694. *Heterocyclic Syntheses with Malonyl Chloride. Part IV.* Pyronodioxins from an Enolic Ketone, Diketones, and Benzaldehyde, and a Modification of the Doebner Condensation.*

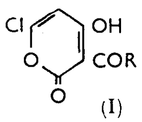
By S. J. Davis and J. A. Elvidge.

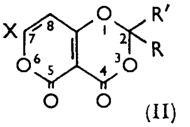
The formation of pyronodioxins from malonyl chloride occurs with acetone-1,3-dicarboxylic ester, biacetyl, benzil, and benzaldehyde. Hexanal induces the self-condensation of malonyl chloride, and 6-chloro-4-hydroxy-2-oxopyran-3-carboxylic acid was isolated, but attempts to cause the corresponding pyrone acid chloride to react with this and other aliphatic aldehydes failed. Piperonaldehyde, *p*-anisaldehyde, and cinnamaldehyde condensed with the methylene group of malonyl chloride.

Details of the reaction between malonyl chloride and simple ketones, discussed in Part III,* made it appear very unlikely that highly enolised ketones would yield pyronodioxins. Such ketones would be insufficiently basic to induce the first stage of the reaction, the self-condensation of malonyl chloride to 6-chloro-4-hydroxy-2-oxopyran-3-carbonyl chloride (I; R = Cl). Indeed, the unsaturated oxo-ester

$$CO_2Et\cdot CH{:}CH\cdot CO\cdot CH(CO_2Et)_2,$$

which is more acidic than carbonic acid,[1] failed to react cleanly with malonyl chloride, and no definite product could be isolated. On the other hand, the weakly enolic ethyl acetoacetate and ethyl pyruvate readily afforded pyronodioxins,[2] and we now find that diethyl acetone-1,3-dicarboxylate also does so. The chloropyronodioxin product (II; $R = R' = CH_2\cdot CO_2Et$, $X = Cl$) was converted by morpholine into the expected derivative (II; $R = R' = CH_2\cdot CO_2Et$, $X = N{<}[CH_2\cdot CH_2]_2{>}O$). The light absorptions (Table) support these structures (cf. refs. 2 and 3).


(I)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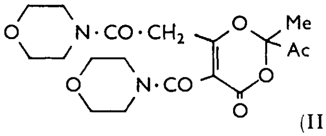
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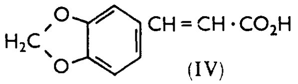
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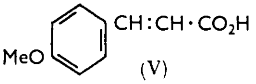
(V)

$$Ph\cdot CH{:}CH\cdot CH{:}C(CO_2H)_2$$
(VI)

Diketones might possibly have undergone a double reaction with malonyl chloride. In the cases of biacetyl and benzil, only one of the carbonyl groups was found to react. The products, $C_{10}H_7ClO_6$ and $C_{20}H_{11}ClO_6$, respectively, were evidently the chloropyronodioxins (II; R = Me, R′ = Ac, X = Cl) and (II; R = Ph, R′ = Bz, X = Cl) as shown by their reactions. Thus the biacetyl product with aniline and with morpholine gave the expected monosubstitution products (II; R = Me, R′ = Ac, X = NHPh and $N{<}[CH_2\cdot CH_2]_2{>}O$), and further treatment of the latter with morpholine yielded the 4-oxo-1,3-dioxin (III) and thence acetone-1,1,3-tricarboxymorpholide. From the chloropyronodioxin derived from benzil, a diethylamino-derivative (II; R = Ph, R′ = Bz, $X = NEt_2$) was made, which had the light absorption (Table 1) expected of a substituted aminopyronodioxin.[3]

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* Part III, *J.*, 1962, 2606.

[1] Eisner, Elvidge, and Linstead, *J.*, 1951, 1501.

[2] Davis and Elvidge, *J.*, 1952, 4109.

Davis and Elvidge, *J.*, 1953, 2251.

