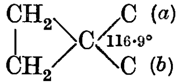
III.—*The Influence of Carbon Rings on the Velocity of Reactions involving their Side Chains. Part I. The Hydrolysis of Cyclic and Open-chain Malonic Esters.*

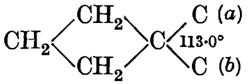
By RICHARD GANE and CHRISTOPHER KELK INGOLD.

IT has been shown during the last 10 years that the angle between two of the valencies of a carbon atom may be materially affected by structural conditions relating to the other two valencies, such as, for instance, their inclusion in a ring (Beesley, Ingold, and Thorpe, J., 1915, **107**, 1080, and later papers) or their attachment to groups of larger or smaller molecular volume (Ingold, J., 1921, **119**, 305, and later). Thus, on passing through the series (I) to (IV) an increasing tendency towards the interaction of groups attached to carbon atoms (*a*) and (*b*) proves that these two carbon atoms are brought together by the widening of the angle between the remaining two valencies of the central carbon atom.

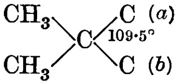
(I.)



(II.)



(III.)



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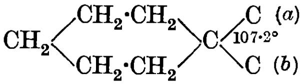
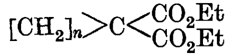


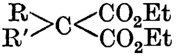
The opposite sequence would be expected if we were to examine, not the *inter*action of groups attached to carbon atoms (*a*) and (*b*), but their *independent* action on some external reagent. Evidently the proximity of the carbon atoms would now be, not an accelerating, but a retarding influence, and a *decreasing* tendency to reaction should be observed on passing through the series (I) to (IV).

We have been induced to examine this inference, not only for its own interest, but also because the large choice of replacement and addition reactions available renders it possible to select reactions capable of more exact study than the violent ring-forming processes employed in the investigations referred to above. This paper contains a record of experiments on the relative rates of hydrolysis by alkalis of a series of cyclic malonic esters of type (V), certain open-chain malonic esters (type VI) being included for comparison.

(V.)



$$[CH_2]_n{>}C{<}\genfrac{}{}{0pt}{}{CO_2Et}{CO_2Et}$$



$$\genfrac{}{}{0pt}{}{R}{R'}{>}C{<}\genfrac{}{}{0pt}{}{CO_2Et}{CO_2Et}$$

(VI.)

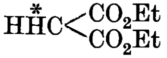
The remarkable effect of different carbon rings in promoting or retarding reactions in which only their side-chains and not the rings themselves are involved was first impressed on us when comparing the experiences of Fischer and Dilthey (*Ber.*, 1902, **35**, 844) with those of Ingold, Sako, and Thorpe (J., 1922, **121**, 1177) when studying the formation of amides from malonic esters by the aid of aqueous ammonia. This case appears to have special analogies with results recorded in this paper, and must briefly be considered.

The most rational view of amide formation from esters appears to be that it is the result of two consecutive reversible addition reactions, the first of the aldehyde–ammonia, and the second of the ketone–alcoholate (semi-acetal) type :

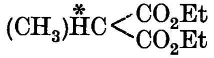
$$-C(OEt){:}O + NH_3 \rightleftharpoons -C(OEt)(OH){\cdot}NH_2 \rightleftharpoons -C({:}O){\cdot}NH_2 + EtOH.$$

Fischer and Dilthey, however, were influenced by the fact that, whilst ethyl malonate and ethyl methylmalonate (VII and VIII) readily yield amides with aqueous ammonia, ethyl dimethylmalonate (IX) refuses to do so, and they therefore formulated the reaction, not as a direct attack by ammonia upon the carbethoxyl groups, but as a complex process involving a tautomeric hydrogen atom (*), the presence of which in (VII) and (VIII) enables a salt of type (X) to be formed as an intermediate product.

(VII.)



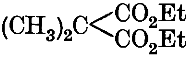
$H\overset{*}{H}C{<}\substack{CO_2Et\\CO_2Et}$



$(CH_3)\overset{*}{H}C{<}\substack{CO_2Et\\CO_2Et}$

(VIII.)

(IX.)

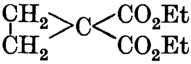


$(CH_3)_2C{<}\substack{CO_2Et\\CO_2Et}$

$-C{<}\substack{CO_2Et\\C(ONH_4)OEt}$

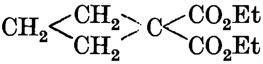
(X.)

