The Formation of Ketones. Part II. The Formation of Some Substituted* cyclo*Pentanones by the Dieckmann Reaction.*

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Ring closure of some alkyl-substituted esters by sodium ethoxide is in accord with the accepted course of the reaction, the rate-determining steps being ring closure and ring fission in the forward and reverse reactions respectively. Some evidence has been obtained for the existence of steric retardation.

ALTHOUGH many investigations have been made into the formation of β-keto-esters (Ingold, "Structure and Mechanism in Organic Chemistry," Bell and Sons Ltd., London, 1953, p. 787), no kinetic studies have been reported, and, for comparison with the pyrogenic formation of ketones, some studies of the Dieckmann reaction (*Ber.*, 1849, **27**, 102; *Annalen*, 1901, **317**, 51) have been undertaken.

Initially the investigation has been confined to the cyclisation of some adipic esters, the overall reaction being

$$EtO_2C{\cdot}[CH_2]_2{\cdot}CHR'{\cdot}CHR{\cdot}CO_2Et \xrightleftharpoons{NaOEt} EtO_2C{\cdot}\underset{OC}{CH}{\cdot}CH_2{\cdot}CHR'{\cdot}CHR + EtOH$$

where R = H, Me, Et, Pr^i, and R′ = H, or R = H and R′ = Me. Evidence for the direction of ring closure has been provided for the α-methyl- (Dieckmann, *Annalen*, 1901, **317**, 51; Cornubert and Borrel, *Bull. Soc. chim.*, 1930, **47**, 301) and β-methyl-adipic ester (Dieckmann and Groenveld, *Ber.*, 1900, **33**, 595; Chakravarti, *J.*, 1947, 1028; Craig, unpublished work). In the other cases, a single product was obtained whose configuration was deduced by analogy. Use of a large excess of sodium ethoxide leads to a first-order reaction, and a formal demonstration of this for diethyl adipate is reported in Table 1.

TABLE 1.—Temp. 40·0°. (2·85 ± 0·05)M-NaOEt.

Ester, mole:	0·089	0·110	0·198	0·220
10^3k (min.$^{-1}$) [a]	4·34	4·23	4·31	4·37
10^3k_1 (min.$^{-1}$) [a]	[b]	3·21	3·43	3·48
10^3k_{-1} (min.$^{-1}$)	—	1·02	0·88	0·89

[a] k represents the overall velocity constant, k_1 that for ring closure, and k_{-1} that for the ring-opening reaction. [b] Equilibrium value rather too small for an accurate determination of k_1.

TABLE 2. (2·85 ± 0·05)M-NaOEt.[a]

Substituent, R	R′	35° k_1	35° k_{-1}	40° k_1	40° k_{-1}	45° k_1	45° k_{-1}	50° k_1	50° k_{-1}	E_1 (kcal.)	E_{-1} (kcal.)	A_1 (min.$^{-1}$)	A_{-1} (min.$^{-1}$)
H	H	1·68	0·48	3·16	1·00	5·34	1·21	13·0	2·72	24·0	23·9	$4·9 \times 10^{13}$	$3·0 \times 10^{12}$
				3·44	0·89								
Me	H	1·61	1·01	2·36	2·15	3·83	2·46	—	—	17·5	17·7	$1·2 \times 10^{9}$	$1·1 \times 10^{9}$
Et	H	1·32	1·13	2·52	2·62	4·75 [b]	3·81 [b]	7·01	6·87	25·2	24·2	$3·0 \times 10^{14}$	$4·5 \times 10^{13}$
Pr^i	H	Too slow for measurement				1·26	1·11	—	—	—	—	—	—
H	Me	—	—	—	—	16·9 [c]	5·22	—	—	—	—	—	—

[a] All velocity constants are $\times 10^3$ (min.$^{-1}$). [b] Values obtained by interpolation. [c] We are indebted to R. S. Craig for the preparation of, and preliminary measurements on, this compound.