The 1,3-diketone, acetylacetone, behaved differently with malonyl chloride and afforded a chlorine-free compound, m. p. 162°, isomeric with dehydroacetic acid. This and related reactions are being studied separately.

The 1,4-diketone, acetonylacetone, converted malonyl chloride vigorously into malonic acid, in spite of precautions to exclude moisture. Presumably the chloride effects a cyclodehydration of the diketone to dimethylfuran. From *p*-benzoquinone with malonyl chloride, the product was intractable. 9,10-Anthraquinone was largely unaffected.

A brief examination was then made of the behaviour of aldehydes with malonyl chloride. Aliphatic aldehydes showed a marked tendency to give tars. However, from an attempted condensation with butyraldehyde, malonic acid was isolated in good yield, presumably as a result of self-condensation of the aldehyde and formation of water. From a reaction with hexanal, the pyrone acid (I; R = OH) was isolated. This demonstrated that an aliphatic aldehyde could induce the self-condensation of malonyl chloride, as a ketone does, but the further reaction to a chloropyronodioxin appeared not to take place. Indeed, after hexanal had been heated with the preformed pyrone acid chloride (I; R = Cl),[4] only the pyrone acid (I; R = OH) was eventually recovered. Acetaldehyde likewise failed to condense with the chloride (I; R = Cl).

In contrast, from benzaldehyde and malonyl chloride, a product with the expected composition $C_{13}H_7ClO_5$ was obtained. That this was the chloropyronodioxin (II; R = Ph, R′ = H, X = Cl) was indicated by its reaction with morpholine to yield a morpholine derivative, $C_{17}H_{15}NO_6$, which had the correct light absorption (Table) for the aminopyronodioxin structure (II; R = Ph, R′ = H, X = $\mathrm{N}{<}[\mathrm{CH_2{\cdot}CH_2}]_2{>}\mathrm{O}$).

TABLE 1.

Light absorptions, in dioxan.

Compound	$\lambda_{max.}$ (mμ)	ε	Compound	$\lambda_{max.}$ (mμ)	ε
(II; R = R′ = $CH_2{\cdot}CO_2Et$, X = Cl)	251	3600	(II; R = Ph, R′ = Bz, X = NEt_2)	251	16,000
	307 *	5600		256	
	315	6400		338	32,300
II; R = R′ = $CH_2{\cdot}CO_2Et$, X = $\mathrm{N}{<}[\mathrm{CH_2{\cdot}CH_2}]_2{>}\mathrm{O}$	231	14,000	(II; R = Ph, R′ = H, X = $\mathrm{N}{<}[\mathrm{CH_2{\cdot}CH_2}]_2{>}\mathrm{O}$	251	7200
	251	4700		257	
	338	34,000		335	27,000

* Inflexion.

Modified Doebner Condensation.—Other aromatic aldehydes condensed with the methylene group of malonyl chloride, apparently to the exclusion of alternative reactions. Thus the unsaturated acids (IV), (V), and (VI) were obtained from piperonaldehyde, *p*-anisaldehyde, and cinnamaldehyde, after the reaction mixtures had been treated with moist ether. It was notable that these αβ-unsaturated acids were formed much more quickly than by the conventional Doebner procedure. Thus cinnamylidenemalonic acid (VI) was formed from malonyl chloride in 47% yield in 25 minutes. In contrast, the condensation of cinnamaldehyde with malonic acid requires 7—9 hours[5] for a comparable yield.

EXPERIMENTAL

2,2-*Disubstitution Products of* 7-*Chloro*-4,5-*dioxopyrano*[4,3-*d*]-[1,3]-*dioxin*.—The carbonyl compound was heated with malonyl chloride on the steam-bath and the *product* triturated with a solvent and recrystallised. Details are given in Table 2.

