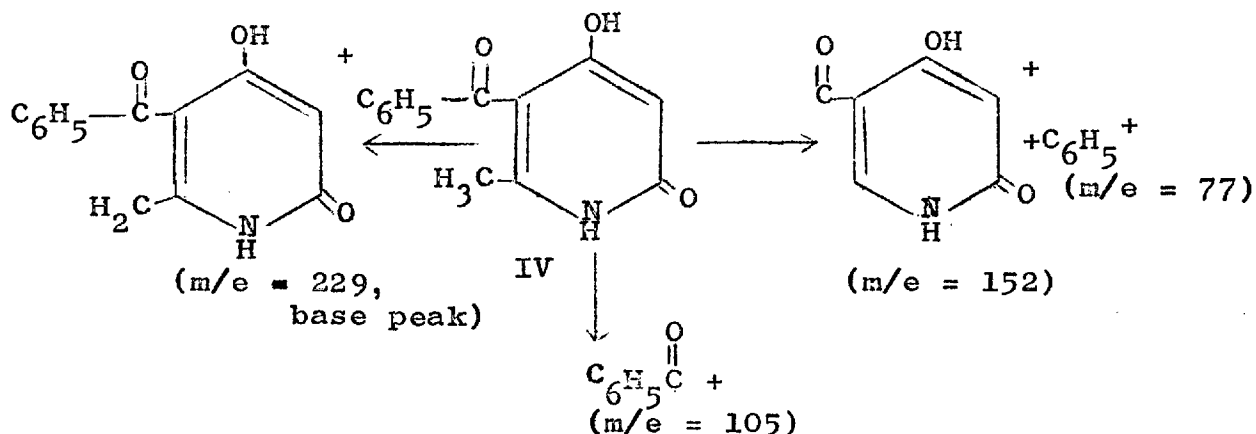


Therefore, it was decided to reinvestigate the reaction of malonyl chloride and benzoyl acetone. The product of this reaction was seen under the microscope of the Kofler hot stage melting point apparatus to consist of a mixture of two types of crystals melting at about 165° (with resolidification) and at 220° respectively. The nuclear magnetic resonance spectrum of this mixture showed the percentages of these two compounds as 54 and 46% respectively. With great difficulty, both these compounds were separated from each other by repeated crystallization. One compound melted at 167° (with immediate resolidification) and the

second one melted at 224° . Their infra red spectra resembled those reported by Butt et. al. The nuclear magnetic resonance spectra of these two compounds were also the same as reported by Butt et. al. Both these compounds were dissolved separately in aqueous sodium hydroxide solution and reprecipitated by hydrochloric acid. In both the cases only the starting compound was recovered. The mass spectrum of the second compound (m.p. 224°) showed its molecular weight to be 230. The base peak was at m/e 105. The intensity of the parent peak was 12% of the base peak. The other important intense peaks were at m/e 43(50%), 77(70%), 78(50%), 202(55%), 201(20%) and 229(8%). The base peak at m/e 105 is most probably due to the benzoyl fragment ion ($C_6H_5CO^+$). The peak at m/e 77 is due to the phenyl ion ($C_6H_5^+$) and the peak at m/e 202 may result from a loss of carbon monoxide which is a characteristic fragmentation of enolic compounds. The relative intensity (66%) of the peak at 229 with respect to the parent peak showed the loss of one proton from the parent molecule which is a characteristic of aromatic compounds attached to a methyl group. Therefore, it can be concluded that its mass spectrum supported the benzoyl structure (III) for this compound.

The molecular weight of the first compound (m.p. 167°) from its mass spectrum (at 120°) was also 230. But in this spectrum the relative intensities of peaks at m/e 43 and m/e 105 were almost equal. The peak at m/e 43 is probably due to the acetyl fragment ion (CH_3CO^+). It is interesting to note that when the spectrum of the same sample was run at 240° the relative intensity of the peak at m/e = 43 decreased to 50% of the peak at m/e = 105. Therefore, it appears that this compound has the acetyl structure (I), but either it is contaminated with compound (III) or it is partly isomerised into compound (III) in the probe of mass spectrometer at 120°.