Ingold, Sako, and Thorpe (*loc. cit.*), and at about the same time Dox and Yoder independently (*J. Amer. Chem. Soc.*, 1921, **43**, 2097), prepared without difficulty amides from the cyclic malonic esters (XI) and (XII) which, however, are devoid of a malonyl hydrogen atom.



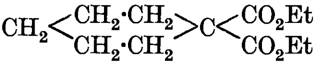
$\substack{CH_2\\|\\CH_2}{>}C{<}\substack{CO_2Et\\CO_2Et}$

(XI.)



$CH_2{<}\substack{CH_2\\CH_2}{>}C{<}\substack{CO_2Et\\CO_2Et}$

(XII.)



$CH_2{<}\substack{CH_2{\cdot}CH_2\\CH_2{\cdot}CH_2}{>}C{<}\substack{CO_2Et\\CO_2Et}$

(XIII.)

These observations appear to some extent to rehabilitate the reversible addition mechanism, and to suggest a spatial explanation of the differences noticed. When it is reflected also that amide-formation occurred more easily with the *cyclo*propane than with the *cyclo*butane ester, it seems clear that at least a part of the observed differences is to be accounted for on stereochemical grounds. The special mechanism suggested by Fischer and Dilthey cannot be positively excluded from participation in the cases to which it applies; it must, however, be regarded, not as the general mechanism of amide formation, but only as a possible auxiliary process by means of which amide formation may be facilitated when enolisation of the ester can occur.

Bearing these points in mind, we have examined the velocity of hydrolysis not only of cyclic and disubstituted malonic esters such as (IX), (XI), (XII), and (XIII), but also of a series of malonic esters possessing a mobile hydrogen atom. The results of some of these determinations, carried out under strictly comparable conditions, are displayed in Figs. 1 and 2.

FIG. 1.

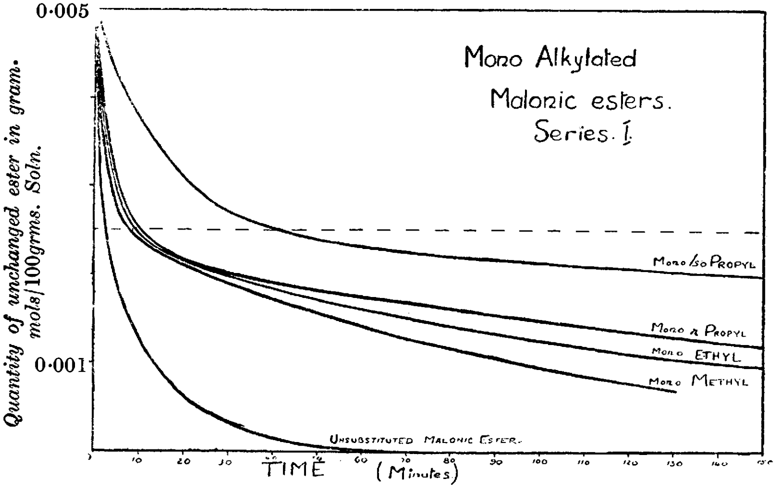
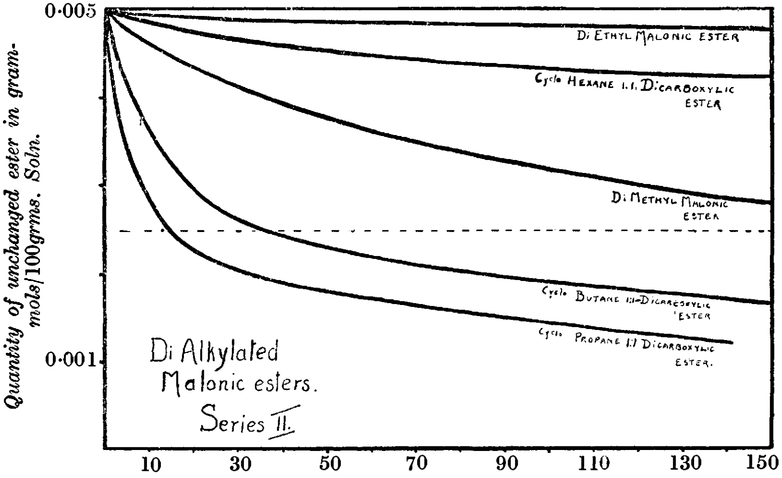


FIG. 2.



Time (Minutes).

