A THESIS ENTITLED

" SOME NEW REACTIONS OF MALONYL CHLORIDE "

BY

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J.J. Davis

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SOME NEW REACTIONS OF MALONYL CHLORIDE.

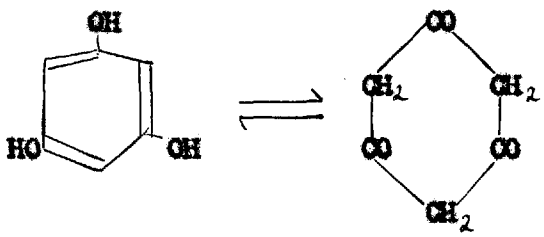
SECTION A - THEORETICAL.

I. The Nature of the Reaction Products from Ketones and Malonyl Chloride.

That malonyl chloride and acetone react vigorously when warmed together was discovered by Komninos (Comyt.rend., 1918, 167, 781; Bull. Soc. Chim., France, 1918, 23, 449). He claimed that 3:5-diketohexanoyl chloride (I) and phloroglucinol (II) were produced in this reaction as follows:-

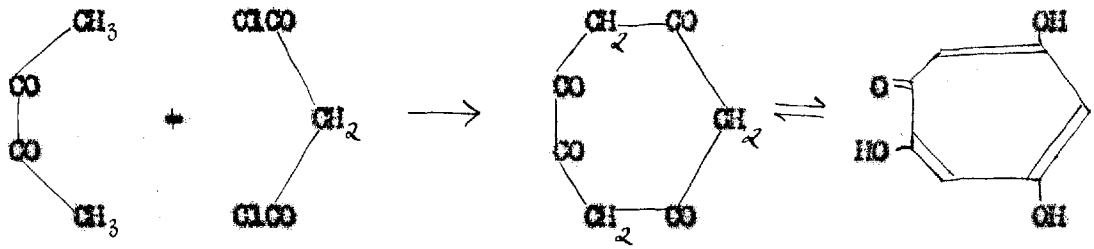
$$CH_3COCH_3 + ClOOCH_2COCl \longrightarrow CH_3COCH_2COCH_2COCl + HCl$$

(I) / -HCl



(II)

The reaction thus appeared to involve direct acylation of methyl groups adjacent to carbonyl and such a ready method of forming C - C links ought to have many applications. Nevertheless, the reaction has not been exploited or even reinvestigated with a view to its utilisation. At the outset of this work there was no reason to doubt that phloroglucinol was in fact formed. If the reaction set out above was correct, diketones would be expected to give seven-membered rings,thus enabling direct syntheses of members of the tropolone series to be carried out; diacetyl would produce the dihydroxytropolone (III), as follows:-



(III)

This prediction was not in fact realised, because reinvestigation of Kamminos's reaction has shown it to be much more complicated than he postulated and neither (I) nor (II) is formed. The product proved to be 6'-chloro-2';4-diketo-2;2-dimethylpyrano(3';4'-5;6)γ-dioxin (IX; R-R'=Me).

In view of this, the following references to the reaction as a synthesis of phloroglucinol now require revision: Beilstein, 4th Edn., EI, 6, 545; Richter, "The Chemistry of the Carbon Compounds", Elsevier, New York, 1946, 3, 230; Bernsthen, "A Textbook of Organic Chemistry", Blackie and Son, Glasgow, 1943, p. 403.

Repetition of Kamminos's experiments (loc. cit.) confirmed that malonyl chloride and acetone reacted readily, but no phloroglucinol could be detected in the product. Furthermore, other differences from Kamminos's descriptions were also found. Thus, Kamminos reported that in the presence of marble chips, the reaction afforded mainly a vermillion-coloured compound, $C_6H_7O_3Cl$, decomposing at 160° with discolouration from 95-100°, and to this he attributed the structure (I). With hot water, chloride ion was formed and with boiling water in the presence of marble chips an excellent conversion of (I) to phloroglucinol was claimed. It has now been shown that the malonyl chloride-acetone

reaction mixture rapidly deposits a crystalline solid in good yield even in the absence of marble. If collected at once and recrystallised, the product is obtained colourless; otherwise it rapidly becomes dark red, although it may be decolourised with the aid of charcoal. The purified product has m.p. 183° (decomp.) and the empirical formula $C_9H_7O_5Cl$. Treatment with hot water (or alcohols) liberates hydrogen chloride, but no conversion to phloroglucinol could be effected. However, with cold water and with ethanol, solutions were obtained which gave red colours with ferric chloride - phloroglucinol gives a violet colour. Hence some <u>other</u> enolic substance was evidently produced under these conditions.

At this point in the investigation it was decided to see whether a ketone not containing methylene groups (α- to carbonyl) would react. If such a ketone reacted with malonyl chloride, it would seem that only the carbonyl group was involved in the reaction. Benzophenone was found to react easily with malonyl chloride to give a well-defined crystalline product, m.p. 179° (decomp.). This reaction was evidently not a C-acylation by malonyl chloride, as had been implied by Komninos for the case of acetone.

It was then shown that the reaction was a general one for ketones. The products that have been so produced are listed in Table I, which includes light-absorption data; the compounds have a characteristic absorption band in the U.-V. at <u>ca.</u> 3140Å., $\varepsilon \simeq$ 7000-1100.

Table 1. Products from malonyl chloride and ketones.

Ketone.	Product	M.P.	Light absorption in dioxan.	
			$\lambda_{max.}$ (Å.)	ε
acetone	$C_9H_7O_5Cl$ (III)	183° (decomp.)	3020*	9700
			3140	10900
			3180*	9700
benzophenone	$C_{19}H_{11}O_5Cl$ (IV)	179° (decomp.)	2450*	14200
			2510	16700
			2580	15300
			2900*	7100
			3040	8200
			3120*	7100
acetophenone	$C_{14}H_9O_5Cl$	147°	2800	4700
			3140	10000
diethyl ketone	$C_{11}H_{11}O_5Cl$	104°		
methyl n-propyl ketone	$C_{11}H_{11}O_5Cl$	89°	3140	8000
cyclohexanone	$C_{12}H_{11}O_5Cl$	129°		
ethyl aceto-acetate	$C_{12}H_{11}O_7Cl$	118° (decomp.)		
ethyl pyruvate	$C_{11}H_9O_7Cl$	87.5°		

*inflection.

Molecular weight determinations on the acetone (III) and benzophenone (IV) products, by the cryoscopic method in bromoform, showed that the compounds were monomeric. The formation of the chloro-compounds could therefore be represented by the following general equation:-

$$RR'CO + 2CH_2(COCl)_2 = RR'C_7HO_5Cl + 3HCl \qquad (1.)$$

At this stage it was apparent that further information on the structure of the malonyl chloride products could only come from degradative work and it appeared pertinent to investigate the action of water and alcohols. This work can be conveniently divided into degradation using (a) vigorous and (b) mild conditions.

(a) Degradations under vigorous conditions.

Treatment of the benzophenone-derived compound (IV) (Table I) with boiling ethanol and then with ammonia in the cold, gave benzophenone and malonamide. On reacting (IV) with boiling water, carbon dioxide (83% of 3 mols.), hydrogen chloride (1 mol.), benzophenone (1 mol.) and acetone (as the 2:4-dinitrophenylhydrazone) were obtained in accordance with the equation:-

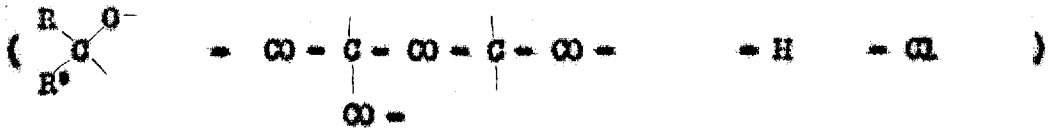
$$C_{19}H_{11}O_5Cl + 3H_2O = Ph_2CO + HCl + 3CO_2 + Me_2CO \qquad (2.)$$

The formation of the 3-carbon fragment, acetone, together with the evolution of carbon dioxide, had especial significance: evidently the molecule of the chloro-compound contained two malonyl residues joined through carbon atoms, i.e. a potential acetone-tricarboxylic grouping, as a structural feature. This was strongly supported by further results.

The benzophenone-derived chloro-compound (IV) was, for a short time, heated on the steam-bath with three mols. of ethanol. Hydrogen chloride was evolved and from the residue, which contained benzophenone and which gave a strong reddish colour with ferric chloride, a crystalline copper derivative was prepared. This was found to be identical with the copper enolate of acetone-1:1:3-tricarbethoxylate, synthesised via the reaction of malonic ethyl ester acid chloride with ethoxymagnesiomalonic ester, an

unambiguous method of preparation. From a similar degradation of the acetone-derived chloro-compound (III) with three mols. of boiling ethanol an identical copper derivative was isolated.

The results at this stage suggested the following partial structure for the malonyl chloride-ketone reaction products, $RR'C_7HO_5Cl$:-



The ease of disruption of the molecule made it unlikely that the ketone and bis-malonyl moieties were joined by C - C links.

(b). Degradation under mild conditions.

By treating the benzophenone-derived chloro-compound (IV) in dioxan with water in the cold, benzophenone was obtained, together with a water-soluble crystalline acid (V), $C_6H_3O_5Cl$, m.p. 134.5° , which gave a deep red colour with ferric chloride. The formation of this new product can be represented ~~xxxx~~ by the equation (3), which should be compared with equation (2) for the reaction with hot water.

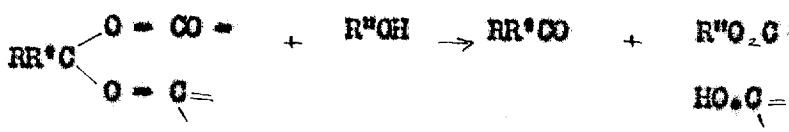
$$C_{19}H_{11}O_5Cl + H_2O = Ph_2CO + C_6H_3O_5Cl \qquad (3)$$

With methanol or ethanol, in dioxan in the cold, compound (IV) underwent similar fissions to yield benzophenone plus crystalline products (VI), $C_7H_5O_5Cl$, and (VII), $C_8H_7O_5Cl$, respectively, which were also enolic (red ferric colours).

These products were respectively methyl and ethyl homologues of (V) and therefore probably the methyl and ethyl esters. On attempted hydrolysis of (VII) with one equivalent of aqueous sodium hydroxide,

the compound decomposed with violent evolution of carbon dioxide. From the solution, which contained chloride ion, ethyl acetoacetate was isolated as the 2:4-dinitrophenylhydrazone: the degradation to this ester supported the view that (VII) was an ethyl ester of (V). Reaction of (V) with diazomethane, in an attempt to obtain (VII) yielded a chlorine-free enolic product, $C_8H_8O_6$. However, since the identical compound was formed by treating (VI) with diazomethane, the suspected structural connection between the water and methanol products was nevertheless established.

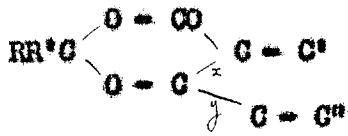
The fission of the benzophenone-derived chloro-compound (IV) by water and alcohol to benzophenone and the enolic products (V), (VI) and (VII), suggested that the ketone moiety was linked to the C_6 fragment via potential carboxyl and enol functions, as in (A), so that the hydrolysis (and alcoholysis) could be accounted for thus:-



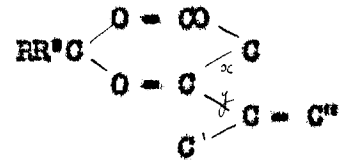
(A)

(R" = H, Me, or Et)

Examination of the structural possibilites shows that there are only two ways in which the C_6 fragment, an acetone 1:1:3-tricarboxylic residue, can be arranged so as to be bound to the ketone moiety as in (A). These arrangements are shown in (B) and (C):-

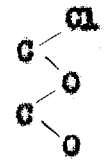


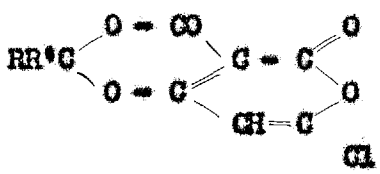
(B)



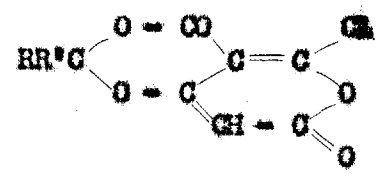
(C)

One or other of the linkings, x and y was necessarily a double bond [see (A)] . Additional atoms to be placed in the structure were Cl, H and 2 O, in such a manner as to express (a) that the chlorine atom was less reactive than in its initial state of combination (as a -COCl grouping) and (b) that positions C' and C" were both potential carboxyl groups. The requirements (a) and (b) seemed to be met satisfactorily by the arrangement shown inset for the carbon atoms C' and C". This grouping could be accomodated better on skeleton (B) than (C) because the latter would lead to a four-membered ring structure which would probably not be formed in such a facile reaction as that which was under investigation: this would be expected to give rise to a system containing the more stable six-membered ring structure. Accepting skeleton (B), the possible formulae for the malonyl chloride-ketone products were reduced to two in number, viz. (IX) and (X).

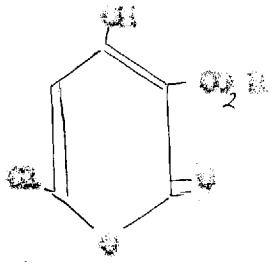




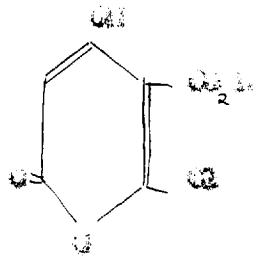
(IX)



(X)



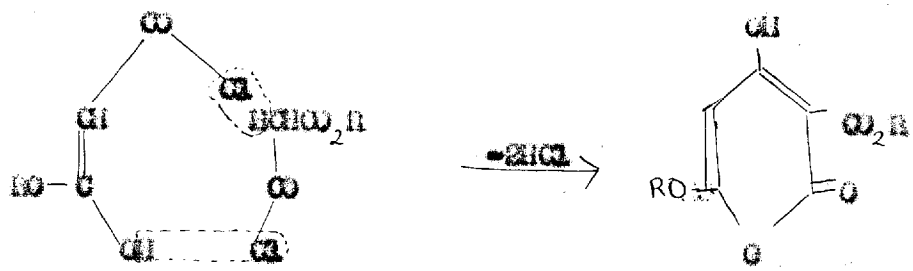
(Va)



(Vb)

It then necessarily followed that the degradation product (V) had one of the structures (Va) and (Vb) (R=H), whilst the products (VI) and (VII) were most probably the corresponding methyl and ethyl esters (R=Me and Et).

Compounds with related structures were known. The pyrone derivatives (XI) (R=Me and Et) had been prepared by Staudinger and Becker (Ber., 1917, 50, 1016) by the action of quinoline upon an ether solution of malonic half ester acid chlorides:-

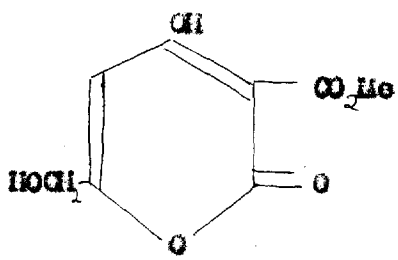


(XI)

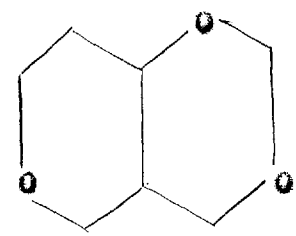
Of the possible structures for the products (XI) had been shown to account fully for the observed properties and could be accepted as correct. The compounds (XI; R=Me and Et) were therefore prepared and the light absorption characteristics determined. The spectra bore a close resemblance to those of the degradation products (V), (VI) and (VII) (see Table 3); thus a clear indication that these products had

the suspected pyrano structures was forthcoming. By reaction of the chloro-compound (VI) (from the methanol degradation) with sodium methoxide, a methoxy-derivative, $C_7H_5O_5OMe$, m.p. 148.5°, was produced, which was identical with the pyrano derivative (XI; R=Me) synthesised by Staudinger's method. It was thus shown that the degradation products (V), (VI) and (VII) were 6-chloro-4-hydroxy-3-ketopyran-2-carboxylates (Va; R=H,Me and Et, severally), and not the isomers (Vb).

The compound $C_8H_8O_6$ formed from (V) and (VI) with diazomethane, and isomeric with (XI; R=Me), was then most probably the 6-hydroxymethyl derivative (XII).



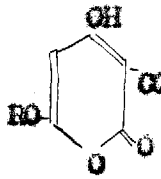
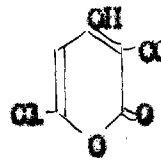
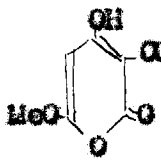
(XII)



(XIII)

It followed then, that the malonyl chloride-ketone reaction products, listed in Table 1, had the structures (IX) - and not (X). The compounds are thus 2,2-disubstituted derivatives of 6'-chloro-3',4'-diketopyrano (3',4'-5,6)m - dioxin. No representatives of the unsaturated pyrano (3',4'-5,6)m - dioxin ring system have hitherto been described, so that it constitutes a novel heterobicyclic system.

Table 2. Light absorption of pyrone derivatives in dioxan.