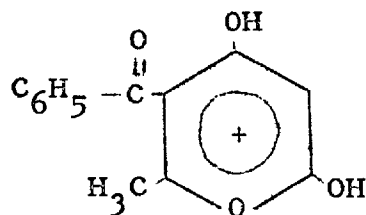
The corresponding pyridone was also obtained from compound (III). The molecular weight of this pyridone from its mass spectrum was 229, thus indicating the presence of an odd number of nitrogen atoms. The base peak was at m/e = 228, which might be due to the loss of one proton from the methyl group attached to the nucleus of the pyridine. The parent peak was about 17% of the base peak. The other important intense peaks were at m/e 152(65%), 105(50%), 77(70%). The appearance of intense peaks at m/e 152 and 105 might be explained in the following way by assuming the benzoyl structure (IV) for the pyridone.



There is no significant peak at $m/e = 43$ (CH_3CO^+) or at $m/e = 214$ ($\text{C}_{13}\text{H}_{11}\text{NO}_3\text{-CH}_3$)⁺ which further indicated the absence of an acetyl group in this compound.

Nuclear magnetic resonance results for compounds (I), (III) and (IV) are given in Table 1.

The chemical shifts of the protons at C-3 in compounds (I) and (III) are at a lower field for the solution in trifluoro acetic acid than in chloroform. This change in chemical shift might be due to protonation of the oxygen of carbonyl group to give the pyrylium cation:-



The multiplicity of the signals of phenyl protons in compounds (III) and (IV) suggest that the position of

TABLE 1

Compound	τ	Intensity	Multiplicity	Assignment
(I)	2.44	5	singlet	Ph
(in $\text{CDCl}_3 + \text{CH}_3\text{OH}$)	4.40	1	"	H(3)
	7.79	3	"	CH_3
(I)	2.33	5	"	Ph
(in trifluoro	3.88	1	"	H(3)
acetic acid)	7.80	3	"	CH_3
(III)	2.10	2	quartet	Ph(2H)
(in $\text{CDCl}_3 + \text{CH}_3\text{OH}$)	2.2-2.55	3	multiplet	Ph(3H)
	4.53	1	singlet	H(3)
	7.86	3	singlet	CH_3
(III)	1.95	2	quartet	Ph(2H)
(in trifluoro	2.1-2.5	3	multiplet	Ph(3H)
acetic acid)	3.7	1	singlet	H(3)
	7.7	3	singlet	CH_3
(IV)	2.0	2	quartet	Ph(2H)
(in trifluoro	2.1-2.5	3	multiplet	Ph(3H)
acetic acid)	3.17	1	broad	H(3)
	7.51	1	singlet	CH_3

phenyl group is almost the same in both these compounds. Moreover, the signal for the proton at C₃ in compound (IV) is slightly broadened and it looks as if split into a quartet by the methyl protons at C-6. Therefore, from its mass spectrum and the nuclear magnetic resonance spectrum it appears that compound (IV) is 5-benzoyl-4-hydroxy-6-methyl-2-pyridone.

It can be concluded that the reaction of malonyl chloride and benzoylacetone produced 5-acetyl-4-hydroxy-6-phenyl-2-pyrone(I) and 5-benzoyl-4-hydroxy-6-methyl-2-pyrone(III). Compound (I) isomerized into compound (III) at its melting point. Both compounds give 4-hydroxy-6-phenyl-2-pyrone with sulphuric acid and 4-hydroxy-5-benzoyl-6-methyl-2-pyridone with ammonia. So the pyrone(I) undergoes rearrangement with ammonia and the pyrone(III) with acid.

EXPERIMENTAL

Reaction of Malonyl Chloride with Benzoylacetone

A mixture of benzoyl acetone (10g.) and malonyl chloride (8g.) was heated on steam bath for ten minutes. After cooling the product was triturated with ether. The solid product (10g.) thus obtained on fractional crystallization from the mixture of ether and tetrahydrofuran and finally from ethyl alcohol yielded 5-acetyl-4-hydroxy-6-phenyl-2-pyrone (m.p. 167°) and 5-benzoyl-4-hydroxy-6-methyl-2-pyrone (m.p. 224°).

Preparation of 5-benzoyl-4-hydroxy-6-methyl-2-pyridone

5-benzoyl-4-hydroxy-6-methyl-2-pyrone (1g.) was dissolved in aqueous ammonia (0.88)(40ml) and kept for two days. Then the solution was evaporated up to dryness. The solid residue after triturating with ether was crystallized from ethyl alcohol into colourless needles of 5-benzoyl-4-hydroxy-6-methyl-2-pyridone (0.71g., 70%, m.p. 322°d.).

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