2,2-*Disubstituted* 7-*Amino*-4,5-*dioxopyrano*[4,3-d]-[1,3]-*dioxins*.—The finely powdered chloro-compound (1 g.), suspended in chloroform (10 c.c.), was treated slowly with the amine (2 mol.). After 15 min., the solution was washed with water, and the chloroform was separated, dried (Na_2SO_4), and evaporated. The following 4,5-*dioxopyrano*[4,3-*d*]-[1,3]-*dioxins* were thus obtained: 2,2-*di*(*ethoxycarbonylmethyl*)-7-*morpholino*- (0·5 g.) (from No. 1 and morpholine) as

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[4] Elvidge, *J.*, 1962, 2606.

[5] Liebermann, *Ber.*, 1895, **28**, 1438; Boxer and Linstead, *J.*, 1931, 740.

leaflets, m. p. 157°, from ethanol (Found: C, 53·7; H, 5·6; N, 3·2. $C_{19}H_{23}NO_{10}$ requires C, 53·65; H, 5·45; N, 3·3%); 2-*acetyl*-7-*anilino*-2-*methyl*- (from No. 2 and aniline), m. p. 183° (decomp.), from acetone (Found: C, 60·85; H, 4·4; N, 5·1. $C_{16}H_{13}NO_6$ requires C, 60·95; H, 4·15; N, 4·7%); 2-*acetyl*-2-*methyl*-7-*morpholino*- (0·4 g.) (from No. 2 and morpholine) as needles, m. p. 187° (decomp.), from ethanol (Found: C, 54·6; H, 5·05; N, 4·7. $C_{14}H_{15}NO_7$ requires C, 54·35; H, 4·9; N, 4·55%); 2-*benzoyl*-7-*diethylamino*-2-*phenyl*- (from No. 3 and diethylamine) as buff crystals, m. p. 190° (decomp.), from chlorobenzene (Found: C, 68·45; H, 5·05; N, 3·55. $C_{24}H_{21}NO_6$ requires C, 68·75; H, 5·05; N, 3·35%); and 7-*morpholino*-2-*phenyl*- (from No. 4 and morpholine), m. p. 193°, from chlorobenzene (Found: C, 62·2; H, 4·6; N, 4·25. $C_{17}H_{15}NO_6$ requires C, 62·0; H, 4·6; N, 4·25%).

TABLE 2.

2,2-Disubstituted 7-chloro-4,5-dioxopyrano[4,3-*d*]-[1,3]-dioxins.

No.	Carbonyl compound	$CH_2(COCl)_2$ (c.c.)	Time (hr.)	Trituration medium	Deriv. of (II; X = Cl)	Yield (%)	Recrystn. from
1	$CO(CH_2{\cdot}CO_2Et)_2$ (4·5 c.c.)	4·85	0·5	C_6H_6-Ligroin	2,2-$(CH_2{\cdot}CO_2Et)_2$	32	EtOAc *
2	Ac_2 (14 g.)	16·0	1	CCl_4	2-Ac-2-Me	73	EtOAc
3	$(CO{\cdot}Ph)_2$ (2·1 g.)	1·95	0·5	Et_2O	2-Bz-2-Ph	60	PhCl
4	Ph·CHO (2·08 c.c.)	4·0	2·5	C_6H_6	2-Ph	21	PhCl or MeCN *

			Found (%)			Required (%)		
No.	M. p. †	Formula	C	H	Cl	C	H	Cl
1	122°	$C_{15}H_{15}ClO_9$	48·2	4·3	9·65	48·1	4·05	9·45
2	140·5	$C_{10}H_7ClO_6$	46·65	3·05	13·5	46·45	2·75	13·7
3	>300	$C_{20}H_{11}ClO_6$	62·75	2·9	9·25	63·1	3·3	9·9
4	>300	$C_{13}H_7ClO_5$	56·0	3·0	12·95	56·05	2·55	12·75

* Needles. † With decomp.