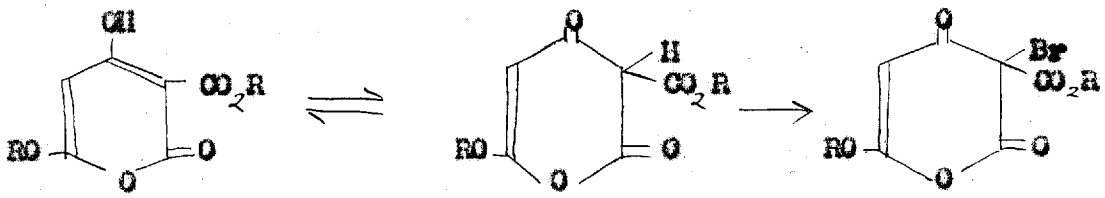
Compound			$\lambda_{max.}$ (Å)	ε
 (XI)	[synthesised by Staudinger's method]	R = Me	3050	16400
		R = Et	3040	15500
	[from degradation of (IV)]	R = H, (V)	2950*	8600
			3040	10100
		R = Me, (VI)	3040	12300
		R = Et, (VII)	3040	11500
			3190*	10500
	[from (VI) with HaOMe]		3040	17600

* inflection

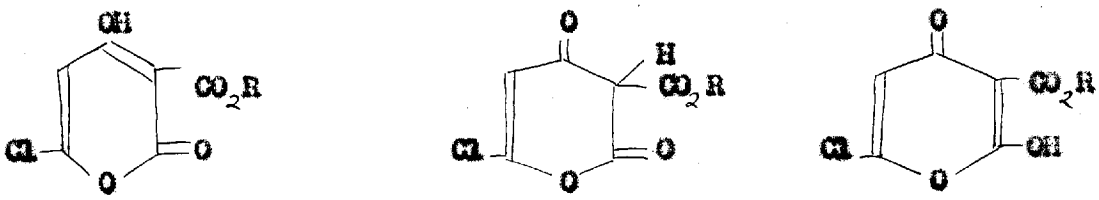
However, a few derivatives of the fully reduced system (XIII) have been prepared by Späth, Lorenz and Freund (Ber., 1943, 76, 722; 1944, 77, 354) by the condensation, under acid conditions, of lower aliphatic aldehydes.

The compounds (Va), i.e. the chlorohydroxypyrone carboxylates also constitute a unique type of compound. Thus, firstly, the chlorine atom is in the reactive 6-position and secondly, the 4(2)-hydroxy-2(4)-ketopyran system is present so that the structures (Vc) and Vd) are possible tautomeric or reaction forms. Thus, Staudinger and Becker (loc. cit.) found that (XI; R = Me, Et) could be brominated, the product

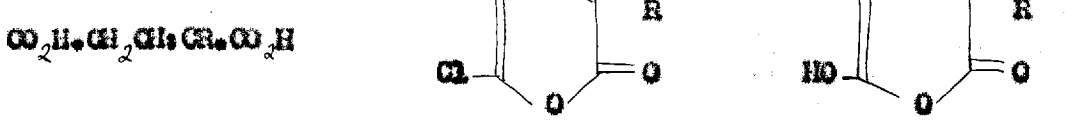
appeared to have the structure (XIV) and this suggests that (XI) had reacted in the form (XIa).



(XI) (XIa) (XIV)



(Va) (Vc) (Vd)



(XV) (XVI) (XVII)

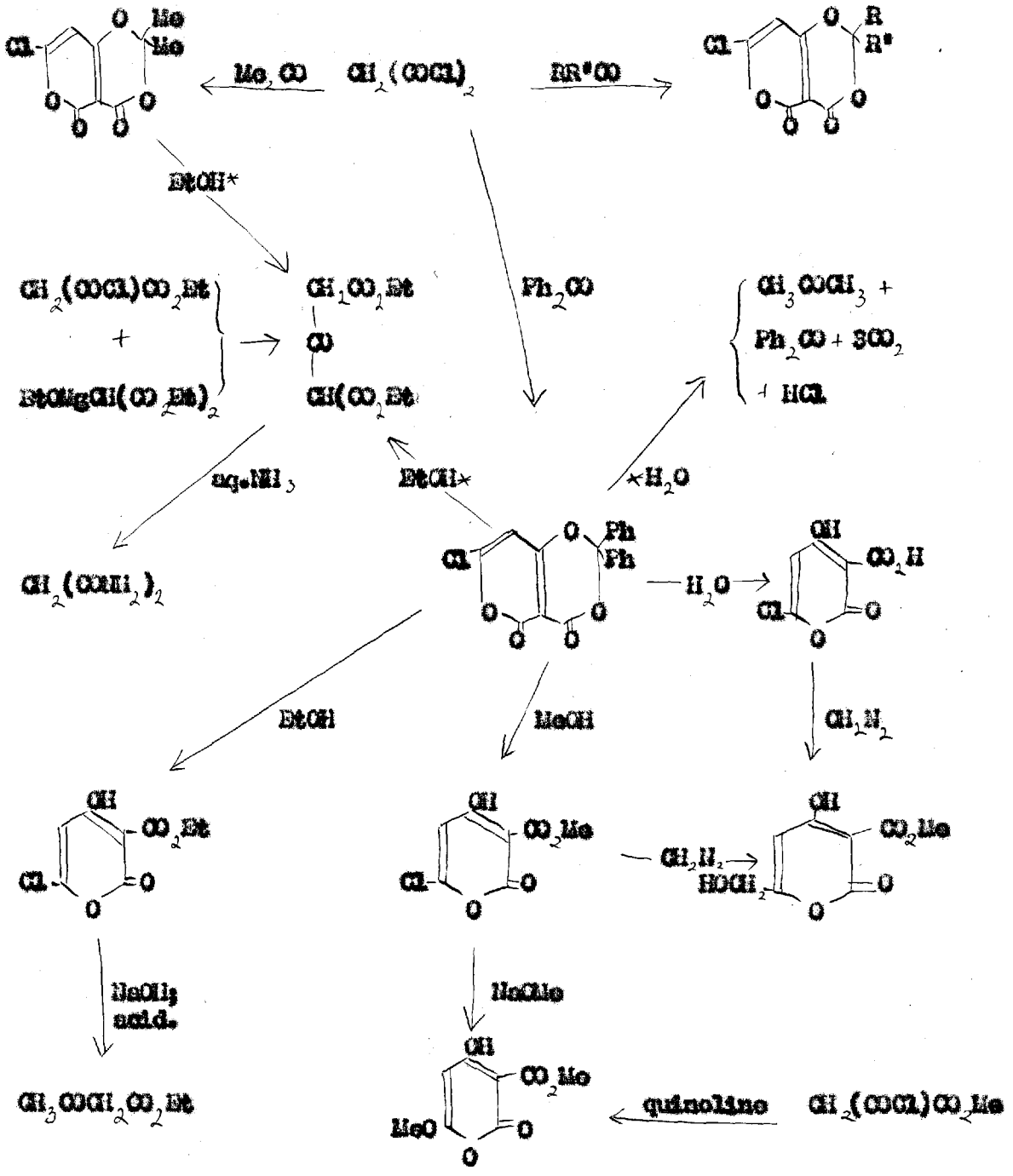
Structure (Va), in which the double bonds are completely conjugated, is strongly supported by light absorption data (Table 2). The forms (Vc) and (Vd) would not be expected to absorb at such long wave-length.

Very few 6-chloropyrones have actually been prepared; Thorpe and co-workers (J.Chem.Soc., 1911, 99, 2208-41 and 1912, 101, 856-70; Proc.Chem.Soc., 1911, 27, 252 and 1912, 28, 49) prepared four (XVI; R= H, Me, Et and Bz) by reaction of glutaconic acids (XV) with acetyl

chloride, the 6-hydroxypyrone (XVII) also being formed. It should be noted that (XVII), which are glutaconic anhydrides, behave as monobasic acids, giving for example crystalline monopotassium salts, as well as ferric colours, so that they evidently exist in the hydroxy-pyrone form.

The reactions that have been carried out in order to establish the structure of the ketone-malonyl chloride products are grouped together in Table 3.

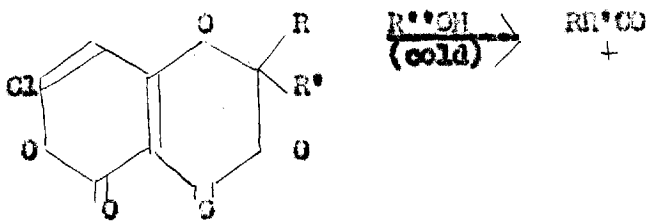
Table 3. Summary of the reactions involved in establishing the structure of the ketone-polyaryl chloride products.



* boiling

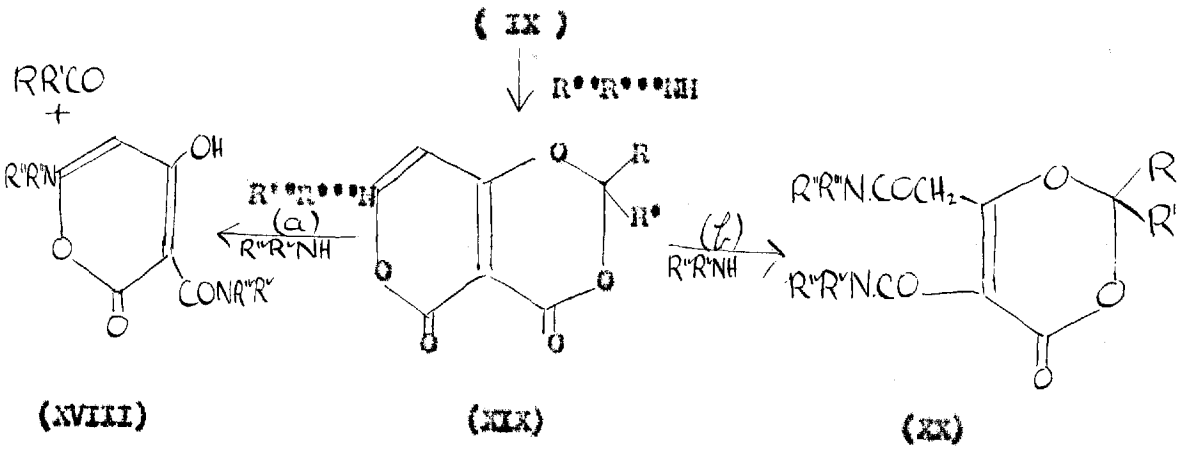
II. The Reactions of the Chloropyranodioxins with Amines.

The work hitherto described in this thesis has been primarily concerned with establishing the structure of the ketone-malonyl chloride reaction products (IX), but has also included the reactions of the system with alcohols, water and related reagents. It has been shown that alcohols and water, in the cold, attack the 4-keto-2-dioxin ring preferentially, giving rise to the chloropyrones (Va):-



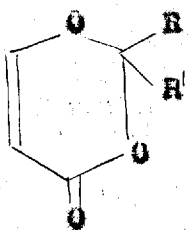
(IX) (Va)

It was conceivable that organic bases would react with the chlorine atom, forming N-substituted aminopyranodioxins which might undergo ring-opening with a further molecule of base, in either or both of the following ways:-



(XVIII) (XIX) (XX)

Examination of the action of primary and secondary bases on the system (IX) has shown that the chlorine atom is first substituted; then, the pyrone ring is opened as in (b), above, affording derivatives of 4-keto-g-dioxin (XXI); finally, the ketone fragment is split off giving an acetone-1:1:3-tricarboxylic acid triamide (XXII):-



(XXI)

(XX) $\longrightarrow$ $R_2'CO + HNR''R'''.COCH_2COCH(OR'')R^V$

$OHNR''R'''$

(XXII)

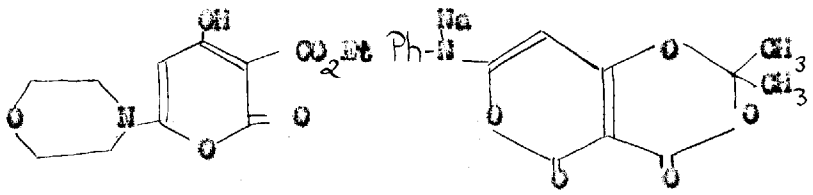
On treatment of the chloropyrone-g-dioxins (IX) in suitable solvents with two mols. of various primary and secondary bases, base hydrochloride formed immediately, with much evolution of heat, and the mono-substitution products (XIX) were obtained (see Table 4). These absorb light strongly in the 330-400 Å region, and resemble in this respect the simpler derivative obtained from the chloropyrone (Va; R'' = Et) with morpholine. The nitrogenous products (XIX) unlike the parent chloro-compounds (IX) are stable to water and alcohols; thus many of them can be recrystallised from boiling ethanol in good yield. They also lack basic properties and in this respect may be compared with amides. Thus the aniline product (XIX; R = R' = Me; R'' = H, R''' = Ph) is pseudo-amidic and gives crystalline metal derivatives with the aqueous hydroxides of lithium, sodium and potassium, though not ammonium; this aniline product dissolves easily in the appropriate aqueous solution of

Table 4. Products from the chloro-compounds with bases.

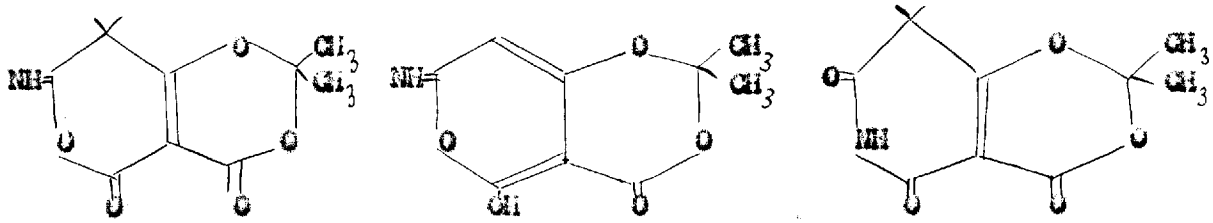
Product (XIX)				M.P. (°C)	Light absorption in dioxan.	
R	R^{I}	R^{II}	R^{III}		$\lambda_{max.}$ (Å)	ε
Me	Me	Ph	H	192.5 *	3400	35,000
"	"	Bz	"	176 *	3300	28,300
"	"	Et	Et	145 *		
"	"	$O(CH_2)_2$:		182 *	2270 3360	17,400 30,900
"	"	$(CH_2)_5$:		151.5 *		
"	"	Ph	Me	160		
Ph	Ph	Bu	H	107.5 *	3320	29,400
"	"	$O(CH_2)_2$:		166 *	2270 2510 2570 3380	25,100 6,100 36,500
"	"	$(CH_2)_5$:		182 * [illegible]		
Me	Pr	$O(CH_2)_2$:		143 *	2510 2560 3330	7,700 21,700
"	Ph	"		196 *	2270 2510 2580 3370	15,800 6,200 36,000
"	CO_2Et	Et	Et	110.5	3330	25,400
$(CH_2)_5$:		$O(CH_2)_2$		191 *		
		(XXIII)		[illegible] 165	2270 3250	14,800 31,800
		(XXV)		300 *	2800 3090	15,700 14,900

* with decomposition.

alkali, which soon deposits the crystalline metallic derivative. Reaction of the sodio-derivative with methyl iodide afforded a methyl derivative identical with (XIX; R = R' = Me, R'' = Me, R''' = Ph), which was prepared from the chloropyrano-*p*-dioxin (IX; R = R' = Me) and methylaniline; it therefore followed that the metal derivative had the structure (XXIV) :-



(XXIII) (XXIV)



(XXV) (XXVI) (XXVII)

With ammonia, the chloro-compound (IX; R = R' = Me) afforded a mono-substitution product of the expected composition, but this had a much less intense light-absorption maximum at somewhat shorter wave-length than the compounds (XIX). It appears, therefore, that this ammonia product exists in an isomeric form: the structure (XXV) seems the most probable. The alternative tautomeric form (XXVI) can be discounted because the compound has no enolic properties. Moreover, the ease with which the ring is split by amines (see below) rules out the cyclic imide

structure (XXVII) or tautomeric forms of this. For the same reason, condensation of the ammonia compound (XXV) with amines could evidently not be achieved in the way possible with other imino-heterocycles (Elvidge and Linstead, J. Chem. Soc., 1952, in the press).

Treatment of the nitrogenous compounds (XIX) and (XXV) with a further molecule of a primary or secondary amine caused fission of the pyrone ring, and the derivatives (XX) of 4-keto-1:3-dioxin (XXI) were formed (see Table 5). Those derivatives (XX) having $R^{II}R^{III} = R^{IV}R^{V}$ were also obtained direct from the chloropyrano-1:3-dioxins (IX) using the appropriate quantity of amine. The structure of the dimorpholide (XX; $R^{II}R^{III} = R^{IV}R^{V} = O(CH_2)_2$:) was confirmed by degradation with boiling water. Carbon dioxide and acetone were formed, together with enolic acetone-1:3-dicarboxymorpholide, the identity of which was verified by a synthesis from acetone-1:3-dicarbethoxylate and morpholine. Sodium hydroxide in the cold also gave the acetone dicarboxymorpholide in good yield.

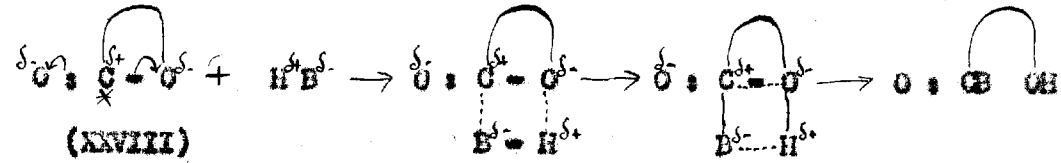
The only representative of the simple 4-keto-1:3-dioxin ring system previously described seems to be the parent substance itself (Carnero and Calvet, Anales Soc. espan. fis. quim., 1934, 32, 1168.). Hence the general properties of the new compounds (XX) have been determined. Since they contain an enol ether link and an $\alpha\beta$-unsaturated lactone grouping, these keto-dioxins bear an interesting relationship to both of the two main types of unsaturated lactone (see Buehl, Linstead and Orkin, J. Chem. Soc., 1950, 2213) and their reactions demonstrate that the system (XX) is indeed a composite type.