Attempts to calculate coefficients and construct such curves theoretically led to considerable mathematical difficulties, principally owing to the distortion which experimental errors underwent in the process of evaluating coefficients. In its simplest aspect, and neglecting all corrections, the complete hydrolysis must be regarded as a pair of consecutive bimolecular reactions, but calculating on this basis it was found that effects of an arbitrary variation of one of the determined coefficients could often be largely counterbalanced by adjusting the other. Finally an approximate numerical comparison of the different cases was obtained by calculating the initial velocities from a series of curves representing identical conditions of temperature and initial concentration.

These initial velocities, $\dot{x}_0$, which were calculated from the following equations,

$$\dot{x} = K(a - x)(b - x)\,; \quad K_0 = \lim_{x \to 0} K\,; \text{ and } \dot{x}_0 = K_0 ab,$$

are exhibited for the disubstituted malonic esters (cyclic and open-chain) in the following table, the last column of which displays the angle between the valencies carrying the carboxyl groups calculated according to the principles advanced by Beesley, Ingold, and Thorpe (*loc. cit.*).

TABLE I.

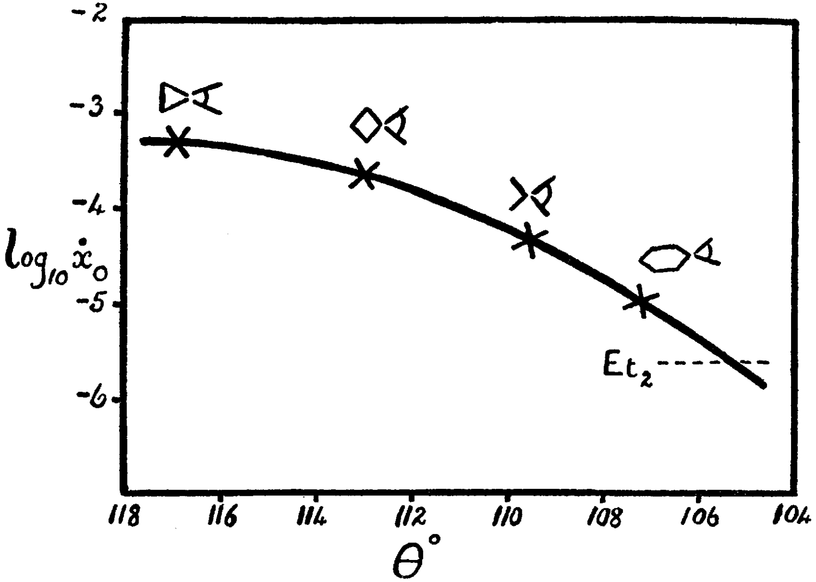
	$\dot{x}_0 \times 10^4$.	$\log_{10} \dot{x}_0$.	θ.
*cyclo*Propane-1 : 1-dicarboxylic ester	4·95	$\bar{4}\cdot69$	116·9°
*cyclo*Butane-1 : 1-dicarboxylic ester	2·3 (5)	$\bar{4}\cdot37$	113·0
gem-Dimethylmalonic ester	0·45	$\bar{5}\cdot65$	109·5
*cyclo*Hexane-1 : 1-dicarboxylic ester	0·10	$\bar{5}\cdot00$	107·2
gem-Diethylmalonic ester	0·02 (5)	$\bar{6}\cdot40$	(105·3)

Reference to Fig. 3 shows that the points connecting the logarithms of the initial velocities and the calculated angles lie on a smooth curve both for the cyclic esters and the *gem*-dimethyl ester. There is no means at present of calculating the angle appropriate to the *gem*-diethyl ester, but the curve indicates a value of 105·3°, which is lower than might be expected from previous investigations with glutaric acids.

It was not found possible to deduce initial velocities in the cases of the tautomeric malonic esters represented in Fig. 1, as the reactions of these substances (excepting *iso*propylmalonic ester) were too rapid at their commencement for accurate measurement. The curves show, however, that the various alkyl groups exert an influence appropriate to their relative size, although it is difficult to express this effect quantitatively.

The fact that the reactions of this group proceed with much greater rapidity than the steric theory would indicate seems to show the operation of an additional mechanism when tautomeric hydrogen is present. Such a supposition would be consistent with that discussed in the case of amide formation, with racemisation by alkalis of compounds containing potentially mobile hydrogen attached to asymmetric carbon, with the interconversion of sugars by alkalis, and numerous other well-known phenomena.

FIG. 3.



EXPERIMENTAL.

Preparation of Material.—(1) *Ethyl malonate.* A sample of Boots's pure ethyl malonate was carefully fractionated, head and tail fractions being rejected, and the main portion, which boiled well within 1°, being used.

