503. *Heterocyclic Syntheses with Malonyl Chloride. Part III.*[1] *The Course of the Reaction with Simple Ketones, and Additional Evidence for the Constitutions of the Products.*

By J. A. Elvidge.

The formation of dicyclic chlorodioxopyranodioxins from the reaction of malonyl chloride with simple ketones takes place in two main stages, by way of a self-condensation to 6-chloro-4-hydroxy-2-oxopyran-3-carbonyl chloride. These stages have been separately performed. Details of the mechanism of the reaction are discussed.

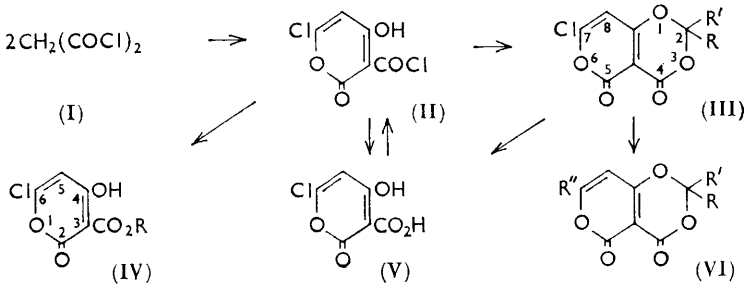
The nuclear magnetic resonance and infrared absorption spectra of the ethyl ester derived from the pyrone acid chloride have been measured. These results together with chemical transformations, indicate the 4-hydroxy-2-oxopyran constitution (IV) and exclude the two tautomerides.

It was suggested in Part I[2] that the reaction between malonyl chloride (I) and simple ketones, which yields 2,2-disubstituted 7-chloro-4,5-dioxopyrano[4,3-*d*]-[1,3]-dioxins (III), probably proceeded in two main stages. The first appeared to be a self-condensation of malonyl chloride to the pyrone acid chloride (II), induced by the weakly basic ketone. In favour of this was the characteristic pyrone absorption at 3040 Å detectable soon after treatment of malonyl chloride with dioxan, a comparably weak but non-reactive base. I now provide further support for the two-stage nature of the reaction with ketones by showing that these stages (I) ⟶ (II) and (II) ⟶ (III) can be performed separately. The fine structure of the hydroxypyrone ring, as (IV), is also discussed.

Formation and Reactions of the Pyrone Acid Chloride (II).—Extinction measurements

[1] Part II, Elvidge and Davis, *J.*, 1953, 2251.
[2] Elvidge and Davis, *J.*, 1952, 4109.

on a 0·6% solution of malonyl chloride in dioxan indicated an approximately 38% conversion into the pyrone (II) in 4 days at room temperature. Presumably further change is inhibited by the hydrogen chloride produced. Substantiation of the conversion was obtained by evaporating a portion of the dioxan solution and treating the residue with water, whereupon the crystalline pyrone acid (V) was isolated in 41% yield. From the



filtrate, malonic acid was obtained, derived from the unchanged malonyl chloride. Treatment of a further portion of the dioxan solution with methanol afforded the pyrone ester (IV; R = Me). To make certain of the origin of this ester, it was ascertained that the pyrone acid (V) was not esterified in a similar time by cold methanol containing a little hydrogen chloride. It was thus established that malonyl chloride underwent self-condensation to 6-chloro-4-hydroxy-2-oxopyran-3-carbonyl chloride (II) under very weakly basic conditions.

It is of interest that Schulte and Yersin [3a] isolated the chloropyrone acid (V) after attempting to condense malonyl chloride with thiourea. It is possible therefore that the pyrone acid chloride (II) is an intermediate in the formation of the dicyclic compound which Schulte [3b] obtained from diphenylthiourea and malonyl chloride.