Qualitative tests, largely with the readily available derivative (XX; $R''R''' = R^{V}R^{V} = O(CH_2)_2$:) showed that the 4-keto-g-dioxin ring was stable to cold water and aqueous hydrochloric acid, as well as to boiling alcohols and dilute methanolic hydrogen chloride. At pH9, the Légal and dichlorophenol-indophenol colour tests (Idem, loc.cit.) were negative, and ammoniacal silver nitrate was reduced only on heating. Rupture of the ring occurred in methanolic sodium methoxide, besides boiling water and cold sodium hydroxide, and also with primary and secondary amines. It should be pointed out however, that the behaviour of the keto-dioxin ring to the reagents may be a function of the particular substitution encountered in the derivatives (XX) examined. This is suggested by the differing reactivity of the fused pyrano-g-dioxin system to ethanol when substituted by chlorine, as in the compounds (IX) and when substituted by amine residues, as in the compounds (XIX).

This fact, namely, that aminopyranodioxins are more stable to ring-opening agents than the corresponding chloropyranodioxins might be explained as follows. In anyring-opening reaction of a lactone, the reagent will be to a greater or lesser extent ionised thus:-

$$HB \longrightarrow H^{\delta+}\ B^{\delta-}$$

To enable such a reagent to attack the system there should be no influence in the latter tending to oppose the existence of the lactone groupings in the form (XXVIII). The reaction would then be formulated



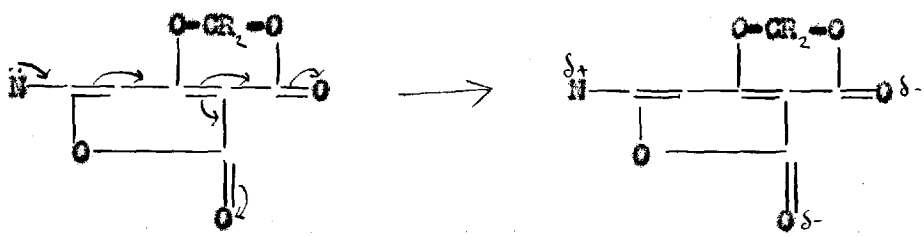
(XXVIII)

Table 5. Ketodioxins (XX).

R = R'	NR"R"	NR'R'	M.P. (°C)	Light absorption $\lambda_{max.}$ (Å)	ε	
Me	NH_2-	$O(CH_2)_2N$-	223			
"	$(CH_2)_5N$-	"	131.5			
"	$O(CH_2)_2N$-	"	134	2270 2510 2560	9,200 11,100 11,800	D
"	"	Et_2N-	117			
"	PhNH-	PhNH-	100	2400 2510 2900	20,900 17,100 14,000	C
"	BuNH-	BuNH-	86	f 2700 2800	8,600	C
Ph	$O(CH_2)_2N$-	$O(CH_2)_2N$-	135	2510 2570	11,300	D
"	BuNH-	"	117.5	2560* 2660 2760*	6,900 7,900 4,800	C

*inflection. C=chloroform.
f-fluoresces D-dioxan.

It is evident that if the electron deficiency on C* (XXVIII) is compensated, the attack of the $B^{\delta-}$ group will not be facilitated. This state of affairs would occur with an amino group in the system, as follows:-

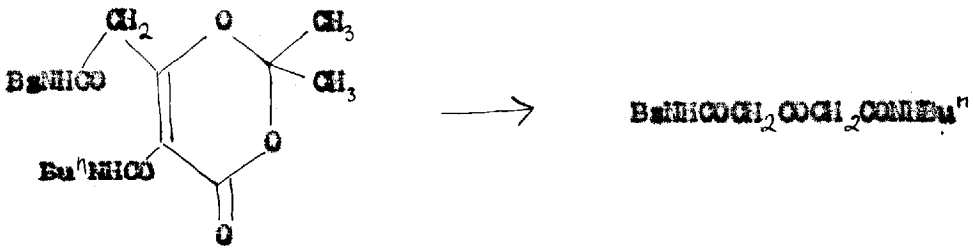


This situation also readily explains the lack of basicity in the

aminopyranodioxins (XIX) as the lone pair of electrons on the nitrogen atom would not now be available to co-ordinate a proton.

The reactivity and availability of the chloropyrano-p-dioxin compounds (IX) and of the pyrone (Va) and keto-dioxin (XX) degradation products, provide good preparative routes to esters, amides and mixed ester amides of acetone-1:3-di- and -1:1:3-tri- carboxylic acid, many of which have hitherto been inaccessible. The preparations of acetone-1:1:3-tricarbethoxylate (p.5) and acetone-1:3-dicarboxymorpholide (above) were the first examples of this possibility. The following additional examples are given to illustrate the scope of this preparative methods-

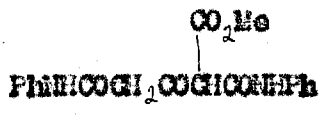
The keto-dioxin derivative (XXIX) prepared from (IX; R=R'=Me) by reaction first with benzylamine and then p-butylamine was



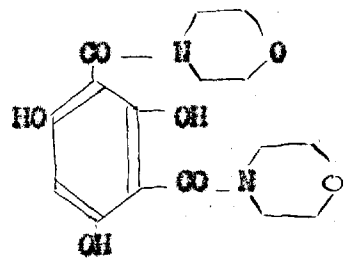
(XXIX) (XXX)

treated with boiling water. The mixed benzylamide p-butylamide (XXX) of acetone-1:3-dicarboxylic acid was thus obtained. Treatment of the dioxin (XX; R=R'=Me, R"R"' N-R"'R"N-NHPh) with methanolic sodium methoxide afforded the mixed methyl ester dianilide of acetone-1:1:3-tricarboxylic acid (XXXI). The alternative reaction of aniline with the chloropyrone ester (Va; R'=Me), obtained from (IX; R=R'=Ph) with methanol, yielded an identical acetone-tricarboxylic ester dianilide. When heated with an

excess of aniline, it underwent 'acid fission' being degraded to malonanilide.



(XXXI)



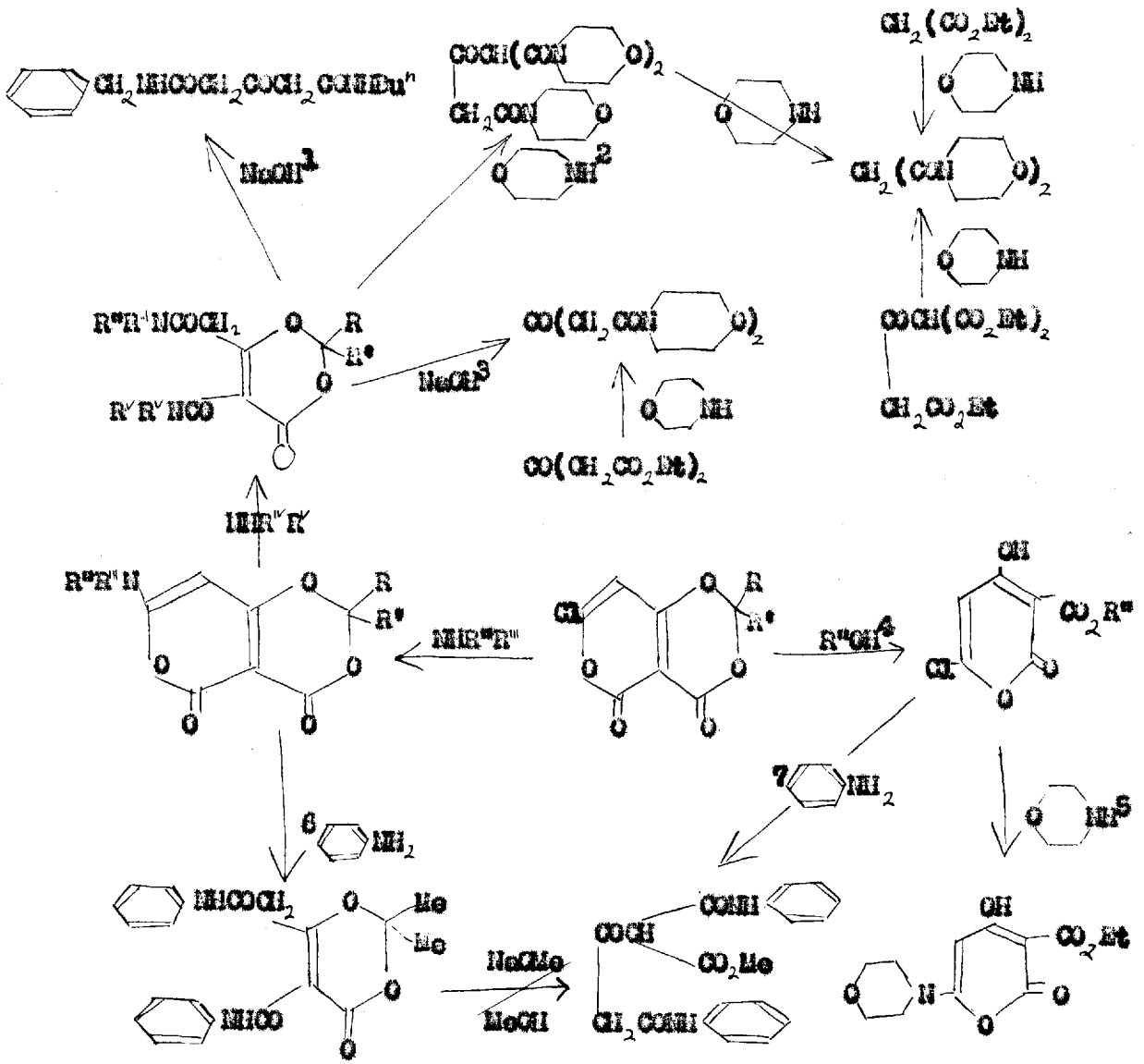
(XXXII)

From the chloropyranodioxins (IX; R-R'=Me and R-R'=Ph) with an excess of morpholine, acetone-1:1:3-tricarboxymorpholide was readily prepared. Its formation from the diphenyl compound (IX; R=R'=Ph) was also carried out stepwise, (IX) → (XIX) → (XX) → (XXII; R"R"'=R"R'=R'R"' =O(CH_2)$_2$) ; benzophenone was a second product at the last stage. The structure of the trimorpholide was confirmed by heating it with an excess of morpholine when over 70% of two mols. of malonmorpholide was obtained. Attempts to synthesise the trimorpholide by standard routes failed. This illustrates the power of the new methods. When heated with morpholine, ethyl acetone-1:1:3-tricarboxylate underwent 'acid fission' and gave only malonmorpholide. As an alternative, it had been hoped to condense malonmorpholidic acid chloride (for which the ethyl ester was prepared) with a metal derivative of malonmorpholide. However, dissolution of magnesium in methanolic malonmorpholide (as for magnesiomalonic ester) did not yield a metal derivative, and neither did treatment with sodium in formamide, because after subsequent attempted reactions with acetyl chloride, the malonmorpholide was recovered.

Dissolution of sodium in molten malonmorpholide caused a self-condensation. The enolic product, $C_{16}H_{20}O_7N_2$ which was hygroscopic, is given the structure (XXXII) by analogy with the production of phloroglucinol dicarbethoxylate from sodium and malonic ester (Moore, J. Chem. Soc. 1904, 85, 168).

The reactions that have been carried out under the heading of "The Reactions of the Chloropyranodioxins with Amines" are grouped together in Table 6.

Table. 6. Summary of the Reactions of Chloropyranodioxins with Amines, and Associated Reactions.



KEY

	R = R'	R''	R'''	R''	R'
1.	Me	H	Bz	H	Bu^n
2.	Me or Ph	O(CH$_2$)$_2$ *		O(CH$_2$)$_2$ *	
3.	Me	"		"	
4.	Ph				
5.		Et			
6.	Me	H	Ph		
7.		Me			

III. The Mechanism of the Reaction of Malonyl Chloride with Ketones.

Phosgene and oxalyl chloride react directly with ketones (and aldehydes) to yield gem-dichloro compounds and it has been suggested by Staudinger (Ber., 1909, 42, 3966) that the initial process is an addition of the acid chloride to the carbonyl group, followed by disproportionation, as follows:-

$$RR'CO + COCl_2 \longrightarrow RR'C(Cl)(O.COCl) \xrightarrow{-CO_2} RR'CCl_2$$

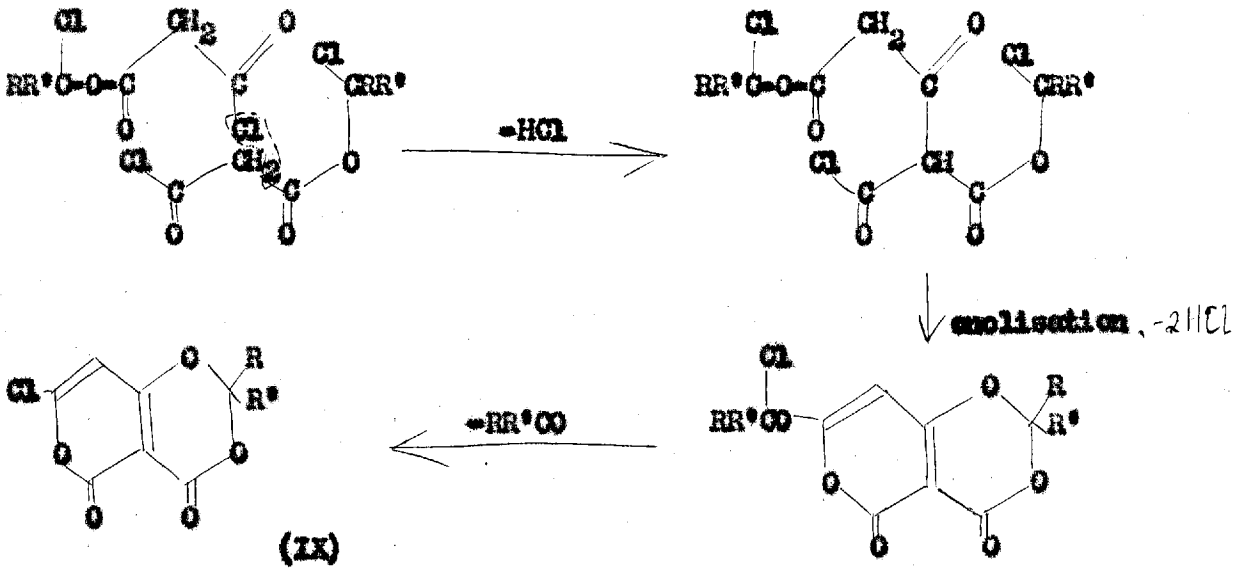
$$RR'CO + (COCl)_2 \longrightarrow RR'C(Cl)(O.CO.COCl) \xrightarrow{-(CO_2+CO)} RR'CCl_2$$

It might seem reasonable to suppose that the first stage in the malonyl chloride reaction was also an addition to the carbonyl group of the ketone giving an intermediate of structure; $RR'C(Cl)(OCOCH_2COCl)$ The next stages, to yield (IX), would involve condensation of this product either with itself, followed by elimination of one ketone residue, (as in A) or with malonyl chloride (as in B).

However, the above possibilites can safely be discounted, because good evidence has been obtained for the mode of reaction (C.).

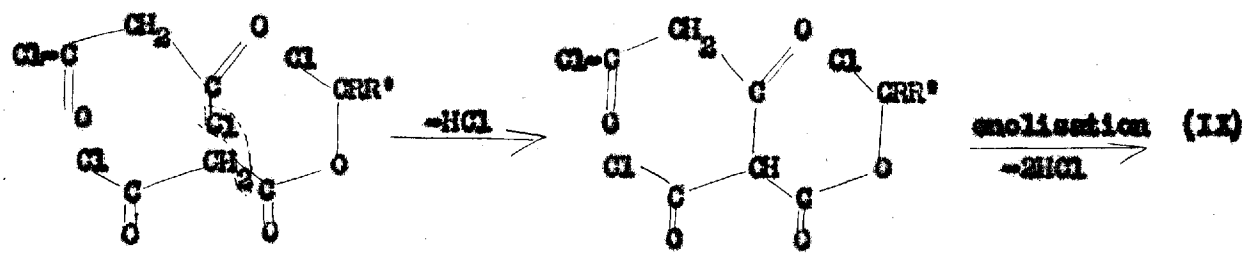
In this scheme, the ketone RR'CO acts as a very weak base, inducing the first stage of the reaction; use of a non-reactive base of comparable strength (see Braude, J.Chem.Soc., 1948, 1971) should therefore produce the intermediate (XXXIII) from malonyl chloride.

(a)

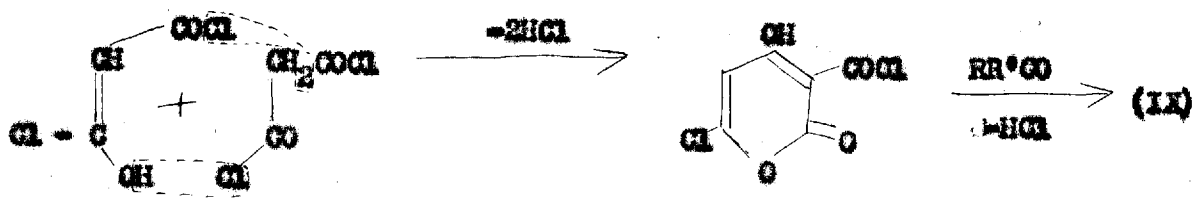


(IX)

(b)



(c)

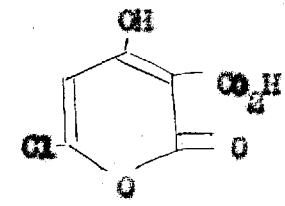


(XXXIII)

A dilute solution of the latter in anhydrous dioxan was examined spectroscopically with the following results:-

Table 7.