(2) *Ethyl methylmalonate.* To avoid possible contamination of the monomethylation product of ethyl malonate with traces of the latter and of ethyl dimethylmalonate, the crude ester was hydrolysed and the acid crystallised several times from ether and water, and, after washing with hot chloroform, from ethyl acetate. The fully purified acid (m. p. 130°; recorded m. p. 129°) was then re-esterified by Fischer and Speier's method. The ester had b. p. 196—197°/754 mm.

(3) *Ethyl dimethylmalonate.* The crude dimethylation product of malonic ester was distilled (b. p. 193—195°) and, in view of possible contamination with incompletely methylated products, digested with an equal weight of ammonia (*d* 0·880), which rapidly converts the latter into amides. The pure dimethyl ester had b. p. 194—194·3°/751 mm. and b. p. 196—197°/765 mm.

(4) *Ethyl ethylmalonate.* Like (2).

(5) *Ethyl diethylmalonate.* Boots's sample of this ester was shaken with cold 30% sodium hydroxide sufficiently to hydrolyse any ethyl monoethylmalonate, recovered, and distilled (Michael, *J. pr. Chem.*, 1905, **72**, 537).

(6) *Ethyl* n-*propylmalonate.* The ester prepared as described by Conrad (*Annalen*, 1880, **204**, 124) was purified by distillation until it boiled within 1°.

(7) *Ethyl* iso*propylmalonate.* Like (6) (compare Preiswerck, *Helv. Chim. Acta*, 1923, **6**, 192).

(8) *Ethyl* cyclo*propane*-1 : 1-*dicarboxylate* (XI) was prepared and purified as described by Perkin (J., 1885, **47**, 810). B. p. 210—211°/718·5 mm.

(9) *Ethyl* cyclo*butane*-1 : 1-*dicarboxylate* (XII), prepared as described by Perkin (J., 1887, **51**, 2) and purified by repeated fractional distillations, had b. p. 224·5—225·5°/757·7 mm.

(10) *Ethyl* cyclo*hexane*-1 : 1-*dicarboxylate* (XIII). The specimen used was kindly given by Mr. W. A. Wightman. It had been subjected to partial hydrolysis, which would have removed any monosubstituted malonic ester if present [see (5)].

Method of Experiment.—The hydrolyses were carried out by means of carbonate-free aqueous-alcoholic sodium hydroxide contained in strong bottles, into which thin glass tubes containing the weighed ester (usually 0·005 g.-mol.) were dropped to start the reaction, the alkali having previously attained the thermostat temperature. The portions withdrawn for analysis were run as rapidly as possible into an excess of hydrochloric acid to terminate the reaction and titrated with *N*/50—*N*/60-barium hydroxide. Various temperatures and concentrations of alkali were employed, but in the experiments selected for this record the temperature was uniformly 27·0°, whilst the alkali consisted of 0·8380 g. of sodium hydroxide, 23·26 g. of water and 75·90 g. of alcohol in each case.

Results.—The general method of calculating the limiting velocities has been described above, and an instance may here be given of its application. In the following table, the figures of the first row are read from the slope of the smoothed x–t curve, and those in the bottom row show the asymptotic approach of k to the value $k_0 =$ 0·0000090; whence $\dot{x}_0 =$ 0·00049 can be calculated.

TABLE II.

(Ethyl *cyclo*propane-1 : 1-dicarboxylate.)

$\dot{x} \times 10^4$ ...	4·45	3·55	2·95	2·40	1·70	1·30	0·78
$x \times 10^4$ ...	2·25	6·20	9·50	1·21	1·62	1·92	2·24
$k \times 10^4$ ...	9·2	9·1	9·5	9·6	10·4	12·4	17·4 (rapidly increasing)

TABLE III.

(Mobile Esters.)

Ethyl malonate.		Ethyl methylmalonate.		Ethyl ethylmalonate.	
t (mins.).	$x \times 10^4$ (g.-mols.).	t (mins.).	$x \times 10^4$ (g.-mols.).	t (mins.).	$x \times 10^4$ (g.-mols.).
0·50	16·2	0·75	8·5	1·00	6·3
1·50	22·5	3·00	17·8	2·00	11·1
2·50	27·4	4·00	20·7	3·25	15·3
3·75	29·6	6·00	23·1	6·00	20·8
5·75	32·7	8·50	24·9	8·25	24·0
6·75	34·1	11·00	26·2	10·75	25·7
9·75	37·3	15·25	27·4	14·25	26·9
12·00	39·2	20·00	28·5	21·00	28·1
14·75	40·9	25·00	30·0	33·00	30·1
19·50	43·3	30·00	31·1	41·75	31·4
26·50	45·8	35·50	32·3	54·00	32·8
35·50	47·3	46·50	34·3	71·25	34·6
46·00	48·8	60·50	36·5	89·00	35·9
59·00	49·6	75·25	38·1	104·00	37·4
75·0	49·9	89·00	39·3	127·00	39·0
		100·00	40·7	144·00	39·9
		117·00	41·8	165·00	41·2
		131·00	43·0	194·00	42·2