For the demonstration of the second stage of the malonyl chloride–ketone reaction, (II) ⟶ (III), the pyrone acid chloride (II) was prepared from the crystalline acid (V), in turn obtained [2] from the oxopyranodioxin (III; R = R′ = Ph) and water. Treatment of the pyrone acid (V) with thionyl or oxalyl chloride, or 1 mol. of phosphorus pentachloride in benzene, followed by evaporation, gave a viscous oil. This was essentially the acid chloride (II) because methanol and ethanol, respectively, converted it at once into the crystalline esters (IV; R = Me and Et), and exposure to atmospheric moisture gave back the acid (V). When the oily chloride was warmed with benzophenone a vigorous reaction ensued, with evolution of hydrogen chloride and the mixture solidified, to give the chlorodioxopyranodioxin (III; R = R′ = Ph). The identity of the product was confirmed by its conversion with butylamine into 7-butylamino-4,5-dioxo-2,2-diphenylpyrano[4,3-*d*]-[1,3]-dioxin [1] (VI; R = R′ = Ph, R″ = NHBu). In a parallel experiment it was shown that the pyrone acid (V) did not react with benzophenone: the acid chloride (II) was essential. Further, it was shown that the pyrone acid chloride reacted readily with ethyl acetoacetate, with acetophenone, and with acetone to give the known pyronodioxins (III; R = Me, R′ = CH_2·CO_2Et, Ph, and Me, respectively). In the last case the product was converted with *N*-methylaniline into the derivative (VI; R = R′ = Me, R″ = NMePh) which has also been prepared before.[1]

The Mechanism of the Reaction between Malonyl Chloride and Ketones.—The main stages by which the dicyclic pyranodioxins (III) are formed from malonyl chloride and ketones thus appear to be (I) ⟶ (II) and (II) ⟶ (III), but undoubtedly each stage is a multistep process. The initiation of the first stage (I) ⟶ (II) is probably through both or one of the equilibria (a) and (b).

[3] (*a*) Schulte and Yersin, *Chem. Ber.*, 1956, **89**, 714; (*b*) Schulte, *Chem. Ber.*, 1954, **87**, 820.

(a) (I) + $RR'CO \rightleftharpoons {}^{-}CH(COCl)_2$ (VII) + $RR'C{:}OH^{+}$

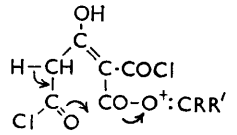
(b) (I) + $RR'CO \rightleftharpoons Cl{\cdot}CO{\cdot}CH_2{\cdot}CO{\cdot}O^{+}{:}CRR'$ (VIII) + Cl^{-}

followed by a combination of the first-formed species, as in (c), or of one or other with malonyl chloride to give the substance (IX).

(c) (VII) + (VIII) $\longrightarrow Cl{\cdot}CO{\cdot}CH_2{\cdot}C(OH){=}C(COCl)_2$ (IX) + $RR'CO$

$\rightleftharpoons COCl{\cdot}CH_2{\cdot}C(OH){=}C(COCl)(CO{\cdot}O^{+}{:}CRR')$ + Cl^{-}

By analogy with related esters,[4] the products of step (c) should have enolic structures as shown. Cyclisation could ensue as in (d), the initiating proton-loss being assisted by the ketone:

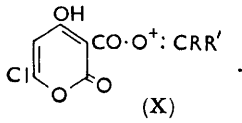
(d) (IX) or  → (II) + H^{+} + Cl^{-} or H^{+} + $RR'CO$ respectively

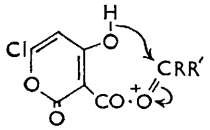
The alternative direction of cyclisation, less likely on general grounds, has been excluded by a proof of the relative positions of chlorine and carboxyl substituents.[2] The light-absorption maximum detectable at 2800 Å shortly after addition of malonyl chloride to dioxan disappears later as the pyrone band at 3040 Å grows,[2] and is probably derived from the enolic intermediates produced transiently at step (c).

The second stage in the formation of the pyranodioxins, (II) → (III), probably involves the species (X), as in (e) and (f).