Time.	Maxima λ (Å)	E^{1}_{1}
1 hour	2800	40
	2930	31
	3040	26
25 hours	3040(only)	130
4 days	3040(only)	185
7 days	3040(only)	185



(XXXIV)

The appearance of the characteristic absorption band at 3040 Å indicated that a pyrone, presumably (XXXIII), had been formed quite rapidly at room temperature. No such band was obtained from a cyclohexane solution of malonyl chloride.

The estimated yield of (XXXIII) after 4 days, assuming ε = 10,000 (see Table 2), is 36%. So far the evidence was purely spectroscopic. Evaporation in the atmosphere of a measured portion of the solution, after standing for 13 days, afforded a solid which was triturated with water to remove malonic acid. The insoluble residue was 6-chloro-4-hydroxy-2-ketopyran-3-carboxylate (XXXIV; 41% yield), identical with a specimen previously prepared from the benzophenone-derived compound (IX; R=R'=Ph), and gave a deep-red ferric colour. Evaporation of the aqueous solution afforded malonic acid from the unreacted malonyl chloride.

The pyrone-acid chloride (XXXIII) was prepared from the pyrone acid (XXXIV) with thionyl chloride and reacted with benzophenone, when the chloropyranodioxin (IX; R=R'=Ph) was obtained; this was characterised as the n-butylamino-derivative (XIX; R=R'=Ph; R''=Bu; R'''=H. See Table 4).

Both stages of mechanism (C) have thus been demonstrated.

An implication of the mechanism (C) is that the reaction could be extended to aldehydes and nitriles; the work that has been carried out with these substances is described subsequently.

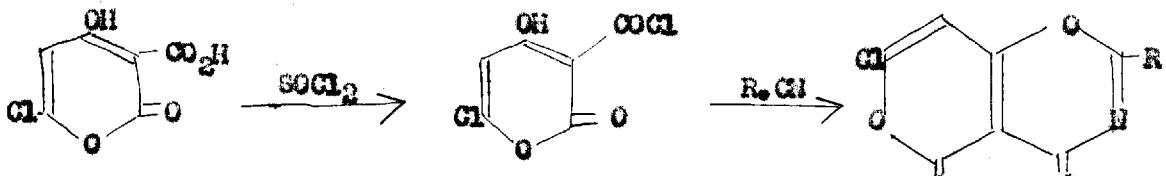
IV. The Reaction of Malonyl Chloride with Nitriles.

a) Pyrano-metoxazines.

The work on the mechanism of the reaction of ketones with malonyl chloride made it apparent that nitriles should react similarly to give substances of structure (XXXV). This hope has, in fact, been realized. Thus, reaction of benzonitrile with malonyl chloride afforded a substance of empirical formula $C_{13}H_6O_4NCl$, so that its formation could be represented as follows :-

$$C_6H_5CN + 2CH_2(COCl)_2 \longrightarrow C_{13}H_6O_4NCl + 3HCl$$

That this material had the structure (XXXV; R=Ph) was easily shown by synthesising it from the pyrone-acid chloride (XXXIII) which was in turn prepared from the pyrone-acid (XXXIV) with thionyl chloride thus :-



(XXXIV) (XXXIII) (XXXV)

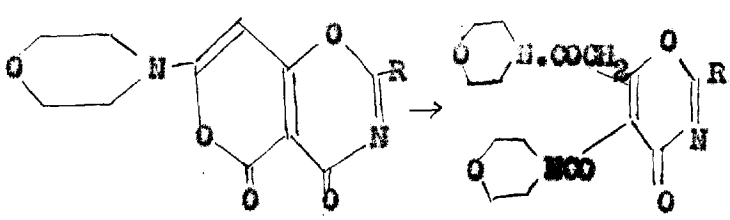
The identity of the synthetic material (XXXV; R= Ph) with that prepared directly from malonyl chloride was established through the hydroxypyrano-metoxazine (XXXIX), a simple derivative of (XXXV; R= Ph). (For the preparation and properties of (XXXIX) see p.32). The benzonitrile-derived compound was therefore 6'-chloro-2':4-diketo-2-phenylpyrano(3':4'-5:6) metoxazine. Similarly, acetonitrile and α- and β- naphthonitrile reacted with malonyl chloride giving products which are formulated as

(XXXV; R=Me, α -naphthyl and β -naphthyl), severally. No derivatives of the diketopyrano-metoxazine ring system appear to have been prepared before.

By analogy with the pyrano-dioxins, it seemed that the chlorine atom in (XXXV) would be reactive towards bases and also that the aminopyrano-metoxazine so formed would react further with bases, with fission of the pyrone ring, giving derivatives of 4-ketometoxazine.

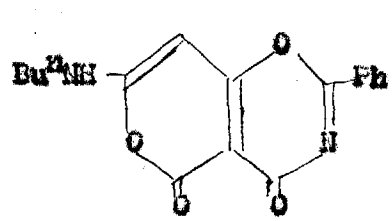
These predictions were borne out in practice thus providing confirmation of the structure (XXXV). Thus (XXXV; R=Ph, α- and β- naphthyl), reacted vigorously with two molecules of morpholine; the morpholinopyrano-metoxazines (XXXVI; R=Ph, α- and β-naphthyl), severally, were isolated from the reactions. Similarly, (XXXV; R=Ph) afforded (XXXVIII) by reaction with n-butylamine.

Reaction of the morpholino-derivatives (XXXVI) with a further molecule of morpholine readily gave the expected 4-ketometoxazines (XXXVII; R=Ph, α- and β- naphthyl), severally. No 4-ketometoxazine derivatives have been previously described in the chemical literature, and so the stability of this new ring system to ring-opening reagents has been examined. The results are shown in Table 8. It is seen that there is a close resemblance to the reaction of the ketodioxin ring (p.58).



(XXXVI)

(XXXVII)



(XXXVIII)

Table 8.

Reagent	Cold	Reflux
Aq.HCl	negative[1]	-
MeOH/HCl	-	negative[2]
H_2O	-	purple colour[2] with $FeCl_3$
MeOH	-	negative[3]
BuOH	-	" [3]
AqNaOH	purple colour[4] with $FeCl_3$	-
NaOMe/MeOH	-	red colour[2] with $FeCl_3$

1. after 1 hour. 2. after 5 minutes. 3. after 10 minutes. 4. after 2 minutes.

With excess of morpholine, the derivative (XXXVI; R = Ph) afforded acetone-1:1:3-tricarboxylic acid trimorpholide, identical with specimens that had previously been prepared from the chloropyranodioxins (see p.23).

Treatment of the benzonitrile compound (XXXV; R = Ph) with aqueous alkali gave benzoic acid, and also a resinous substance probably identical with the product of the reaction of acetone with aqueous alkali. If this is so, this reaction can be interpreted thus :-

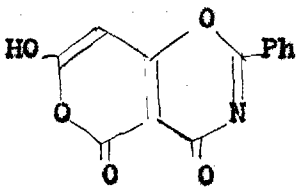
$$C_{13}H_6O_4NCl + 5NaOH \longrightarrow CO_2NaCH_2COCH(CO_2Na)_2 + C_6H_5CO_2Na + NH_3 + NaCl$$

$$\downarrow 3NaOH$$

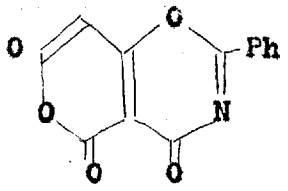
$$3Na_2CO_3 + CH_3COCH_3 \longrightarrow \text{acetone resin}$$

The hydroxypyrano-metoxazine, $C_{13}H_7O_5N$ (XXXIX), mentioned previously (p. 30), was formed by the reaction of (XXXV; R = Ph) with water in dioxan

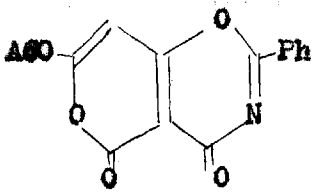
as solvent (Cl replaced by OH). It is seen that (XXXIX) is an anhydride and could be written as (XXXIXa), but the facts that the compound gave a red ferric colour and dissolved with effervescence in aqueous sodium bicarbonate are evidence for the enol structure. Reaction of (XXXIX) with acetic anhydride afforded the enol acetate (XL), which gave no ferric colour, nor effervesced with bicarbonate solution. The hydroxypyrano-metoxazine (XXXIX) reacted additively with one molecule of morpholine giving an acid product which is assigned the structure (XLI) by analogy with



(XXXIX)

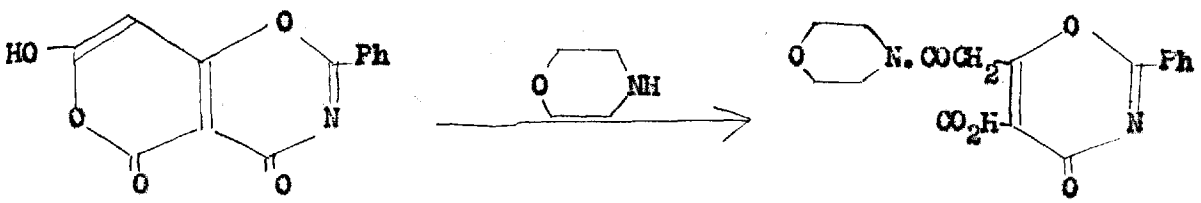


(XXXIXa)

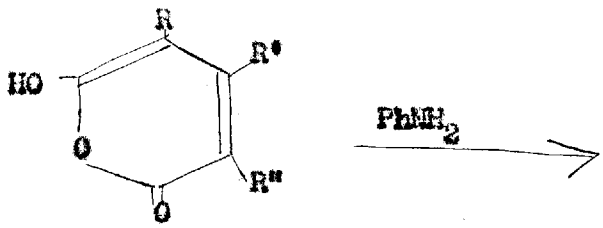


(XL)

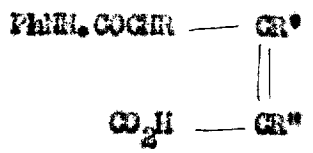
(a) the reaction of the 6-hydroxypryones (XLII) with aniline when the glutaconic acid semianilides (XLIII) are produced (Thole and Thorpe, J.Chem.Soc. 1911, 99, 2218 & 2222) and (b) the reaction of the hydroxypyrano-tropolone (XLIV) with ammonia when the tropolone derivative (XLV) is formed (Crow, Hawarth and Jefferies, J.Chem.Soc., 1952, 3707).



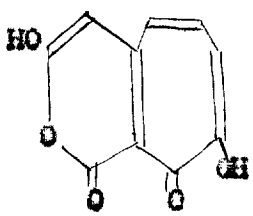
(XXXIX) (XLI)



(XLII)

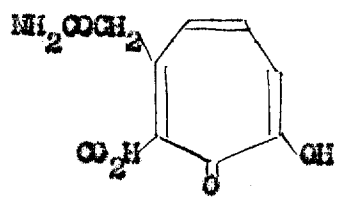


(XLIII)



(XLIV)





(XLV)

Table 9 records U-V spectrographic data for some of the pyrano-motoxnazines and motfoxazines.

Table 9. Light absorption of pyrano-metoxazines and metoxazines.

Compound	λ_{max} (a)	ε	Solvent
(XXXVI; R = α- naphthyl)	3380	40,800	C
(" R = β- ") f	2510	30,100	"
	2580, 2650	33,900	
	3040	15,100	
	3350	33,900	
(XXXVII; R = Ph)	2510, 2570	24,800	D
(" Rα naphthyl)	2510	26,000	C
	3300	13,900	
(" R β- ") f	2510	38,500	"
	2570, 2650	44,000	
	3080	15,300	
	3470	3,200	
(XXXIX)	2510	13,600	D
	2580	14,400	
	2690	17,000	
	3580	8,700	
(XL)	2510	9,600	"
	2690	17,100	
	2780	14,700	
	3560	17,100	
(XLI)	2270, 2360	29,600	"
	2510	13,800	
	3330	36,800	

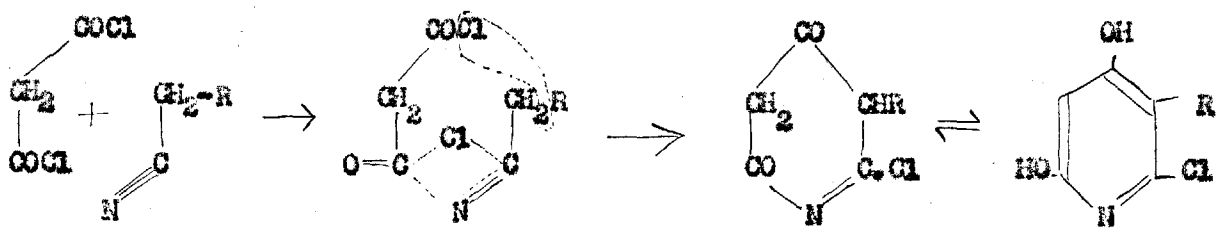
f - fluorescee C - Chloroform D - Dioxan

(b) 2-Chloro-4:6-dihydroxypyridines.

When the study of the reaction of malonyl chloride with nitriles was commenced, it was thought that the products in every case would probably be the pyrano-metoxazines (XXXV). This idea was at first supported by the formation of this type of product from acetonitrile (as has been described), as well as from aromatic nitriles.

Further study showed, however, that if the reacting nitrile contains the cyanomethylene grouping $-CH_2CN$, the nature of the product depends upon the reaction conditions. Thus, acetonitrile afforded a product m.p. 233°, which had the empirical formula $C_5H_4O_2NCl$; it gave a weak ferric colour and was dissolved by aqueous alkali from which it could be reprecipitated on acidification. The product was 2-chloro-4:6-dihydroxy-pyridine (XLVI; R=H), which had been previously prepared by Schroeter and Finck (Ber., 1938, 71B, 671), who gave m.p. 234°.

The following nitriles of general formula RCH_2CN, gave the same type of products which had similar properties to the compound (XLVI; R=H) from acetonitrile:- propionitrile, γ-chlorobutyronitrile, β-valeronitrile, cyanoacetic ester and benzyl cyanide. The products have the general formula (XLVI), and their formation can be represented thus:-



(XLVI)

A molecular-weight determination on (XLVI; R = CO_2Et) showed that this

compound was a monomer.

Spectrographic data for these pyridine derivatives is listed in Table 10. It is seen that there are two distinct types of absorption spectra. Where there is a negative substituent in the 3-position of the pyridine ring, λ max. $\approx$ 2270, 2510 & 2560 Å and $\varepsilon \approx$ 11-14,000, 7-8,000 & 6-9,000 severally; where there is a positive substituent in the 3-position, $\lambda_{max.} \approx$ 2600Å and $\varepsilon \approx$ 3,000.

Table 10. Light absorption of pyridine derivatives.

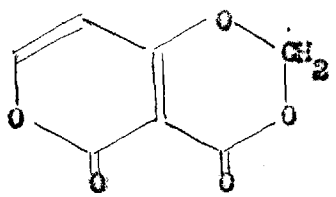
Compounds (XLVI: R =)	λ_{max} (Å)	ε	Solvent
$-CO_2C_2H_5$	2270	10,900	D
	2510	8,300	
	2570	9,400	
	2640*	8,300	
-Ph	2280	14,200	"
	2360	11,500	
	2510	7,100	
	2560	6,200	
-CH $-Pr^n$	2700	3,300	"
	2800	2,600	
-Me	2260	5,600	"
	2690	3,500	
$-(CH_2)_2Cl$	2800 } 2900 }	3,500	E

* inflection

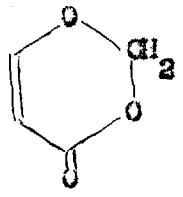
D = Dioxan
E = Ethanol

(V) Some Miscellaneous Reactions of Malonyl Chloride.

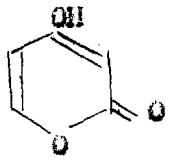
It is convenient at this point to summarise the new reactions of malonyl chloride that have been described in this thesis and to suggest possible extensions of these reactions. Derivatives of the following heterocyclic systems have been produced from malonyl chloride:-



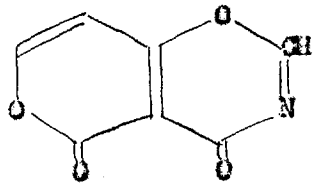
2':4-Diketopyrano(3':4'-5:6)-1:3dioxin.



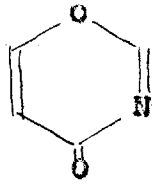
4-Keto-1:3-dioxin.



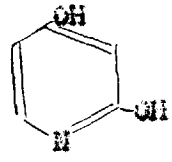
4(2)-hydroxy-2(4)-ketopyran



2':4-Diketopyrano(2':4'-5:6)-1:3-oxazine

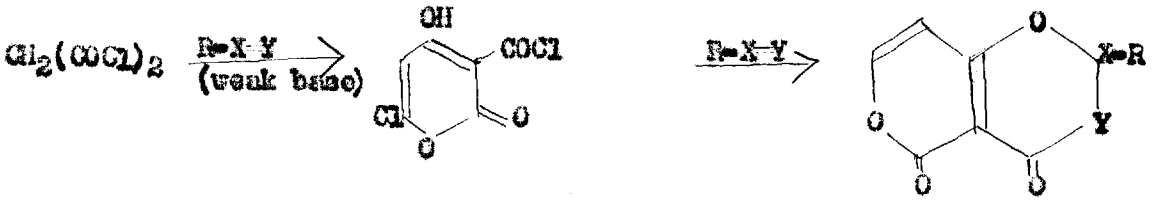


4-Keto-1:3-oxazine.