Degradation of 2-*Acetyl*-4,5-*dioxo*-2-*methyl*-7-*morpholinopyrano*[4,3-*d*]-[1,3]-*dioxin with Morpholine.*—The morpholinopyronodioxin (II; R = Me, R′ = Ac, X = $N{<}[CH_2{\cdot}CH_2]_2{>}O$) (0·35 g.) was heated with morpholine (0·1 c.c., 1 equiv.) in chloroform (10 c.c.) under reflux for 0·5 hr. The solution was evaporated under reduced pressure and the residue triturated with light petroleum (b. p. 60—80°). From benzene–light petroleum (b. p. 60—80°), 2-*acetyl*-2-*methyl*-5-*morpholinocarbonyl*-6-*oxo*-1,3-*dioxin*-4-*ylacetomorpholide* (III) (0·35 g.) formed prisms, m. p. 134° (decomp.) (Found: C, 54·8; H, 6·3; N, 7·25. $C_{18}H_{24}N_2O_8$ requires C, 54·55; H, 6·1; N, 7·05%). It was soluble in water and gave no colour with ferric chloride.

This dioxin (0·27 g.) with morpholine (0·06 c.c.) in boiling chloroform (2 c.c.) for 1 hr. gave (after evaporation and trituration of the residue with ethanol–ether and then chlorobenzene) acetone-1,1,3-tricarboxymorpholide (deep red with aqueous ferric chloride), m. p. 178° undepressed by authentic material.[3] The filtrate smelt of biacetyl.

Interaction of Malonyl Chloride with Aliphatic Aldehydes.—(*a*) When malonyl chloride (1 c.c.) was mixed with butyraldehyde (1 c.c.; fractionated) heat was generated, hydrogen chloride evolved, and the liquid darkened. Several extractions of the brown oil with a boiling mixture (5 : 1) of light petroleum (b. p. 60—80°) and ether, and evaporation of the extracts, afforded malonic acid (0·8 g., 76%), m. p. and mixed m. p. 134—135° (decomp.). The acid gave no intense colour with ferric chloride.

(*b*) The chloride (0·5 c.c.) and hexanal (0·5 c.c.; fractionated) were heated together for several minutes. Hydrogen chloride was evolved. Addition of dry ether then precipitated a dark gum. The solution was decanted and allowed to evaporate, whereupon 6-chloro-4-hydroxy-2-oxopyran-3-carboxylic acid (I; R = OH) crystallised as prisms, m. p. and mixed m. p. 134—135° (decomp.). A red colour was given with aqueous ferric chloride.

Unsaturated Acids from Aromatic Aldehydes.—(*a*) Malonyl chloride (1·55 c.c.) and an excess of piperonaldehyde (12 g.) were heated together on the steam-bath for 2 hr. Trituration of the product with ether (undried) afforded 3,4-methylenedioxycinnamic acid (IV) (1·25 g., 41%), m. p. 242° (decomp.)[6] (Found: C, 62·25; H, 4·3. Calc. for $C_{10}H_8O_4$: C, 62·45; H, 4·2%).

(*b*) Malonyl chloride (3·9 c.c.) and *p*-anisaldehyde (24 c.c.) at 90—100° for 1 hr. similarly

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[6] Piccinini, *Chem. Zentr.*, 1904, I, 880.

yielded 4-methoxycinnamic acid (V) (1·2 g., 17%), which crystallised from chlorobenzene as leaflets, m. p. 172° (decomp.) [7] (Found: C, 67·35; H, 5·8. Calc. for $C_{10}H_{10}O_3$: C, 67·4; H, 5·65%).

(*c*) Malonyl chloride (3·9 c.c.) was heated with cinnamaldehyde (23·8 c.c.) on the steam-bath for 25 min. and the product then triturated with ether (undried). The cinnamylidene-malonic acid (VI) (4·1 g., 47%) crystallised from nitrobenzene as yellow leaflets, m. p. 206° (decomp.) [5] (Found: C, 65·7; H, 4·95. Calc. for $C_{12}H_{10}O_4$: C, 66·05; H, 4·6%).

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

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[7] Beilstein's " Handbuch der organischen Chemie," 4th edn., Hauptwerk, Vol. X, p. 298.