Cyclisation through a hemiketal seems improbable because ketones do not form simple ketals (as aldehydes give acetals) on treatment with hydroxy-compounds and a proton source. The further possibility of tautomerism of the structure (II) into (XI; R = Cl) and condensation of this with ketone to yield the pyranodioxin (XII), can also be discounted. It is not possible, on the basis of structure (XII) to explain fully the course of the further reaction with amines and the properties of the products reported in Part II [1] of this series.

Fine Structure of the Monocyclic Pyrones.—The proton magnetic resonance spectrum of a 5% solution of the chloropyrone ethyl ester (IV; R = Et) in deuterochloroform showed (i) a quartet centred at 5·54 τ and a triplet at 8·57 τ which arise, respectively, from the

(e) (II) + $RR'CO \rightleftharpoons$  + Cl^{-} (X)

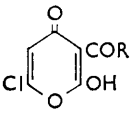
(f)  → (III) + H^{+}

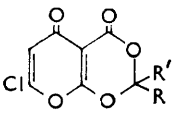
methylene and the methyl protons of the ethyl ester group, (ii) a sharp line in the olefinic-proton region at 3·81 τ, attributable to the single hydrogen at the 5-position, and (ii) one other resonance line at −4·25 τ (just over 800 c./sec. to low field of tetramethylsilane) which must arise from the proton of a strongly bonded hydroxyl group.[5] The spectrum excludes the tautomer (XIII) and is compatible with the constitution (IV; R = Et) preferred on chemical grounds.

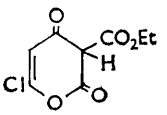
[4] Eisner, Elvidge, and Linstead, *J.*, 1950, 2223; 1951, 1501.

[5] Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, London, 1959.

The infrared characteristics (see Table) also support the constitution (IV; R = Et) and exclude both the tautomers (XI; R = OEt) and (XIII). The assignments for the


(XI)


(XII)


(XIII)

established, fixed-bond structures (III; R = R′ = Me) and (VI; R = R′ = Me, R″ = NMePh) are straightforward. Of the two strong carbonyl bands, that at the higher frequency must arise from the group at the 5-position of the pyrone ring because this is effectively a vinyl ester carbonyl.[6a] The interpretation of the spectrum of the chloro-

Absorption max. ($cm.^{-1}$) in the 2·5—6·6 μ region.

(III; R = R′ = Me) *	3086	H–C (8)
	1776	O=C (5)
	1720	O=C (4)
	1613, 1535	C=C (skeletal)
(VI; R = R′ = Me, R″ = NMePh) †	1779	O=C (5)
	1696	O=C (4)
	1603, 1581, 1542	C=C (skeletal)
(IV; R = Et) ‡	3110	H–C (5)
	2983, 2938	H–C
	2662 (broad)	H–O (bonded)
	1789	O=C (2)
	1650	O=C (ester; H-bonded)
	1627, 1530	C=C

* Nujol mull. † In $CHCl_3$. ‡ In CCl_4.

pyrone ester follows unambiguously and indicates the structure (IV; R = Et) in which the 4-hydroxyl is hydrogen-bonded to the ester carbonyl group (cf. ref. 6*b*). As this ester (IV; R = Et), the methyl ester, the acid (V), and the acid chloride (II) have similar electronic absorptions, it is concluded that all of these compounds are best represented as 4-hydroxy-2-oxopyrans. The earlier constitutional choice [2] is therefore upheld.