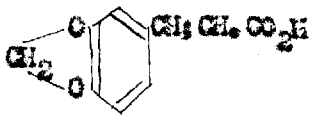
2:4-Dihydroxypyridine

The reaction might be extended by using compounds containing a reactive double (or treble) bond, R-X=Y, capable of acting as a weak base and thus allowing the self condensation of malonyl chloride to occur by promoting the elimination of hydrogen chloride; at the same time the pyrone-acid chloride formed should be capable of reacting with the double bond thus:-

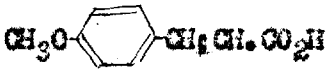


Even if R-XmY was not a weak base, the reaction might still be carried out, using dioxan as solvent. The following types of compounds might perhaps be used in this way: $>C=NR$, $>CH.OR$, $>C=S$, $R-C=N\rightarrow O$, $R-S-C=N$, $R-N.C=S$, $R-N=C=O$.

Perhaps the most obvious way of extending these reactions is to use an aldehyde instead of a ketone. Benzaldehyde was found to react with malonyl chloride giving (L; X=Cl). This reacted with morpholine giving (L; $X=OC_4H_8N$); the absorption spectrum of this compound is recorded in Table 11. However, when attempts were made to react other aromatic aldehydes with malonyl chloride, -ylidine-acetic or -malonic acids were obtained in good yield, even with excess of malonyl chloride which should have promoted pyrano-dioxin formation. Thus, piperonal, anisaldehyde and cinnamaldehyde gave (XLVII), (XLVIII) and (XLIX), severally.



(XLVII)



(XLVIII)

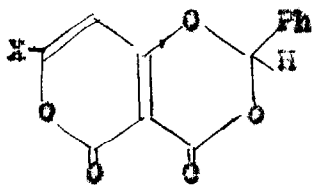


(XLIX)

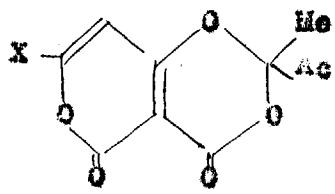
It is notable that these products were formed in much shorter time than the corresponding Doebner reactions recorded in the literature (e.g. Boxer & Linstead, J.Chem.Soc., 1931, 740; v.Auwers, Ann., 1923, 432, 58; Doebner, Ber., 1900, 33, 2140; Liebermann, Ber., 1895, 28, 1439.); thus, (XLIX) was obtained in 52% yield in 25 minutes, whilst Liebermann's reaction took 9 hours. Attempted reactions with aliphatic aldehydes gave only tarry products.

Another possible way of extending the reaction is to use difunctional compounds, e.g. diketones and cyanoketones, when quite large molecules should result from the reaction if both functional groups reacted with

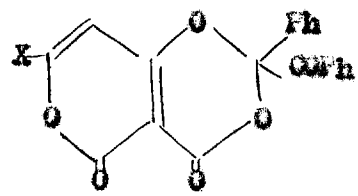
malonyl chloride. The only experiments undertaken in this respect were with diacetyl and benzil; analyses on the compounds obtained indicated that only one of the keto groups in each molecule had reacted. The probable formulae of these compounds are [illegible] (LI; X=Cl) and (LII; X=Cl) respectively. Two 6'-amino-derivatives were prepared in the usual manner: (LI; X=PhNH) from aniline, and (LII; $X=Et_2N$) from diethylamine. It should be noted that the pyranodioxin formulation for (LII; $X=Et_2N$) is supported by the U-V absorption spectrum, (Table 11) which agrees well with those of the aminopyrano-dioxins from monoketones (Table 4).



(L)



(LI)



(LII)

Table 11. Light absorption in dioxan solution

Compound	λ_{max} (Å)	ε
(L; $X=OC_4H_8N$)	2510	
	2570	7,200
	3350	27,000
(LII; $X=Et_2N$)	2510	
	2560	16,000
	3380	32,300

SECTION B - EXPERIMENTAL.

Reaction of Malonyl Chloride with Acetone. -

a) Repetition of Kanning's experiment.

Malonyl chloride (8.6 g.; 6 c.c.) and acetone (A.R.; 3.5 g.; 4.3 c.c.) were mixed and small marble chips (6 g.) added. The mixture soon became warm and gas was evolved. When the reaction slackened, acetone (2 c.c.) was added and the mixture set aside overnight with protection from atmospheric moisture. The mixture of discoloured crystals and calcium salts was extracted (3X) with hot acetone and the combined extracts concentrated under reduced pressure. Pale yellow prisms (3.2 g.), m.p. ca. 180 (decomp.) (with darkening from 135), were obtained. This product was identical (mixed m.p.) with that obtained by method (b), below.

The filtrate was made alkaline with 2N-sodium hydroxide, evaporated to dryness and the residue extracted with boiling alcohol. Evaporation of the extract afforded very little of a semi solid residue, from which no phloroglucinol was isolated by treatment with water and ether.

The yellowish crystalline product (above) (3 g.), water (10 c.c.), and marble chips (5 g.) were warmed together on the steam bath for 2 hours and the mixture was then filtered. The filtrate contained chloride ion (white curdy precipitate with silver nitrate in aqueous nitric acid, soluble in excess of ammonia), but gave no characteristic colours with ferric chloride or with Brady's reagent (aqueous phloroglucinol gives violet and dark orange colours, respectively). The residue given on

evaporating the filtrate to dryness consisted of calcium salts and no phloroglucinol was obtained by ether extraction.

b) Modified procedure.

Acetone (A.R., 10 c.c.) and malonyl chloride (5 g., 3.5 c.c.) were heated together under reflux until solid separated. On cooling and addition of dry ether, golden tablets separated (2.6 g., 63%, based on malonyl chloride.) Recrystallisation from dry benzene afforded 6'-chloro-2',4-diketo-2,2-dimethylpyrano(3',4'-5,6)m-dioxin (III) as colourless prisms, m.p. 183° (decomp.) (Found: C, 46.9; H, 3.4; Cl, 16.25; M (cryoscopic in bromoform), 234. $C_9H_7O_5Cl$ requires C, 46.9; H, 3.1; Cl, 15.4%; M, 230.6). The yield was increased by using equivalent amounts of the reactants, but the product was more discoloured. The compound did not react with aqueous sodium hydrogen carbonate during 5 minutes and gave no colour with ferric chloride in aqueous ethanol. When kept at room temperature in ethanol, and in aqueous dioxan, acidity developed and the solutions then gave red ferric colours.

Reaction of the Acetone Compound with Ethanol. -

The compound (III) (1 g.) was heated with ethanol (0.75 c.c.) on the steam bath for 15 minutes. Hydrogen chloride was evolved. The resulting oil was kept under reduced pressure for several minutes, and then shaken vigorously with cupric acetate (0.4 g.) in water (10 c.c.). The pale green precipitate (1.3 g., 98%) had m.p. 85° undepressed by an authentic specimen (v. infra) of the hydrated copper enolate of acetone-1:1:3-tricarbothoxylate.

Reaction of Benzophenone with Malonyl Chloride. -

Benzophenone (15.2 g.) and malonyl chloride (16.2 c.c.; 2 mols.) were heated at 100° until the vigorous evolution of hydrogen chloride had ceased. Trituration of the solid product with dry ether gave 6'-chloro-2':4-diketo-2:3-diphenylpyrano(3':4'-5:6)m-dioxin (IV) (24.45 g.; 82%) which crystallised from benzene as almost colourless needles, m.p. 179° (decomp.) (Found: C, 63.9; H, 3.3; Cl, 9.8; M (cryoscopic in bromoform), 299. $C_{19}H_{11}O_5Cl$ requires C, 64.3; H, 3.1; Cl, 10.0%; M, 354.7). A solution in aqueous ethanol gradually became acid and then gave a reddish purple colour with ferric chloride.

Reaction of Other Ketones with Malonyl Chloride. -

The products listed in Table 12 were prepared similarly to the acetone and benzophenone compounds.

Degradation of the Benzophenone Product. -

a) With boiling ethanol.

(i) The compound (IV) (1 g.) and ethanol (0.45 c.c.) were heated on the steam bath till evolution of hydrogen chloride ceased. Ether and ammonia (sp. gr., 0.88) were added and the mixture was well shaken and allowed to stand for 24 hours. On evaporation, the ether layer gave benzophenone, m.p. 43-44°, and the aqueous layer malonamide, which after recrystallisation from ethanol had m.p. 164° (Found: N, 27.15. Calc. for $C_3H_6O_2N_2$: N, 27.4%), undepressed by authentic material.

(ii) Formation of acetone-tricarbethoxylate.

The benzophenone compound (IV) (0.71 g.), anhydrous dioxan (1 c.c.), and

Table 12.

No.	Carbonyl compound.	Malonyl chloride.	Product triturated with.	Pyrano(3'4'-5:6)-m-dioxin.	Yield.
1	Ac.CO_2Et (2.2 c.c.)	4 c.c.	Et_2O	2-Carbethoxy-6'-chloro-2':4-diketo-2-methyl-	2.6 g. (46%)
2	Ac.CH_2CO_2Et (2.5 c.c.)	4 c.c.	"	2-Carbethoxymethyl-6'-chloro-2':4-diketo-2-methyl-	3.04g. (60%)
3	COMePr^n (2.24 c.c.)	4 c.c.	Pet (b)	6'-Chloro-2':4-diketo-2-methyl-3-n-propyl-	4.9 g. (92%)
4	$COEt_2$ (10 c.c.)	3.5 c.c.	*	6'-Chloro-2:2-diethyl-2':4-diketo-	1.5 g. (33%)
5	COPhMe (3.4 c.c.)	4 c.c.	"	6'-Chloro-2':4-diketo-2-methyl-3-phenyl-	3.4 g. (62%)
6	$(CH_2)_5CO$ (2.1 c.c.)	3.9 c.c.	Et_2O	6'-Chloro-2':4-diketo-3-spirocyclohexyl-	2.9 g. (53%)

Pet = light petroleum, b.p. (a) 60-80°, (b) 80-100°.
* 5 g. $CaCO_3$; product isolated by extraction with chloroform.

No.	Form & solvent.	M.P.		Analyses. C	H	Cl.(%).
1	Needles, CCl_4	87.5°	Found:	45.45	3.25	11.9
			$C_{11}H_9O_7Cl$ requires	45.75	3.15	12.3
2	Needles, CCl_4	118	Found:	47.55	3.8	11.85
			$C_{12}H_{11}O_7Cl$ requires	47.6	3.65	11.7
3	Leaflets, Pet(b)	89	Found:	51.6	4.6	14.05
			$C_{11}H_{11}O_5Cl$ requires	51.1	4.3	13.7
4	Needles, Pet(a)	104	Found:	50.7	4.2	13.8, 13.6
			$C_{11}H_{11}O_5Cl$ requires	51.1	4.3	13.7
5	Needles, CCl	147	Found:	57.0	3.1	12.15
			$C_{14}H_9O_5Cl$ requires	57.1	3.1	12.1
6	Sq.plates, CCl_4	129	Found:	53.2	4.5	13.6
			$C_{12}H_{11}O_5Cl$ requires	53.2	4.1	13.1

ethanol (0.345 c.c.) were heated together on the steam bath for 10 minutes. The solid had then dissolved and the initial vigorous evolution of hydrogen chloride had ceased. The solution was shaken vigorously first with cupric acetate (0.2 g.) in water (10 c.c.) and then with a 1:1-mixture (30 c.c.) of light petroleums (b.p.s. 40-60° and 100-120°) to remove benzophenone. The aqueous layer was run through a filter and cooled: the pale green crystalline precipitate had m.p.85° alone and in admixture with an authentic specimen of the hydrated copper enolate of acetone-1:1:3-tricarbethoxylate (m.p. 85°)(v. infra).

b) With cold ethanol to give 3-carbethoxy-6-chloro-4-hydroxy-2-ketopyran.

The compound (IV) (1 g.) was dissolved in chloroform and ethanol (0.45 c.c.) added, with thorough mixing. Next day, the solution was filtered from a little insoluble matter, and evaporated under reduced pressure. The residue was stirred with light petroleum (b.p. 80-100°) and the mixture filtered (filtrate P). Crystallisation of the solid from light petroleum (b.p. 80-100°) afforded 3-carbethoxy-6-chloro-4-hydroxy-2-ketopyran (VII) (0.3 g.) as needles, m.p. 121° (Found: C, 43.2; H, 3.3; Cl, 15.9. $C_8H_7O_5Cl$ requires C, 43.95; H, 3.25; Cl, 16.2%). In aqueous dioxan a deep reddish-purple colour was given with ferric chloride. Evaporation of filtrate P yielded benzophenone, m.p. ca. 40°, which was characterised as the 2:4-dinitrophenyl-hydrazone, m.p.234°, undepressed by an authentic specimen.

On adding the preceding pyran derivative (VII) (0.66 g.) in dioxan (4. c.c.) to sodium hydroxide (0.25 g.; 1 equiv.) in water (6.c.c.), there was a rapid evolution of carbon dioxide. After acidification with

2N-hydrochloric acid (3.1 c.c.) and addition of Brady's reagent, the 2:4-dinitrophenylhydrazone of ethyl acetoacetate precipitated. This crystallised from ethanol and had m.p. 89°, undepressed by authentic material.

c) With boiling water.

The benzophenone compound (IV) (340 mg.) and water 0.1 c.c.) were heated under reflux for 15 minutes. Gaseous acidic products were aspirated in a stream of dry, CO_2-free nitrogen and absorbed in an excess of standard aqueous barium hydroxide. The evolved carbon dioxide (83.15% of 3 mols.) and hydrogen chloride (101.4% of 1 mol.) were estimated as barium carbonate and by back-titration of the barium hydroxide filtrate, respectively. The reflux condenser was removed from the reaction vessel, which was then warmed in a current of nitrogen, and the gases passed into Brady's reagent. Acetone 2:4-dinitrophenylhydrazone precipitated, m.p. 119.5°, undepressed by authentic material. The residue in the reaction vessel consisted of benzophenone (17.5 mg.; 100% of 1 mol.), m.p. 35-40°, which was characterised as the 2:4-dinitrophenylhydrazone, m.p. 238°, undepressed by authentic material.

d) Reaction with cold water to yield 3-carboxy-6-chloro-4-hydroxy-2-ketotetrahydrofuran.

The benzophenone compound (IV) (1.42 g.) was dissolved in dry dioxan (25 c.c.) by heating, the solution cooled, and water (0.14 c.c.) added. Next day, the solution was concentrated to small bulk under reduced pressure, ether was added, and the precipitate collected.

The 3-carboxy-6-chloro-4-hydroxy-2-ketopyran (0.5 g.) crystallised as needles, m.p. 134.5°, from light petroleum (b.p. 80-100°) (Found: C, 38.2; H, 1.95; Cl, 18.75. $C_6H_3O_5Cl$ requires C, 37.85; H, 1.6; Cl, 18.6%). The compound gave a deep red colour with ferric chloride and dissolved with effervescence in aqueous ammonium hydrogen carbonate.

e) Reaction with methanol to yield 3-carbomethoxy-6-chloro-4-hydroxy-2-ketopyran.

The benzophenone compound (IV) (7.6 g.), dissolved in dioxan by heating, was treated in the cold with methanol (1.6 c.c.). Next day, the solution was evaporated to small bulk, petroleum ether (b.p. 60-80°) and ether were added, and the precipitate collected. From benzene, the 3-carbomethoxy-6-chloro-4-hydroxy-2-ketopyran (3.7 g.; 90%) separated as needles, m.p. 149° (Found C, 41.45; H, 2.8; Cl, 17.05. $C_7H_5O_5Cl$ requires C, 41.1; H, 2.4; Cl, 17.35%). In aqueous dioxan the compound gave a deep red colour with ferric chloride.

3-Carbomethoxy-4-hydroxy-6-hydroxymethyl-2-ketopyran. -

(1) To 3-carboxy-6-chlor-4-hydroxy-2-ketopyran (320 mg.) in dioxan, a solution of diazomethane in ether (undried) was added in portions until the vigorous evolution of gas ceased. Evaporation, and trituration of the residue with petroleum ether (b.p. 40-60°) gave a chlorine and nitrogen-free product (Lassaigne's test). The 3-carbomethoxy-4-hydroxy-6-hydroxymethyl-2-ketopyran (50 mg.) had m.p. 147° after recrystallisation from benzene (Found: C, 48.1; H, 4.4. $C_8H_8O_6$ requires C, 48.0; H, 4.05%). A mixture with 3-carbomethoxy-4-hydroxy-6-methoxy-2-ketopyran (m.p. 149°) (below) had m.p. 130-122°. The 6-hydroxymethyl-pyran gave a deep red

colour with ferric chloride.

(ii) Similar treatment of 3-carbomethoxy-6-chloro-4-hydroxy-2-ketopyran (300 mg.) in dioxan with ethereal diazomethane (undried) also afforded the 6-hydroxymethyl product (50 mg.), m.p. and mixed m.p. 147°.

Conversion of 3-Carbomethoxy-6-chloro-4-hydroxy-2-ketopyran to the 6-Methoxy Derivative with Sodium Methoxide. -

Sodium (0.15 g.) was dissolved in methanol (several c.c.) and the solution added, during 15 minutes, to the pure chloro-pyran (0.65 g.) in dioxan (50 c.c.), with cooling and swirling of the mixture. A precipitate formed at once. After 30 minutes, the mixture was acidified with very dilute sulphuric acid (ca. 50 c.c.) and the solution extracted with ether (50, 25 c.c.). The combined extracts were dried (Na_2SO_4) and then evaporated under reduced pressure. From benzene-petroleum ether (b.p. 60-80°), colourless needles separated (90 mg), which had m.p. 148.5° depressed to 120° by the starting material, and which were halogen-free (Lassaigne's test) (Found: C, 47.8; H, 4.1; Cal. for $C_8H_8O_6$: C, 48.0; H, 4.05%). The m.p. was not depressed by authentic 3-carbomethoxy-4-hydroxy-2-keto-6-methoxypyran prepared by the self-condensation of malonic half ethyl ester half chloride with ethereal quinoline (Staudinger and Becker, loc.cit.). The 6-methoxy-pyran gave an orange colour with ferric chloride in ethanol.