The measured velocity constants for the homologous series, together with the Arrhenius factors, are in Table 2.

In accordance with the accepted mechanism (Ingold, *op. cit.*), it is convenient to consider the overall reaction as composed of stages (I—IV). Anion formation (I) is not, under

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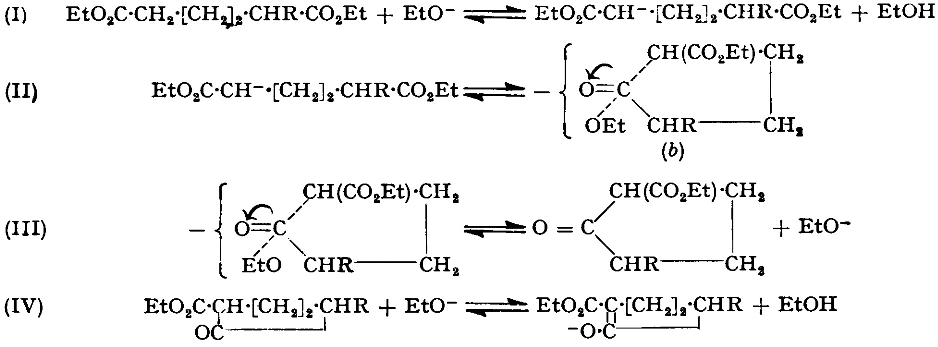
* Part I, *J.*, 1953, 3911.

the present conditions, the rate-determining step. By a consideration of known electron-displacement effects, it can be predicted that the influence of the alkyl groups on the ionisation would lead to the order H, β-Me, α-Et, α-Me, for the velocity constants, which is not in accord with observation, and, by similar argument, enolisation (IV) can also be shown



(I) $EtO_2C{\cdot}CH_2{\cdot}[CH_2]_2{\cdot}CHR{\cdot}CO_2Et + EtO^- \rightleftharpoons EtO_2C{\cdot}CH^-{\cdot}[CH_2]_2{\cdot}CHR{\cdot}CO_2Et + EtOH$

not to be rate-determining. The importance of the enolisation is that in the presence of the high ethoxide concentration the amount of keto-form present will be reduced to a low equilibrium value, which in the absence of detailed information has been assumed to be of the same order of magnitude for all the cases here described.

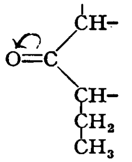
Under the experimental conditions used—a solvent of low dielectric constant and a high concentration of sodium ethoxide—the reaction is bimolecular, which is supported by the qualitative observation that the rate of reaction increases with increasing basic strength, the order being $MeO^- < EtO^- \sim Pr^nO^- < Pr^iO^-$. The transition state (II*b*) has been considered, in view of the high stability made possible by mesomerism, as a reaction intermediate, and its formation and decomposition are here considered as two distinct processes.

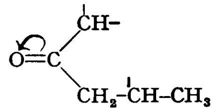
In ring closure, the approach of the anionic centre will be facilitated by a positive charge on the future ketonic carbon atom, and the loss of the ethoxide ion is retarded. Thus, if the former is rate-determining, the presence of adjacent alkyl groups should progressively retard ring formation, which is in general agreement with the measured velocity constants (H > α-Me, α-Et). The overall process is, however, complicated by the polarisation which

will facilitate ring-closure by enolisation and either ring fission, or loss of ethoxide ion, by the return to the ketonic form, and in consequence the agreement with simple theory may not be quantitative.

The reverse process, ring opening, has the opposite electronic requirements, and hence the presence of alkyl substituents should hinder the addition of the ethoxide ion to give the complex and facilitate breakdown of the intermediate so formed. The latter is in accordance with the observations, and the order of the velocity constants (H < α-Me < α-Et) is in agreement with the known electron-release of the respective alkyl groups. In both reactions it appears that the rate-determining process is associated with the carbon–carbon bond of the intermediate and not with the concomitant loss or gain of the ethoxide ion.