Ethyl *n*-propylmalonate.				Ethyl *iso*propylmalonate.			
t (mins.).	$x \times 10^4$ (g.-mols.).	t (mins.).	$x \times 10^4$ (g.-mols.).	t (mins.).	$x \times 10^4$ (g.-mols.).	t (mins.).	$x \times 10^4$ (g.-mols.).
0·50	5·7	28·50	33·3	0·50	2·3	41·00	24·7
1·44	10·6	38·75	34·0	2·25	5·8	57·50	26·7
2·50	14·6	70·50	34·7	4·25	7·8	75·25	27·7
4·33	16·4	105·50	36·8	8·50	11·1	91·75	28·5
6·67	22·3	132·50	38·7	14·25	16·0	113·50	28·9
9·44	24·7	153·00	39·4	19·25	18·7	134·50	29·6
12·50	26·6	187·50	40·8	25·00	21·6	174·75	30·4
15·84	29·8	210·25	41·6	35·25	23·8		
20·00	31·2						

TABLE IV.

(Static Esters—Open-chain.)

Ethyl dimethylmalonate (" A ").				Ethyl dimethylmalonate (" B ").				Ethyl diethylmalonate.	
t (mins.).	$x \times 10^4$ (g.-mols.).	t (mins.).	$x \times 10^4$ (g.-mols.).	t (mins.).	$x \times 10^4$ (g.-mols.).	t (mins.).	$x \times 10^4$ (g.-mols.).	t (mins.).	$x \times 10^4$ (g.-mols.).
0·75	0·3	84·50	16·4	1·50	0·7	85·00	16·9	1·50	0
1·50	0·6	102·25	17·9	3·75	1·3	102·75	17·8	13·00	0·3
3·00	1·3	116·50	19·2	6·25	2·1	121·50	19·3	22·50	0·6
6·84	2·4	138·00	20·6	10·00	3·4	148·50	21·2	34·50	0·9
14·84	4·9	158·75	22·1	17·00	5·6	174·67	22·4	48·25	1·1
26·00	7·4	183·75	23·1	25·75	7·5	201·00	23·5	110·00	1·5
36·75	9·8	200·50	23·8	33·50	8·5	223·00	23·9	181·00	2·2
46·50	11·3	212·25	23·9	41·75	10·6	244·00	24·8	218·00	2·4
56·84	12·9	229·50	24·6	52·75	11·7	278·50	25·0		
70·50	14·8	238·75	24·9	68·25	14·5	309·75	26·5		
				81·75	16·5				

TABLE V.

(Static Esters—Cyclic.)

Ethyl *cyclo*propanedicarboxylate.				Ethyl *cyclo*butanedicarboxylate.				Ethyl *cyclo*hexanedicarboxylate.	
t (mins.).	$x \times 10^4$ (g.-mols.).	t (mins.).	$x \times 10^4$ (g.-mols.).	t (mins.).	$x \times 10^4$ (g.-mols.).	t (mins.).	$x \times 10^4$ (g.-mols.).	t (mins.).	$x \times 10^4$ (g.-mols.).
0·50	2·8	29·50	29·5	0·50	1·0	44·00	26·3	3·75	0·5
1·75	6·9	34·25	29·9	1·75	3·3	51·00	27·4	7·00	0·8
2·75	10·4	39·00	30·4	3·75	7·2	62·75	28·3	14·00	1·5
4·00	13·1	47·75	31·4	6·50	10·9	78·50	29·8	29·50	2·8
5·50	17·3	56·00	32·6	9·00	13·5	103·50	31·6	49·50	3·9
8·25	19·9	68·50	33·7	14·00	17·0	128·50	32·8	61·00	4·8
11·50	22·6	84·50	35·1	19·33	19·5	147·75	33·2		
14·00	24·6	96·00	35·5	25·33	21·6	170·00	34·4		
17·00	25·7	113·50	36·5	30·00	23·8	188·25	34·9		
20·25	26·9	134·25	37·8	35·20	24·6	207·00	36·1		
24·00	28·3	160·75	38·2						

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