Acetone-1:1:3-tricarbethoxylate. -

Malonic half ethyl ester half chloride (42 g.) in dry ether (15 c.c.) was added to ethyl ethoxymagnesiomalonate prepared from magnesium turnings (6.8 g.), ethanol (6 c.c.), carbon tetrachloride (0.5 c.c.), iodine (a crystal), and ethyl malonate (44.6 g.) in ethanol (25 c.c.), according to Bruylow, Baumgarten, and Hauser, (J. Amer. Chem. Soc., 1944, 66, 1286) and the mixture heated under reflux for 30 minutes, then chilled and treated with an excess of dilute sulphuric acid. The solid which separated was collected (18 g.): from ethyl acetate the magnesium derivative of acetone-1:1:3-tricarbethoxylate formed prismatic needles, m.p. 119° (Found: Mg, 4.65. $C_{24}H_{34}O_{14}Mg$ requires Mg, 4.8%). The ether layer was combined with ethereal extracts (2 x 250 c.c.) of the aqueous phase, and the solution dried (Na_2SO_4) and evaporated. Unchanged diethyl malonate was removed under reduced pressure and the residue treated with 5% sodium hydroxide solution. The alkaline extract was washed with ether, neutralised with dilute sulphuric acid and the oily acetone-1:1:3-tricarbethoxylate (11.2 g.) isolated with chloroform. The pale green hydrated copper enolate, prepared from the ester according to Willstätter (Ber., 1899, 32, 1273), had m.p. 85°.

Reaction of 6'-Chloro-2':4-diketo-2:2-dimethylpyrano(3':4'-5:6)m-dioxin with Morpholine. (Method A).

To the pyrano-m-dioxin (0.5g.) in chloroform (ca. 10 c.c.) was added morpholine (0.38 c.c.) dropwise, with shaking. Washing with water and evaporation of the chloroform layer gave 2':4-diketo-2:2-dimethyl-6'-N-morpholinopyrano(3':4'-5:6)m-dioxin (0.55g.; 93%), obtained as colourless prismatic needles, m.p. 182° (decomp.), from ethanol (Found: C, 55.4; H, 5.4; N, 5.3. $C_{13}H_{15}O_6N$ requires C, 55.5; H, 5.4; N, 5.0%). This compound did not react with hydrogen chloride or picric acid.

Reaction of 6'-Chloro-2':4-diketo-2:2-dimethylpyrano(3':4'-5:6)m-dioxin with Ammonia. (Method B.)

.880 Aqueous ammonia solution (1.1 c.c.;2 mols.) was added dropwise to a supersaturated solution of the pyrano-m-dioxin (2.04 g.) in dioxan (ca. 25 c.c.), with cooling and shaking. The precipitate (mainly ammonium chloride) was filtered, and evaporation of the filtrate gave 6'-amino-2':4-diketo-2:2-dimethylpyrano (3':4-5:6)m-dioxin (0.72g; 38%) as almost colourless microcrystals, m.p. 300° from ethanol (Found: C, 509; H, 4.55; N, 6.65. $C_9H_9O_5N$ requires C, 51.2; H, 4.3; N, 6.65%).

Reaction of 6'-Chloro-2':4-diketo-2:2-dimethylpyrano(3':4'-5:6)m-dioxin with Aniline. (Method C.)

To the pyrano-m-dioxin (5g.) in chloroform solution was added aniline (4 c.c.), with shaking. The precipitate was collected, washed well with water to remove aniline hydrochloride and dried. The 6'-N-aniline-2':4-diketo-2:2-dimethylpyrano (3':4'-5:6)m-dioxin (6.75g.; 98%), had

m.p. 192.5° (decomp.) from ethanol (Found: C, 63.1; H, 4.8; N, 4.95. $C_{15}H_{13}O_5N$ requires C, 62.7; H, 4.55; N, 4.9%).

Reaction of 6'-Chloro-3',4-diketo-2,2-diphenylpyrano (3',4'-5,6)m-dioxin with Morpholine. (Method D.)

To the pyrano-m-dioxin (0.5g.) in dry benzene (40 c.c.) was added morpholine (0.5 c.c.) in dry benzene (10 c.c.); the mixture was then warmed on the steam-bath several minutes to complete the reaction. Washing with dilute hydrochloric acid and water, drying (Na_2SO_4) and evaporation of the benzene solution gave a gum which was crystallised by trituration with dry ether. Extraction of the aqueous layer with chloroform and evaporation of the latter gave a further quantity of product. The 3',4-diketo-2,2-diphenyl-6'-N-morpholinopyrano (3',4'-5,6) m-dioxin (0.4g.; 70%) was obtained as colourless plates, m.p. 186° (decomp.) from chloroform-ether (Found: C, 67.9; H, 4.95; N, 3.4. $C_{23}H_{19}O_6N$ requires C, 68.1; H, 4.7; N, 3.5%). A ferric chloride colour was not obtained in aqueous alcohol.

Reaction of 3-Carbethoxy-6-chloro-4-hydroxy-2-ketopyran with Morpholine.

To a solution of the chloropyran (0.33 g.) in a little chloroform was added morpholine (0.27 c.c.), dropwise, with cooling. After washing with a small amount of water, and drying, removal of the solvent gave 3-carbethoxy-4-hydroxy-2-keto-6-morpholinopyran as colourless rectangular laminae, m.p. 165° from ethanol (Found: C, 54.05; H, 5.85; N, 5.1. $C_{12}H_{15}O_6N$ requires C, 53.5; H, 5.6; N, 5.2%). A purple ferric chloride colour was obtained in aqueous dioxan.

2',4-Diketo-2,2-dimethyl-6'-N-methylanilinopyrano (3',4'-5,6)m-dioxin.

a) From 6'-N-anilino-2',4-diketo-2,2-dimethylpyrano (3',4'-5,6)m-dioxin.

The anilinopyrano-p-dioxin (0.88 g.) was added to a solution of sodium hydroxide (0.245 g.; 2 mols.) in water (10 c.c.). The anilinopyrano-p-dioxan dissolved and after a few minutes, a crystalline precipitate formed, the N-sodio derivative (0.95 g. 100%).

The N-sodio derivative (0.53 g.) was dissolved in a few c.c. of methanol and excess methyl iodide added. After standing overnight, the solution was evaporated and triturated with water to remove sodium iodide. The 2':4-diketo-2:2-dimethyl-6'-N-methylanilinopyrano (3':4'-5:6)m-dioxin (0.34 g., 66%) formed colourless needles, m.p. 160° from ethanol (Found: C, 63.65; H, 5.15; N, 4.9. $C_{16}H_{15}O_5N$ requires C, 63.8; H, 5.0; N, 4.65%).

b) From the corresponding chloropyrano-p-dioxin.

See Table 13.

Formation of other aminopyranodioxins.

Some aminopyranodioxins, other than those described above, are listed in Table 13.

5-Carboxy-2:2-dimethyl-4-keto-m-dioxin-6-acetic Acid Dimorpholide.

(i) 2':4-Diketo-2:2-dimethyl-6'-N-morpholinopyrano (3':4'-5:6) m-dioxin (0.55g.) and morpholine (0.2 c.c.) were heated together under reflux in chloroform (10 c.c.) for 30 minutes. Evaporation gave 5-carboxy-2:2-dimethyl-4-keto-m-dioxin-6-acetic acid dimorpholide, m.p. 134° after recrystallisation from ethyl acetate-ether (Found: C, 55.6; H, 6.7; N, 7.8, 7.8. $C_{17}H_{24}O_7N_2$ requires C, 55.4; H, 6.6; N, 7.6%).

(ii) 6'-Chloro-2':4-diketo-2:-dimethylpyrano (3':4'-5:6)m-dioxin (1g.) in dry benzene (40 c.c.) and morpholine (2.5 c.c.) in dry benzene

Table 13.

No. & Method.	Chloro-compound.	Base.	Pyrano(3':4'-5:6)-m-dioxin.	Yield.
1. (A)	$Me_2.C_7HO_5Cl$ (2.3g.)	Et_2NH (1.46g; 2.06cc)	6'-N-diethylamino-2':4-diketo-2:2-dimethyl-	2.43g. (91%)
2. (A)	" (4.61g.)	$(CH_2)_5:NH$ (3.95cc.)	2':4-diketo-2:2-dimethyl-6'-N-piperidino-	4.03g. (72%)
3. (C)	" (4.61g.)	$BzNH_2$ (4.36cc.)	6'-N-benzylamino-2':4-diketo-2:2-dimethyl-	5.95g. (98%)
4. (A)	" (0.46g.)	PhNHMe (0.435cc)	2':4-diketo-2:2-dimethyl-6'-N-methylanilino-	0.44g. (73%)
5. (D)	$Ph_2.C_7HO_5Cl$ (3.55g.)	$(CH_2)_5:NH$ (2.05cc.)	2':4-diketo-2:2-diphenyl-6'-N-piperidino-	2.8g. (70%)
6. (A)	" (3.55g.)	Bu^nNH_2 (2.0cc.)	6'-N-n-butylamino-2':4-diketo-2:2-diphenyl-	3.35g. (85%)
7. (A)	$Me,Pr^n.C_7HO_5Cl$ (1 g.)	$O:(CH_2)_4NH$ (0.67cc.)	2':4-diketo-2-methyl-6'-N-morpholino-2-n-propyl-	0.8g. (66%)
8. (A)	$Me,Ph.C_7HO_5Cl$ (1 g.)	$O:(CH_2)_4NH$ (0.59cc.)	2':4-diketo-2-methyl-6'-N-morpholino-2-phenyl-	0.6g. (51%)
9. (A)	$MeCO_2Et.C_7HO_5Cl$ (0.98g.)	Et_2NH (0.7cc.)	2-carbethoxy-2':4-diketo-2-methyl-6'-N-diethylamino-	0.54g. (49%)
10. (A)	$(CH_2)_5.C_7HO_5Cl$ (0.5 g.)	$O:(CH_2)_4NH$ (0.32cc.)	2':4-diketo-6'-N-morpholino-2-spirocyclohexyl-	0.34g. (56%)

Table 13 (contd.)

No.	Form and Solvent.	M.P.		Analyses. C	H	N(%)
1.	Prisms EtOH	145°*	Found:	58.4	6.7	5.05
			$C_{13}H_{17}O_5N$ requires	58.4	6.4	5.25
2.	Needles C_6H_6-Pet	151.5*	Found:	60.0	5.95	5.55
			$C_{14}H_{17}O_5N$ requires	60.2	6.15	5.0
3.	- EtOH	176*	Found:	63.9	5.2	5.15
			$C_{16}H_{15}O_5N$ requires	63.8	5.0	4.65
4.	Needles EtOH	160	Found:	63.65	5.15	4.9
			$C_{16}H_{15}O_5N$ requires	63.8	5.0	4.65
5.	Rhombic leaflets $(CH_3)_2CO$	182*	Found:	71.55	5.5	3.1
			$C_{24}H_{21}O_5N$ requires	71.45	5.25	3.5
6.	Prisms EtOH	167.5*	Found:	70.65	5.6	3.8
			$C_{23}H_{21}O_5N$ requires	70.55	5.4	3.6
7.	Microcrystals C_6H_6-Pet	143*	Found:	58.15	6.3	4.45
			$C_{15}H_{19}O_6N$ requires	58.2	6.2	4.55
8.	Microcrystals $C_3H_7NO_2$	186*	Found:	62.5	5.15	4.1
			$C_{18}H_{17}O_6N$ requires	62.9	5.0	4.1
9.	Needles EtOH	110.5	Found:	55.75	5.95	4.65
			$C_{15}H_{19}O_7N$ requires	55.4	5.9	4.3
10.	- C_6H_6	191*	Found:	60.4	6.15	4.10
			$C_{16}H_{19}O_6N$ requires	59.8	5.95	4.35

*with decomposition
Pet = petroleum ether, b.p. 100-120°

(10 c.c.) were mixed and then heated together under reflux for 5 minutes. The mixture was washed with dilute hydrochloric acid, then with water and dried (Na_2SO_4). Evaporation and trituration of the residual gum with dry ether gave 5-carboxy-2:3-dimethyl-4-keto-p-dioxin-6-acetic acid dimorpholide, m.p. 134° after recrystallisation from ethyl acetate-ether. Extraction of the aqueous layer with chloroform (3x) gave an additional quantity of the product (total yield 1.3g.;81%). The product was easily water-soluble and gave no ferric chloride colour.

5-Carboxydiethylamido-2:3-dimethyl-4-keto-p-dioxin-6-acetic Acid Morpholide.

6'-Chloro-2':4-diketo-2:3-dimethylpyrano (3':4'-5:6)p-dioxin (1g.) in chloroform (15 c.c.) and morpholine (0.76 c.c.) in chloroform (10 c.c.) were mixed together with cooling and shaking. The resulting solution was washed with water, dried and heated with diethylamine (0.65 c.c.) for 30 minutes. Evaporation and trituration with petroleum ether (b.p. 40-60°) gave 5-carboxydiethylamido-2:3-dimethyl-4-keto-p-dioxin (0.8g.; 58%) as colourless prisms, m.p. 117° from benzene-petroleum ether (b.p. 60-80°) (Found: C, 57.3; H, 7.3; N, 8.2. $C_{17}H_{26}O_6N_2$ requires C, 57.65; H, 7.4; N, 7.9%).

5-Carbomorpholido-2:3-dimethyl-4-keto-p-dioxin-6-acetic Acid Piperidide.

2':4-Diketo-2:3-dimethyl-6'-N-piperidinopyrano(3':4'-5:6)p-dioxin (1.4 g.) and morpholine (0.436 c.c.) were heated together in chloroform (2.5 c.c.) under reflux for 25 minutes. Evaporation and trituration of the resultant gum with ether gave 5-carbomorpholido-2:3-dimethyl-4-keto-p-dioxin-6-acetic acid piperidide (1.45 g.;80%), m.p. 131.5°, from benzene-petroleum ether (b.p. 60-80°) (Found: C, 59.1; H, 7.05;

N, 8.05. $C_{18}H_{26}O_6N_2$ requires C, 59.0; H, 7.15; N, 7.65%).

5-Carboxyanilido-2:2-dimethyl-4-keto-m-dioxin-6-acetanilide.

6'-N-Anilino-2':4-diketo-2:2-dimethylpyrano (3':4'-5:6)m-dioxin (1 g.) and aniline (0.32 c.c.) were heated together under reflux in dioxan (10 c.c.) for one hour. Cooling, filtration, evaporation of the solvent and trituration with petroleum ether (40-60°) gave 5-carboxyanilido-2:2-dimethyl-4-keto-m-dioxin-6-acetanilide, m.p. 100° from petroleum ether (b.p.100-120°) (Found: C, 66.55; H, 5.6; N, 7.25. $C_{21}H_{20}O_5N_2$ requires C, 66.3; H, 5.3; N, 7.35%).

5-Carboxymorpholido-2:2-dimethyl-4-keto-m-dioxin-6-acetamide.

6'-Amino-2':4-diketo-2:2-dimethylpyrano (3':4'-5:6)m-dioxin (0.42g.) and morpholine (0.18 c.c.) were allowed to react together in dioxan solution overnight at room temperature. Evaporation gave 5-carboxymorpholido-2:2-dimethyl-4-keto-m-dioxin-6-acetamide (0.3 g.; 50%) as colourless needles, m.p. 223° (decomp.) from ethanol. (Found: C, 52.55; H, 6.25; N, 9.65. $C_{13}H_{18}O_6N_2$ requires C, 52.35; H, 6.1; N, 9.4%). The product was easily soluble in cold water.

5-Carboxy-2:2-diphenyl-4-keto-m-dioxin-6-acetic Acid Dimorpholide.

2':4-Diketo-2:2-diphenyl-6'-N-morpholinopyrano (3':4'-5:6)m-dioxin (1.34g.) and morpholine (0.27 c.c.) were heated in chloroform solution on a steam bath for 10 minutes. The solvent was then evaporated and the residual gum crystallised by trituration with alcohol-ether. The 5-carboxy-2:2-diphenyl-4-keto-m-dioxin-6-acetic acid dimorpholide (1.11g.; 73%), had a m.p. 135° from ethanol (Found: C, 65.6; H, 6.0; N, 5.6. $C_{27}H_{28}O_7N_2$ requires C, 65.85; H, 5.75; N, 5.7%).

5-Carboxy-n-butylamido-2:2-dimethyl-4-keto-m-dioxin-6-acetic Acid Benzylamide.

6'-N-Benzylamino-2':4-diketo-2:2-dimethylpyrano (3':4'-5:6)m-dioxin (1 g.) and n-butylamine (0.33 c.c.) were heated together in chloroform (10 c.c.) for forty minutes. Evaporation of the solvent and trituration of the residual gum with petroleum ether (b.p. 60-80°) afforded 5-carboxy-n-butylamido-2:2-dimethyl-4-keto-m-dioxin-6-acetic acid benzylamide (0.3 g.; 24%) as colourless lathes, m.p. 86° from petroleum ether (b.p. 60-80°) (Found: C, 64.3.; H, 7.1; N, 7.45. $C_{20}H_{26}O_5N_2$ requires C, 64.15; H, 7.0; N, 7.5%). This compound gave no ferric colour in aqueous dioxan.