Experimental

Self-condensation of Malonyl Chloride to the Pyrone Acid Chloride (II).—(*a*) [In part with S. J. Davis.] Malonyl chloride (2·48 g.) was added to anhydrous dioxan (50 c.c.), and the light absorption in the 250—350 mμ region measured at intervals.[2] After 4 days, the solution had $\lambda_{max.}$ 3040 Å with $E^{1\%}_{1\,cm.}$ 185, unchanged after a further 7 days. The yield of the chloride (II), on the basis of ε = 10,000 (as for the corresponding acid [2]), was then 38%. A 10-c.c. portion of the solution was evaporated under reduced pressure, and the residue triturated briefly with water (2 c.c.). The solid (140 mg., 41%) was acidic, gave a deep red colour with aqueous ferric chloride, and had m. p. 136° (decomp. and darkening) alone and when mixed with 6-chloro-4-hydroxy-2-oxopyran-3-carboxylic acid [2] (V) (Found: C, 37·8; H, 1·8. Calc. for $C_6H_3ClO_5$: C, 37·85; H, 1·6%). Evaporation of the filtrate afforded malonic acid, m. p. and mixed m. p. 135° (decomp.), which gave no intense colour with ferric chloride. The m. p. of a mixture of malonic acid and the pyran acid (V) was depressed considerably.

(*b*) To a portion of the dioxan solution, an excess of methanol was added. After 10 min., the solution was evaporated under reduced pressure, the residual oil taken up in ether, and the clarified solution allowed to evaporate. The crystalline deposit (35% yield) gave a red colour with ferric chloride in aqueous methanol and had m. p. 148—149° alone or mixed with methyl 6-chloro-4-hydroxy-2-oxopyran-3-carboxylate [2] (IV; R = Me).

[6] Bellamy, "Infra-red Spectra of Complex Molecules," Methuen and Co. Ltd., London, 1958, (*a*) Chapter 11, (*b*) Chapter 9.

Formation of the Pyrone Acid Chloride (II) *from the Pyrone Acid* (V).—(*a*) The acid (V) (0·2 g.) was warmed with thionyl chloride (2 c.c.) on the steam-bath for 15 min. Evaporation of the solution under reduced pressure then yielded the pyrone acid chloride (II) as a viscous oil. Methanol (1 c.c.) was added, and 10 min. later the excess was removed under reduced pressure, whereupon the residue crystallised completely (0·2 g.); the product gave a red colour in aqueous methanol with ferric chloride and had m. p. 147—148° alone or mixed with methyl 6-chloro-4-hydroxy-2-oxopyran-3-carboxylate.[2]

After treatment of the pyrone acid (V) (0·2 g.) with methanol (1 c.c.) containing a trace of hydrogen chloride for 10 min. and evaporation of the solution, the pyrone acid was recovered, with m. p. and mixed m. p. 134—136° (decomp.).

The pyrone acid chloride (1 g.) prepared as above was taken up in dry ether (5 c.c.) and treated with ethanol (1 c.c.). Subsequently the solution was evaporated under reduced pressure and the residue crystallised from light petroleum (b. p. 80—100°), to give ethyl 6-chloro-4-hydroxy-2-oxopyran-3-carboxylate (0·5 g.), m. p. 125° (Found: C, 44·2, H, 3·5. Calc. for $C_8H_7ClO_5$: C, 43·95; H, 3·25).

A further sample of the pyrone acid chloride was exposed to the atmosphere. Next day, the gum was entirely replaced by crystals which gave a red colour with ferric chloride and had m. p. 134—135° (decomp. and darkening) alone or mixed with the pyrone acid (V).

In attempts at short-path distillation of the oily acid chloride a crystalline sublimate, m. p. 90—93°, was obtained. This crystallised from light petroleum (b. p. 80—100°) as prisms, m. p. 96°, but, probably because of extreme reactivity, failed to give satisfactory analytical figures.

(*b*) The pyrone acid (V) (0·2 g.) in dioxan (4 c.c.) was heated with oxalyl chloride (1·25 c.c.) at 80° for 5 hr. Evaporation of the solution under reduced pressure gave an oil. This was taken up in methanol (1 c.c.), and the solution allowed to evaporate. The crystals thus obtained had m. p. 141—143° depressed to *ca.* 110° by the starting acid. A mixture with the pyrone methyl ester (IV; R = Me) of m. p. 149° had m. p. 145—146°.