Some evidence has been obtained for the existence of a steric factor caused by the increasing bulk of the α-alkyl substituent, which appears to be the probable cause of the retardation of ring opening of ethyl 2-oxo-3-*iso*propyl*cyclo*pentanecarboxylate relative to that of the lower homologues in which a progressive acceleration was observed. The possibility that all α-substituents cause some steric retardation has also been examined by a comparison of ring fissions of ethyl 2-oxo-3-ethyl*cyclo*pentanecarboxylate and the analogous 4-methyl compound, whose electronic effects may be considered equal, to a first approximation, the principal difference being the spatial atomic arrangement. The methyl derivative reacts faster by a factor of about 1·4, indicating that the effect is not large in this





direction, whilst the forward reaction may be complicated by other factors, the incursion of some of which have already been noted in the ring-closure process. This work is being continued and extended to the analogous pimelic esters.

EXPERIMENTAL

(2·85 ± 0·05)M-Sodium ethoxide was prepared by dissolving sodium under reflux in the calculated quantity of ethyl alcohol. Gentle heating was necessary in the final stages, and the concentration estimated by titration. The ethoxide solution slowly became brown and was freshly prepared for each set of experiments. Sufficient ester to make an approx. 0·1M-solution was weighed into a graduated flask, brought to the temperature of the thermostat, and made up to the mark with the ethoxide solution already at thermostat temperature. On mixing, the solution became very viscous and vigorous shaking for several minutes was necessary to make the solution homogeneous. Aliquot samples were withdrawn at suitable intervals and analysed for the β-keto-ester present (Cumming, Hopper, and Wheeler, " Systematic Organic Chemistry," Constable & Co. Ltd., London, 1937, p. 496), the accuracy having been tested for ethyl 2-oxo-*cyclo*pentanecarboxylate [Found: (*a*) 4·810; 4·635; (*b*) 5·705, 5·721. Prepared: (*a*) 4·786; (*b*) 5·705 g./l.].

Within individual kinetic experiments, the variation in velocity constants was small, the results of a typical experiment being given in Table 3.

TABLE 3.—Temp. 35·1°. 0·137M-Diethyl adipate. 2·83M-Sodium ethoxide.

Time (min.)	0	30	60	90	120	150	180
10^3k (min.$^{-1}$)	—	2·18	2·11	2·22	2·15	2·14	2·10

Materials.—" Absolute " ethyl alcohol was repeatedly dried (Mg) and distilled; it had b. p. 78·5°/760 mm. Adipic acid (from Messrs. Light & Co.) was recrystallised from water to m. p. 150°. Its diethyl ester had b. p. 130°/14 mm. β-Naphthol (from British Drug Houses Ltd.) was steam-distilled and recrystallised from ethanol, then having m. p. 123°. Bromine (from British Drug Houses Ltd.) was shaken twice with concentrated sulphuric acid and distilled, having b. p. 59°.

α-Alkyladipic acids. 3-Phenoxypropyl bromide (*Org. Synth.*, Coll. Vol. I, 1946, p. 435) was condensed with ethyl sodiomethylmalonate. Hydrolysis of the product with 30% aqueous potassium hydroxide and decarboxylation at 210° gave α-methyl-δ-phenoxyvaleric acid which was converted into the iodo-acid by constant-boiling hydriodic acid and then esterified (Vogel, " Practical Organic Chemistry," Longmans Green & Co., London, 1948, p. 380). The ester, b. p. 180°/16 mm., was converted by alcoholic potassium cyanide into the cyano-ester, which was hydrolysed to α-methyladipic acid. Recrystallisation to constant m. p. gave an acid of m. p. 63°, giving (method: *op. cit.*) a diethyl ester, b. p. 127—129°13 mm.

α-Ethyl-, m. p. 48°, and α-*iso*propyl-adipic acid, m. p. 40—42° (diethyl esters, b. p. 130°/12 mm. and 138—140°/15 mm., respectively), were similarly prepared.

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