5-Carboxymorpholido-2:2-diphenyl-4-keto-m-dioxin-6-acetic Acid n-Butylamide.

6'-N-n-Butylamino-2':4-diketo-2:2-diphenylpyrano (3':4'5:6)m-dioxin (7.1 g.) and morpholine (1.50 c.c.) were shaken together with chloroform (50 c.c.) for 1 day at room temperature. The unused starting material (1.05 g.) was filtered off and the filtrate washed with an equal volume of water. Evaporation of the solvent and trituration of the residual gum with petroleum ether (b.p. 60-80°) afforded 5-carboxy-morpholido-2:2-diphenyl-4-keto-m-dioxin-6-acetic acid n-butylamide (5.45 g.; 73%), (calculated on weight of the pyranodioxin consumed) as colourless leaflets, m.p. 117.5° from benzene-petroleum ether (b.p.100-120°) (Found: C, 67.55; H, 6.5; N, 6.35. $C_{27}H_{30}O_6N_2$ requires C, 67.75; H, 6.3; N, 5.85%). This compound gave no ferric colour in aqueous dioxan.

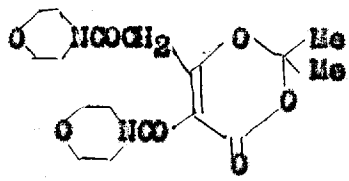
Spot Tests on Some 4-Keto-m-dioxins.

These are shown in Table 4 .

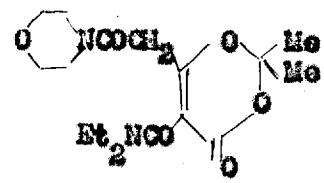
Table 4.

Reagent	Dioxin used	Cold	Reflux
Aq.HCl	a	negative[1]	-
MeOH/HCl	a	-	negative[1]
H_2O	a,b,c	negative[2]	purple col.[3] with $FeCl_3$
MeOH	a	-	negative[4]
BuOH	a	-	" [3]
Aq.NaOH	a	-	purple col.[3] with $FeCl_3$
NaOMe/MeOH	a	-	deep red col.[3] with $FeCl_3$
2:6-Dichlorophenolindophenol	a,c	negative[1]	-
Légal reaction	c	" [4]	-
Ammo.$AgNO_3$	c	" [4]	black ppt.[3]

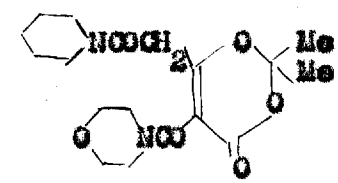
1. after 1 hour. 2. after 3 days. 3. after 5 minutes. 4. after 10 minute



(a)



(b)



(c)

Acetone-1:3-dicarboxylic Acid Dimorpholide.

(a) **From ethyl acetone-1:3-dicarboxylate.**

Ethyl acetone-1:3-dicarboxylate (10 g.) and morpholine (10.25 c.c.) were heated together at 75° in an autoclave for 19 hours. Cooling and addition of benzene precipitated acetone-1:3-dicarboxylic acid dimorpholide (5.2g.; 37%) as colourless needles, m.p. 132°, from ethanol (Found: C, 54.85; H, 7.05; N, 10.0. $C_{13}H_{20}O_5N_2$ requires C, 54.4; H, 7.1; N, 9.85%). An aqueous solution of the dimorpholide gave a purple colouration with

aqueous ferric chloride. Admixture with malonic acid dimorpholide depressed the melting-point by 22°.

b) By decomposition of 5-carboxy-2:2-dimethyl-6-keto-m-dioxin-6-acetic acid dimorpholide.

(i) With aqueous sodium hydroxide.

The dioxin dimorpholide (11g.) in water (10 cc.) and 2N sodium hydroxide (1.5 c.c.) were mixed together and heated at 100° for 10 minutes. After cooling, the solution was neutralised with dilute sulphuric acid when much effervescence of CO_2 occurred. Extraction with 3x10c.c. chloroform and evaporation of the solvent gave acetone-1:3-dicarboxylic acid dimorpholide (0.58g.; 68%), m.p. 131°, undepressed by admixture with authentic material; aqueous ferric chloride gave a purple colouration.

(ii) With water.

The dioxin dimorpholide (0.5g.) in water (10 c.c.) was heated under reflux for 2 hours; CO_2 was detected in the evolved gases as $BaCO_3$. The liquid was then distilled almost to dryness; acetone was detected in the distillate with Brady's reagent (2:4 dinitrophenylhydrazone had m.p. 125° undepressed by admixture with authentic material). The last traces of water were removed under vacuum; trituration of the residue with ether afforded acetone-1:3-dicarboxymorpholide (0.3 g.; 78%), m.p. 132°, undepressed by admixture with authentic material.

Acetone-1:3-dicarboxylic Acid Benzylamide n-Butylamide.

6'-N-Benzylamino-2':4-diketo-2:2-dimethylpyrano (3':4'-5:6)m-dioxin (1 g.) and n-butylamine (0.33 c.c.) were heated together under reflux in chloroform (10 c.c.) for 1 hour. Evaporation of the solvent and boiling the residual oil with excess water for 2½ hours gave acetone-1:3-dicarboxylic

acid benzylamide n-butylimide (0.3 g.; 31%), which had m.p. 139° from water (Found: C, 65.9; H, 7.85; N, 9.55. $C_{16}H_{22}O_3N_2$ requires C, 66.2; H, 7.65; N, 9.65%).

1-Carbomethoxyacetone-1:3-dicarboxylic Acid Dianilide.

a) From 3-Carbomethoxy-6-chloro-4-hydroxy-2-ketopyran.

A chloroform solution of crude chloropyran (0.5 g.) and aniline (0.45 c.c.) was warmed several minutes to complete the initially vigorous reaction. After washing with water and drying, evaporation gave 1-carbomethoxyacetone-1:3-dicarboxylic acid dianilide (0.53 g.; 64%), m.p. 213° (decomp.) from benzene (Found: C, 64.25; H, 4.95; N, 7.6. $C_{19}H_{18}O_5N_2$ requires C, 64.4; H, 5.1; N, 7.9%). The product gave a deep-red ferric chloride colour in aqueous dioxan.

b) From 5-Carboxyanilido-2:2-dimethyl-4-keto-m-dioxin-6-acetanilide.

The dioxin (150 mg.) was heated under reflux for 5 minutes with methanol in which sodium (9 mg.) had been dissolved. The liquid was cooled, poured into very dilute HCl and the precipitate collected. The 1-carbomethoxyacetone-1:3-dicarboxyanilide (100 mg.; 71%) had m.p. 234° (decomp.), undepressed by admixture with a specimen prepared from the chloropyran-carbomethoxylate. The product gave a deep-red ferric chloride colour in aqueous dioxan.

Reaction of 1-Carbomethoxyacetone-1:3-dicarboxylic Acid Dianilide with Aniline: Formation of Malonanilide.

A mixture of dianilide (1 g.), aniline (0.67 c.c.), anhydrous zinc chloride (1.35 g.) and dioxan (5 c.c) were heated together under reflux for 15 minutes and then poured into 2N sulphuric acid (20 c.c.) with

cooling and stirring. Filtration gave malonanilide which had m.p. 227° from ethanol (Found: C, 70.65; H, 5.7; N, 10.95. Calc. for $C_{15}H_{14}O_2N_2$: C, 70.85; H, 5.5; N, 11.0%). An admixture with authentic malonanilide had m.p. 227°

Acetone-1:1:3-tricarboxylic Acid Trimorpholide.

a) From 6'-Chloro-2':4-diketo-2:2-dimethylpyrano (3':4'-5:6)m-dioxin.

To the pyrano-m-dioxin (0.41 g.) in chloroform was added morpholine (0.31 c.c.; 2 mols.) dropwise, with shaking. The solution was washed with water and dried. Morpholine (0.31 c.c.; 2 mols.) was then added and the solution stood overnight. Evaporation of the solvent gave acetone-1:1:3-tricarboxylic acid trimorpholide m.p. 181°, as colourless needles from ethanol (Found: C, 54.9; H, 7.0; N, 10.4. $C_{18}H_{27}O_7N_3$ requires C, 54.4; H, 6.85; N, 10.55%). The product gave a red-purple colouration with aqueous ferric chloride.

b) From 5-Carboxy-2:2-diphenyl-4-keto-m-dioxin-6-acetic Acid Dimorpholide.

The dimorpholide (0.5 g.) and morpholine (0.09 c.c.) were heated together, in dry dioxan solution, on a steam bath for 15 minutes. Evaporation of the solvent gave acetone-1:1:3-tricarboxylic acid trimorpholide (0.4 g.; 100%), m.p. 181°, as colourless needles from ethanol, after previous washing with ether. The ether filtrate contained benzophenone, characterised as the 2:4-dinitrophenylhydrazone, m.p. 232° undepressed by authentic material.

Reaction of acetone-1:1:3-tricarboxymorpholide with Morpholine; formation of Malonmorpholide.

The trimorpholide (0.23 g.) and morpholine (0.5cc. 10 mols.) were heated together for 15 hours on the steam bath. Cooling and trituration

with ether gave malonmorpholide (0.2 g.; 7%), m.p. 132° undepressed by admixture with authentic material.

Reaction of Ethyl Acetone-1:1:3-tricarboxylate with Morpholine: formation of Malonic Acid Dimorpholide.

Ethyl acetone 1:1:3-tricarboxylate (5.5g.) and morpholine (5.2 c.c.) were heated together at 75° in an autoclave for 22½ hours. Cooling and addition of benzene gave malonic acid dimorpholide (2.75g.; 38%), m.p. 135°, undepressed by admixture with authentic material (see below). The product gave no colouration with aqueous ferric chloride.

Malonic Acid Dimorpholide.

Diethyl malonate (100 g.) and morpholine (135g.; 2½ mols.) were heated together at 150° in an autoclave for 42 hours. Filtration gave malonic acid dimorpholide in good yield, m.p. 137°, as colourless needles and rhombic plates from ethanol. (Found: C, 54.25; H, 7.45; N, 11.25. $C_{11}H_{18}O_4N_2$ requires C, 54.5; H, 7.5; N, 11.6%).

Malonic Acid Ethyl Ester Morpholide.

Diethyl malonate (160 g.) and morpholine (87g.; 1 mol.) were heated together at 150° in an autoclave for 24 hours. The malonic acid dimorpholide (41 g.) was filtered off, washed well with ether and the filtrate distilled. The main fraction, b.p. 135-145°/1.5 m.m., which solidified on standing, was malonic acid ethyl ester morpholide (84.1g.; 43%), m.p. 59.5° from petroleum ether (b.p. 40-60°) (Found: C, 53.55; H, 7.6; N, 6.45. $C_9H_{15}O_4N$ requires C, 53.7; H, 7.5; N, 6.95%).

Attempted preparation of metallic derivatives of Malonmorpholide.

The anhydrous solid prepared from the morpholide (1.21 g.) and magnesium (0.12 g.) in methanol (after evaporation of the latter) was

suspended in dry benzene and acetyl chloride (0.36 c.c.)added; much heat was evolved. Evaporation, acidification and extraction with chloroform yielded starting material in 75% yield.

A similar reaction (but double basic scale) using sodium in formamide solution yielded only starting material in good yield. This reaction was carried out in dry formamide-dioxan.

Reaction of Sodium with Malonmorpholide; formation of Phloroglucinol-dicarboxymorpholide.

Sodium (0.23 g.) was added to molten malonmorpholide (4.84 g.) which was heated gently and then more strongly till the sodium had dissolved. Heating was continued till evolution of morpholine vapours slackened. After cooling, water (20 c.c.) was added and the solution extracted with chloroform (5x10 c.c.) to remove neutral material. The aqueous solution was acidified, filtered from sediment and extracted with chloroform (5x25cc.). Evaporation of the solvent and trituration of the residue with ether afforded phloroglucinol dicarboxymorpholide, obtained as a pale yellow powder, m.p. 227° from dioxan-ether (Found: C, 55.2; H, 5.75; N, 8.05. $C_{16}H_{20}O_7N_2$ requires C, 54.55; H, 5.7; N, 7.95%). The product gave a deep-red ferric chloride colouration and dissolved in sodium bicarbonate solution with effervescence.

The Self-Condensation of Malonyl Chloride; Isolation of 6-Chloro-4-hydroxy-2-ketopyran-3-carboxylic Acid.

A solution of malonyl chloride (2.477g.) in anhydrous dioxan (50 c.c.) was allowed to stand at room temperature for 13 days. 10 C.c. of this solution was then evaporated and the residue triturated with water (2.c.c.). The insoluble matter was dried (140 mg.; 41%) and had m.p. 136.5°(decomp.), undepressed by admixture with a specimen of the chloropyrone carboxylic acid prepared by another route (p. 46); a deep-red ferric colour was given in ethanol. The aqueous filtrate gave, on evaporation, malonic acid which had m.p. 135° from chlorobenzene, undepressed by admixture with an authentic specimen.

Reaction of 6-Chloro-4-hydroxy-2-ketopyran-3-carboxylic Acid Chloride with Benzophenone; Formation of 6'-Chloro-2':4-diketo-2:2-diphenylpyrano (3':4'-5:6)m-dioxin.

6-Chloro-4-hydroxy-2-ketopyran-3-carboxylate (200 mg.) was treated with thionyl chloride (0.5 c.c.) and the mixture warmed gently till all solid had dissolved. Excess thionyl chloride was evaporated off and benzophenone (200 mg.) added. The mixture was warmed gently over a free flame, when the contents solidified spontaneously. Trituration with dioxan afforded the chloropyranodioxin (200 mg.) which was reacted with n-butylamine, thus characterising it as the n-butylaminopyranodioxin (see Table 13), m.p. 166°, undepressed by authentic material.

Preparation of 6'-Chloro-2':4-diketo-2-phenylpyrano(3':4'-5:6) metoxazine.

(a) Reaction of Malonyl Chloride with Benzonitrile.

Malonyl chloride (23.4 c.c.) and benzonitrile (120 cc.) were heated together on a steam-bath for 30 minutes. Filtration of the solid, trituration with anhydrous dioxan and drying, afforded 6'-chloro-2':4-diketo-2-phenylpyrano (3':4'-5:6) metoxazine (22.35g.; 67%) as pale yellow leaflets, m.p. >300° (decomp.) from nitrobenzene (Found: C, 56.8; H, 2.5; N, 5.05; Cl, 12.55. $C_{13}H_6O_4NCl$ requires C, 56.65; H, 2.2; N, 5.1; Cl, 12.85%).

(b) By Reaction of 6-Chloro-4-hydroxy-2-ketopyran-3-Carboxylic Acid Chloride with Benzonitrile.

3-Carboxy-6-chloro-4-hydroxy-2-ketopyran (0.23 g.) was treated with a little thionyl chloride; to this solution was added benzonitrile (2 c.c.), and the mixture heated gently under reflux for 10 minutes. 6'-Chloro-2':4-diketo-2-phenylpyrano (3':4'-5:6) metoxazine (0.2 g.; 60%) crystallised out and was collected; it had m.p. >300° and by reaction with water (see below) afforded the corresponding 6'-hydroxypyrano-metoxazine, identical with a specimen obtained from the chloro-product of preparation (a).

6'-Chloro-2':4-diketo-2-methylpyrano (3':4'-5:6) metoxazine.

Malonyl chloride (5 c.c.) and acetonitrile (redistilled; 25 c.c.) were heated together on a steam-bath for 5 minutes. The orange product (1.05g.; 19%) had m.p. 268° (decomp.) after recrystallisation from nitrobenzene (Found: C, 45.3; H, 2.3.; N, 6.55; Cl, 16.05. $C_8H_8O_4NCl$ requires C, 45.0; H, 1.9; N, 6.55; Cl, 16.6%).

6'-Chloro-2':4-diketo-2-α-naphthylpyrano (3':4'-5:6) metoxazine.

Malonyl chloride (1.95 c.c.) and α-naphthonitrile (1.53 g.) were heated together gently on a free flame till all the nitrile had dissolved, and then on a steam-bath for 7 minutes. The solid (1g.; 30%) was filtered, washed well with anhydrous ether and dried. Recrystallisation afforded 6'-chloro-2':4-diketo-2-α-naphthylpyrano (3':4'-5:6) metoxazine as orange leaflets, m.p. >300° (decomp.) from benzonitrile (Found: N, 4.15. $C_{17}H_8O_4NCl$ requires N, 4.3%). A higher yield of the product was obtained if the reaction time was extended, but the quality of the product was poorer.

6'-Chloro-2':4-diketo-2-β-naphthylpyrano (3':4'-5:6) metoxazine.

This was prepared similarly to the α-naphthyl-compound. Malonyl chloride (0.98 c.c.) and β-naphthonitrile (0.77 g.) were heated gently till homogeneous, and then for 4 minutes on the steam-bath. The 6'-chloro-2':4-diketo-2-β-naphthylpyrano (3':4'-5:6) metoxazine (0.37 g.; 33%) formed orange leaflets, m.p. 237° (decomp.) from benzonitrile-ether (Found: N, 4.75. $C_{17}H_8O_4NCl$ requires N, 4.3%).

2':4-Diketo-6'-N-morpholino-2-phenylpyrano (3':4'-5:6) metoxazine.

To a suspension of 6'-chloro-2':4-diketo-2-phenylpyrano (3':4'-5:6) metoxazine (0.55g.) in chloroform (ca. 10 c.c.) was added morpholine (0.35 c.c.) portionwise, with shaking. The mixture was shaken continuously till the evolution of heat slackened, and then heated under reflux for several minutes to complete the reaction. The cold solution was filtered from unused chloro-compound (0.1g.), washed with water (10 c.c.) evaporated and triturated with anhydrous ether, when a solid [yield, 0.45g. (84%) based on weight of starting material consumed] was obtained.