(*c*) A solution of the pyrone acid (V) (0·2 g.) in dry benzene (10 c.c.) was heated under reflux with phosphorus pentachloride (0·225 g.) for 15 min. and then evaporated under reduced pressure. Dry benzene was distilled from the residue several times, finally under reduced pressure. The oil remaining was taken up in methanol (1 c.c.), and the solution allowed to evaporate. A crystalline deposit of the pyrone methyl ester (IV; R = Me) was formed (mixed m. p. undepressed).

Condensation of Ketones with the Pyrone Acid Chloride (II).—For each experiment, the pyrone acid chloride was prepared from the acid (V) (0·2 g.) and thionyl chloride as above.

(*a*) (i) [With S. J. Davis.] The acid chloride (0·2 g.) and benzophenone (0·2 g.) were heated together on the steam-bath. A vigorous reaction occurred with evolution of hydrogen chloride, and the melt solidified. After being washed with benzene, the product (0·2 g., 54%) had m. p. 177—178° (decomp.) (cf. ref. 2). This with butylamine (2 mol., 0·113 c.c.) in chloroform yielded 7-butylamino-4,5-dioxo-2,2-diphenylpyrano[4,3-*d*]-[1,3]-dioxin, m. p. 166° undepressed by authentic material,[1] $\lambda_{max.}$ (in $CHCl_3$) 3320 Å (ε 29,000).

(ii) When the pyrone acid (V) (0·2 g.) and benzophenone (0·2 g.) were similarly heated together there was no noticeable reaction. After 1·5 hr., the benzophenone (mixed m. p.) was recovered almost quantitatively as a white sublimate in the neck of the flask.

(*b*) The acid chloride (0·2 g.) and ethyl acetoacetate (0·13 c.c.) were stirred together and heated on the steam-bath. In a few minutes the mixture became viscous and then solidified, and hydrogen chloride was evolved. The solid was triturated with ether, collected (0·2 g., 63%; m. p. 115—116°), and recrystallised from carbon tetrachloride to afford 7-chloro-2-ethoxycarbonylmethyl-2-methyl-4,5-dioxopyrano[4,3-*d*]-[1,3]-dioxin (III; R = Me, R′ = $CH_2{\cdot}CO_2Et$), m. p. 118° (cf. ref. 2) (Found: C, 47·25; H, 3·8. Calc. for $C_{12}H_{11}ClO_7$: C, 47·6; H, 3·65%).

(*c*) Similarly, the acid chloride (0·2 g.) and acetophenone (0·24 c.c.) afforded a crystalline product (0·25 g., 99%), m. p. 140° (decomp.) undepressed by 7-chloro-4,5-dioxo-2-methyl-2-phenylpyrano[4,3-*d*]-[1,3]-dioxin [2] (III; R = Me, R′ = Ph).

(*d*) The acid chloride (0·2 g.) likewise reacted rapidly with dry acetone (0·1 c.c.), to yield crystals (0·17 g., 71%). From benzene, prismatic needles of 7-chloro-2,2-dimethyl-4,5-dioxopyrano-[4,3-*d*]-[1,3]-dioxin were obtained, with m. p. 185° (decomp.) (Found: C, 46·7; H, 3·8. Calc. for $C_9H_7ClO_5$: C, 46·9; H, 3·1%). As previously described,[1] a portion (0·1 g.) in chloroform

was converted with *N*-methylaniline (0·094 c.c.) into 2,2-dimethyl-7-*N*-methylanilino-4,5-dioxopyrano[4,3-*d*]-[1,3]-dioxin (VI; R = R′ = Me, R″ = NMePh) which crystallised from ethanol as needles, m. p. 160° (decomp.) (Found: C, 64·1; H, 5·4; N, 4·8. Calc. for $C_{16}H_{15}NO_5$: C, 63·8; H, 5·0; N, 4·65%). The m. p. of a mixture with authentic material [1] was the same.

ORGANIC CHEMISTRY RESEARCH LABORATORIES,
IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
SOUTH KENSINGTON, LONDON, S.W.7.

[*Received, January 30th,* 1962.]