The 2':4-diketo-6'-N-morpholino-2-phenylpyrano (3':4'-5:6) metoxazine formed colourless microcrystals, m.p. 231° (decomp.) from dioxan (Found: C, 62.15; H, 4.55; N, 9.0. $C_{17}H_{14}O_5N_2$ requires C, 62.55; H, 4.35; N, 8.6%).

6'-N-n-butylamino-2':4-diketo-2-phenylpyrano (3':4'-5:6) metoxazine.

This was prepared similarly to the morpholinophenylpyrano-metoxazine (above). 6'-Chloro-2':4-diketo-2-phenylpyrano (3':4'-5:6) metoxazine (1g.) and n-butylamine (0.72 c.c.) afforded, after trituration of the resultant gum with ethanol, 6'-N-n-butylamino-2':4-diketo-2-phenylpyrano (3':4'-5:6) metoxazine as yellow plates, m.p. 192° (decomp.) from chlorobenzene (Found: N, 8.6. $C_{17}H_{16}O_4N_2$ requires N, 8.6%).

2':4-Diketo-6'-N-morpholino-2-α-naphthylpyrano (3':4'-5:6) metoxazine

This was prepared similarly to the butylaminophenylpyrano-metoxazine (above). 6'-Chloro-2':4-diketo-2-α-naphthylpyrano (3':4'-5:6) metoxazine (1 g.) and morpholine (0.54 c.c.) afforded 2':4-diketo-6'-N-morpholino-2-α-naphthylpyrano (3':4'-5:6) metoxazine (0.22 g.; 19%) as bright yellow leaflets, m.p. 233° (decomp.) from nitrobenzene-dioxan (Found: C, 66.5; H, 4.4; N, 7.55. $C_{21}H_{16}O_5N_2$ requires C, 67.0; H, 4.3; N, 7.45%).

2':4-Diketo-6'-N-morpholino-2-β-naphthylpyrano (3':4'-5:6) metoxazine.

This was prepared similarly to the butylaminophenylpyrano-metoxazine (above). 6'-Chloro-2':4-diketo-2-β-naphthylpyrano (3':4'-5:6) metoxazine (3 g.) and morpholine (1.6 c.c.) afforded 2':4-diketo-6'-N-morpholino-2-β-naphthylpyrano (3':4'-5:6) metoxazine (0.55 g.;16%) as yellow rectangular plates, m.p. 275° (decomp.) from nitrobenzene. (Found: C, 66.65; H,4.55; N, 8.05. $C_{21}H_{16}O_5N_2$ requires C, 67.0; H, 4.3; N, 7.45%).

6-Acetmorpholido-5-carboxymorpholido-4-keto-2-phenylmetoxazine.

2':4-Diketo-6'-N-morpholino-2-phenylpyrano (3':4'-5:6) metoxazine (0.4 g.) and morpholine (0.105 c.c.) were heated together in chloroform (10 c.c.) under reflux for 17 hours. Evaporation of the solvent and trituration of the residue with anhydrous ether gave 6-acetmorpholido-5-carboxymorpholido-4-keto-2-phenylmetoxazine (0.48 g.;95%) which formed colourless feathery needles, m.p. 215° from ethanol (Found: C, 61.2; H, 5.8; N, 10.5. $C_{21}H_{23}O_6N_3$ requires C, 61.0; H, 5.60; N, 10.15%). The product was slightly soluble in water and gave no ferric colour.

6-Acetmorpholido-5-carboxymorpholido-4-keto-2-α-naphthylmetoxazine.

2':4-Diketo-6'-N-morpholino-2-α-naphthylpyrano (3':4'-5:6) metoxazine (0.22g.) and morpholine (0.05 c.c.) were heated together in chloroform (5.c.c) under reflux for 3 hours. Evaporation of the solvent, and trituration of the residue with anhydrous ether gave 6-acetmorpholido-5-carboxymorpholido-4-keto-2-α-naphthylmetoxazine (0.22g.;81%), which formed colourless laths, m.p. 189° from ethanol (Found: C, 64.6; H, 5.7; N, 9.0. $C_{25}H_{25}O_6N_3$ requires C, 64.8; H,5.45; N, 9.05%). The product gave no ferric colour in aqueous dioxan.

6-Acetmorpholido-5-carboxymorpholido-4-keto-2-β-naphthylmetoxazine.

(a) Directly from the corresponding chloropyrano-metoxazine.

To a suspension of 6'-chloro-2':4-diketo-2-β-naphthylpyrano (3':4'-5:6) metoxazine (2.15 g.) in chloroform (50 c.c.) was added morpholine (1.14 c.c.) portionwise. When the initial evolution of heat had slackened, more morpholine (0.58 c.c.) was added, the solution was heated under reflux for 1 hour and then washed with an equal volume of

water and dried. Evaporation of the solvent and trituration with dry ether gave 6-acetmorpholide-5-carboxymorpholide-4-keto-2-β-naphthyl-metoxazine (2.4g.; 78%), which formed colourless laths, m.p. 229° from ethanol (Found: C, 65.05; H, 5.65; N, 9.3. $C_{25}H_{25}O_6N_3$ requires C, 64.8; H, 5.45; N, 9.05%). Some spot tests on this compound are described on p.32.

(b) From the corresponding morpholinopyrano-metoxazine

2':4-Diketo-6'-N-morpholino-2-β-naphthylpyrano (3':4'-5:6) metoxazine (0.22 g.) and morpholine (0.05 c.c.) were heated together in chloroform (5.c.c.) under reflux for 1 hour. Evaporation of the solvent, and trituration of the residue with anhydrous ether gave 6-acetmorpholide-5-carboxymorpholide-4-keto-2-β-naphthylmetoxazine (0.25g.; 92%). This product was identical (m.p. and mixed m.p.) with a specimen prepared from the chloropyranometoxazine.

Degradation of 2':4-Diketo-6'-N-morpholino-2-phenylpyrano (3':4'-5:6) metoxazine with Morpholine: Formation of Acetone-1:1:3-tricarboxymorpholide.

The morpholinopyrano-metoxazine (0.65g; crude) and morpholine (0·18c.c.) were heated together in chloroform (5.c.c) under reflux for for 3 hours. Evaporation of the solvent, and trituration of the residue with ethanol afforded acetone-1:1:3-tricarboxymorpholide, m.p. 178° from chlorobenzene: admixture with a specimen of the trimorpholide from degradation of a pyrano-dioxin did not depress the m.p. The product gave a deep-red ferric colour.

Degradation of 6'-Chloro-2':4-diketo-2-phenylpyrano (3':4'-5:6) metoxazine with Sodium Hydroxide: Formation of Benzoic Acid.

The chlorpyrano-metoxazine (2.76g.) was heated under reflux with a solution of sodium hydroxide (2g.) in water (20 c.c.) for 1 hours The

resinous precipitate (probably 'acetone resin') was filtered off and the filtrate acidified with dilute HCl; the precipitated benzoic acid had m.p. 118.5°, undepressed by admixture with an authentic specimen. The product effervesced vigorously with sodium bicarbonate solution and gave no ferric colour.

2':4-Diketo-6'-hydroxy-2-phenylpyrano (3':4'-5:6) metoxazine.

6'-Chloro-2':4-diketo-2-phenylpyrano (3':4'-5:6) metoxazine (7.7g.), water (1 c.c.) and dioxan (50 c.c.) were heated together under reflux for 10 minutes, by which time the starting material had dissolved (Hydrogen chloride was evolved and identified as silver chloride). The liquid was filtered from sediment, evaporated to small bulk and a little anhydrous ether added. The 2':4-diketo-6'-hydroxy-2-phenylpyrano (3':4'-5:6) metoxazine (2.58g.; 36%) formed yellow crystals, m.p. 245° (decomp.) from dioxan-ether (Found: C, 60.8; H, 3.35; N, 5.4. $C_{13}H_7O_5N$ requires C, 60.7; H, 2.75; N, 5.45%). This substance gave a pale-red ferric colour in aqueous dioxan, and dissolved in sodium bicarbonate solution with effervescence.

2':4-Diketo-2-phenylpyrano (3':4'-5:6) metoxazine-6'-acetate.

2':4-Diketo-6'-hydroxy-2-phenylpyrano(3':4'-5:6) metoxazine (0.2g.) was heated under reflux with acetic anhydride (1 c.c.) for several minutes when the hydroxypyrano-metoxazine dissolved. On cooling, the liquid deposited 2':4-diketo-2-phenylpyrano (3':4'-5:6) metoxazine-6'-acetate, which formed yellow laths, m.p. 205° (decomp.) from acetic anhydride (Found: N, 4.85; $C_{15}H_9O_6N$ requires N, 4.7%). This substance gave no ferric colour in aqueous dioxan and did not effervesce with sodium bicarbonate solution.

6-Acetmorpholido-5-carboxy-4-keto-2-phenylmetoxazine.

2':4-Diketo-6'-hydroxy-3-phenylpyrano (3':4'-5:6) metoxazine (0.63g.) and morpholine (0.215 c.c.) were heated together with chloroform (10 c.c.) under reflux for 1½ hours. Evaporation of the solvent and trituration with ether afforded 6-acetmorpholido-5-carboxy-4-keto-2-phenylmetoxazine (0.52g.; 61%), which formed yellow laths, m.p. 205° (decomp.) from chlorobenzene (Found: C, 59.15; H, 4.75; N, 8.10. $C_{17}H_{16}O_6N_2$ requires C, 59.3; H, 4.7; N, 8.15%). This product gave a deep-red ferric colour in aqueous dioxan and dissolved with effervescence in ammonium bicarbonate.

The Preparation and Properties of 3-Substituted 2-Chloro-4:6-dihydroxypyridines. (See Table 15).

Malonyl chloride was allowed to stand with the appropriate nitrile for a specified time at room temperature, when the product formed was filtered off, washed with dioxan and purified by recrystallisation.

These products dissolved in alkali without appreciable decomposition and could be recovered on acidification. Pale-orange ferric colours were given in aqueous dioxan.

Table 15.

No.	Nitrile.	Malonyl chloride.	Reaction time.	2-Chloro-4:6-dihydroxypyridine	Yield.
1	MeCN (5.25 c.c.)	9.75 c.c.	3 days	-	3.4 g. (23%)
2	EtCN (2.1 c.c.)	1.95 c.c.	6 hours	3-Methyl-	0.57 g. (18%)
3	$Cl(CH_2)_3CN$ (2.7 c.c.)	"	3 days	3-β-Chloroethyl-	1.47 g. (35%)
4	Bu^nCN (3 c.c.)	"	"	3-n-Propyl-	0.97 g. (26%)
5	$CNCH_2CO_2Et$ (1 c.c.)	1.72 c.c.	"	3-Carbethoxy-	0.77 g. (20%)
6	PhCN (1.15 c.c.)	1.95 c.c.	"	3-Phenyl-	1.3 g. (29%)

No.	Form & solvent.	M.p.		C	H	N	Cl	N
					Analyses.			
1	Colourless laths (H_2O)	233°	Found				24.45	148
			$C_5H_4O_2NCl$ requires	41.95	2.75	9.6	24.35	146
2	Colss. prisms (dil. HCl)	306°(d)	Found	45.4	4.05	8.8	22.3	
			$C_6H_6O_2NCl$ requires	45.15	3.8	8.8	22.2	
3	Colss. laminae (EtOH)	257°(d)	Found	40.25	3.6	6.4	34.9	
			$C_7H_7O_2NCl_2$ requires	40·4	3.4	6.75	34.1	
4	Colss. leaflets ($PhNO_2$)	305°	Found	50.65	5.5	7.25	18.9	
			$C_8H_{10}O_2NCl$ requires	51.2	5.35	7.45	18.9	
5	P.yell.needles ($CNCH_2CO_2Et$)	219°	Found	44.15	3.95	6.5	16.0	225
			$C_8H_8O_2NCl$ requires	44.15	3.70	6.45	16.3	218
6	Colss.leaf.BnCN/ microcrystals EtOH	310°(d)	Found	59.6	3.9	6.2	16.0	
			$C_{11}H_8O_2NCl$ requires	59.6	3.65	6.3	16.0	

6'-Chloro-2':4-diketo-2-phenylpyrano (3':4'-5:6) m-dioxin.

Malonyl chloride (4 c.c.) and benzaldehyde (2.08 c.c.) were heated together on a steam-bath for several hours till the reaction mixture had almost solidified. Dry benzene was added and the solid (1.4.; 24%) filtered off. The 6'-chloro-2':4-diketo-2-phenylpyrano (3':4'-5:6) m-dioxin formed prismatic needles, m.p. $> 300^{0}$ (decomp.) from chlorobenzene or acetonitrile (Found: C, 56.0; H, 3.0; Cl, 12.95. $C_{13}H_7O_5Cl$ requires C, 56.05; H, 2.55; Cl, 12.75%).

2':4-Diketo-6'-N-morpholino-2-phenylpyrano (3':4'-5:6) m-dioxin.

To a suspension of the chloropyrano-dioxin (0.7 g.) in chloroform (10 c.c.) was added morpholine (0.44 c.c.) dropwise, with cooling. The solution was washed with water, dried and evaporated. The 2':4-diketo-6'-N-morpholino-2-phenylpyrano (3':4'-5:6) m-dioxin formed colourless crystals, m.p. 193° (decomp.) from chlorobenzene (Found: C, 62.2; H, 4.6; N, 4.25. $C_{17}H_{15}O_6N$ requires C, 62.0; H, 4.6; N, 4.25%).

Reaction of Malonyl Chloride with Piperonal.

Malonyl chloride (1.55 c.c.) and piperonal (12 g.) were heated together on a steam-bath for 2 hours. Trituration with ether (undried) afforded piperonylidene acetic acid, m.p. 242° (decomp.) (1.25 g.; 41%), which formed colourless laths, from nitrobenzene (Found: C, 62.25; H, 4.3. Calc. for $C_{10}H_8O_4$: C, 62.45; H, 4.2%). A similar experiment using excess of malonyl chloride gave the same product.

Reaction of Malonyl Chloride with Anisaldehyde.

Malonyl chloride (3.9 c.c.) and anisaldehyde (24 c.c.) were heated together on a steam-bath for 1 hour. Trituration with ether (undried) afforded anisylidene acetic acid (1.2g.; 17%),

which formed colourless rhombic leaflets, m.p. 172°(decomp.) from chlorobenzene (Found: C, 67.35; H, 5.8. Calc. for $C_{10}H_{10}O_3$: C, 67.4; H, 5.65%).

Reaction of Malonyl Chloride with Cinnamaldehyde.

Malonyl chloride (3.9 c.c.) and cinnamaldehyde (23.8 c.c.) were heated together on a steam-bath for 25 minutes. Trituration with ether (undried) afforded cinnamylidene malonic acid (4.1g;52%) which formed yellow rhombic leaflets, m.p. 206° (decomp.) from nitrobenzene (Found: C, 65.7; H, 4.95. Calc. for $C_{12}H_{10}O_4$: C, 66.05; H, 4.6%).

2-Acetyl-6'-chloro-2';4-diketo-2-methylpyrano (3';4'-5;6) m-dioxin.

Malonyl chloride (23 g.) and diacetyl (14 g.) were heated together on a steam-bath for 1 hour. Trituration with carbon tetrachloride afforded 2-acetyl-6'-chloro-2';4-diketo-2-methylpyrano (3';4'-5;6) m-dioxin (15.5 g.; 73%) which had m.p. 140.5° (decomp.) from ethyl acetate (Found: C, 46.65; H, 3.05; Cl, 13.5. $C_{10}H_7O_6Cl$ requires, C, 46.45; H, 2.75; Cl, 13.7%). This substance was soluble in dioxan and chloroform.

2-Acetyl-6'-N-aniline-2';4-diketo-2-methylpyrano (3';4'-5;6) m-dioxin.

To the chloropyrano-dioxin (1 g.) in chloroform (5.c.c.) was added aniline (0.8 c.c.) dropwise. The solution was washed with dilute acid and water, and the solvent evaporated. The 2-acetyl-6'-N-aniline-2';4-diketo-2-methylpyrano (3';4'-5;6) m-dioxin had m.p.183° (decomp) from acetone (Found: C, 60.85; H, 4.4; $C_{16}H_{13}O_6N$ requires C, 60.95; H, 4.15%).

2-Benzoyl-6'-chloro-2':4-diketo-2-phenylpyrano (3':4'-5:6) m-dioxin.

Malonyl chloride (1.95 c.c.) and benzil (2.1 g.) were heated together on a steam-bath for 30 minutes. Trituration with ether afforded 2-benzoyl-6'-chloro-2':4-diketo-2-phenylpyrano (3':4'-5:6) m-dioxin (2.3g.;60%) which had m.p. 300°(decomp.) from chlorobenzene (Found: C, 62.75; H, 2.9; Cl, 9.25. $C_{20}H_{11}O_6Cl$ requires C, 63.1; H, 3.3; Cl, 9.9%).

2-Benzoyl-6'-N-diethylamino-2':4-diketo-2-phenylpyrano (3':4'-5:6) m-dioxin.

To a suspension of the chloropyrano-dioxin (1 g.) in chloroform (5 c.c.) was added diethylamine (c. 7 c.c.). The solution was washed with dilute acid and water, and the solvent evaporated. The 2-benzoyl-6'-N-diethylamino-2':4-diketo-3-phenylpyrano (3':4'-5:6) m-dioxin formed buff-coloured microcrystals, m.p. 190°(decomp.) from chlorobenzene (Found: C, 68.45; H, 5.05; N, 3.55. $C_{24}H_{21}O_6N$ requires C, 68.75; H, 5.05; N, 3.35%).