

20. *A Kinetic Examination of the Reactions Concerned in Alkylation with 4-Dialkylaminobutan-2-one Metho-salts.*

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Decomposition of 4-dialkylaminobutan-2-one metho-salts in sodium alkoxide solutions is extremely rapid. The but-3-en-2-one released is then removed in a slower reaction with the solvent, $\text{CH}_2=\text{CH}\cdot\text{COMe} + \text{ROH} \longrightarrow \text{RO}\cdot\text{CH}_2\text{CH}_2\cdot\text{COMe}$, the rate of which is in the order $\text{R} = \text{Pr}^i > \text{Et} > \text{Me}$.

Polymerisation of butenone or 4-alkoxybutan-2-ones increases with the base strength of the alkoxide ion present.

4-Alkoxybutan-2-ones, $\text{RO}\cdot\text{CH}_2\text{CH}_2\cdot\text{COMe}$ ($\text{R} = \text{Me}, \text{Et}, \text{Pr}^i$) have been prepared and shown to alkylate ethyl 2-oxocyclohexanecarboxylate in the presence of the corresponding sodium alkoxide through release of butenone in small concentration.

Whilst the rate of alkylation of ethyl 2-oxocyclohexanecarboxylate with butenone is relatively insensitive to change in solvent (ROH) and base (RO^-) ($\text{R} = \text{Me}, \text{Et}, \text{or } \text{Pr}^i$) the cyclodehydration of ethyl 1-3'-oxobutyl-2-oxocyclohexanecarboxylate is shown to involve two steps whose rates are very dependent on the strength of alkoxide base present.

GENERATION of an $\alpha\beta$ -unsaturated ketone *in situ* by base-induced decomposition of a β -keto-alkyl quaternary ammonium salt has found wide application as a procedure for

Michael-addition alkylation.^{1,2} In the earliest examples^{2,3} the yields were generally low: with improved experimental conditions^{4,5} very acceptable yields have been recorded in many cases,^{5,6} although in some instances the direct use of the unsaturated ketone has been preferred.⁷ In different examples of the use of metho-salt procedure the experimental conditions have, however, been rather varied, notably in the choice of solvent and base. For these reasons, the influence of, in particular, base strength and solvent on the decomposition of a typical β -keto-alkylammonium salt, and on the subsequent stages of the alkylation, appeared to merit closer examination. Limited kinetic data for the related decomposition of a 2-alkylaminoindole are recorded,⁸ but none for the alkylation by a β -keto-alkylammonium salt. An example amenable to examination appeared to be the alkylation of ethyl 2-oxocyclohexanecarboxylate with a 4-dialkylaminobutan-2-one metho-salt. It will be shown that this involves the stages (i)—(vii), which have been followed by means of the attendant change in ultraviolet absorption; and for all but the first step, which is too rapid, rate or equilibrium data have been derived. The reactions have been examined with sodium methoxide, ethoxide, and isopropoxide as bases in the corresponding alcohol.

Decomposition of the quaternary bromide (I) in sodium alkoxide solutions was found to be very rapid. Formation of butenone (II) could be observed from the increase in absorption at 219 $m\mu$, or with the corresponding quaternary iodide at 324 $m\mu$; iodide ion absorbs strongly⁹ at 225 $m\mu$. The subsequent course of the reaction was found to depend on the proportion of alkoxide base. With an excess of the quaternary salt very rapid release of an amount of butenone closely equivalent to the added base was followed by a further slow increase in absorption at 219 $m\mu$ due to reaction (ii). Decomposition of the quaternary salt by an excess of triethylamine in ethanol was independently verified and a second-order rate constant of $\sim 3.8 \times 10^{-2}$ l. mole⁻¹ min.⁻¹ at 18.6° derived. With an excess of alkoxide base, on the other hand, after the initial release of butenone, absorption at 219 $m\mu$ fell progressively, clearly owing to reaction (iii) which is, *a priori*, to be expected. The reaction has been employed preparatively,¹⁰ and we have prepared and characterised 4-methoxy-, 4-ethoxy-, and 4-isopropoxy-butan-2-one in this way. In preparing the alkoxyketones it was noted that whilst $\sim M/25$ -sodium methoxide or ethoxide gave the corresponding alkoxybutanone in good yield with relatively little polymerisation, sodium isopropoxide under very similar conditions caused extensive polymerisation. 4-Isopropoxybutan-2-one was obtained in $\sim 12\%$ yield, and 4-t-butoxybutan-2-one could not be prepared in this way. Polymerisation, which is most reasonably represented¹¹ as in (viii), would be expected to increase with strength of base present. The equilibrium concentration of butenone, $\text{CH}_2=\text{CH}\cdot\text{COMe} \rightleftharpoons \text{RO}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{COMe}$, is shown below to increase in the order $\text{R} = \text{Me} < \text{Et} < \text{Pr}^i$. The concentrations of butenone and of the enolate ions (IX; X; etc.) will be rate-determining.

The base-catalysed butenone-alcohol reaction (iii) is necessarily reversible. We have

¹ Robinson, *J.*, 1936, 1087; Brewster and Eliel, "Organic Reactions," Wiley, New York, 1953, Vol. VII, p. 99, Hellemann, *Angew. Chem.*, 1953, **65**, 476.

² du Feu, McQuillin, and Robinson, *J.*, 1937, 53.

³ (a) Adamson, McQuillin, Robinson, and Simonsen, *J.*, 1937, 1576; (b) McQuillin and Robinson, *J.*, 1938, 1097.

⁴ Wilds and Shunk, *J. Amer. Chem. Soc.*, 1943, **65**, 469.

⁵ Cornforth and Robinson, *J.*, 1947, 1855.

⁶ (a) Johnson, Szmuskowicz, Rogier, Hadler, and Wynberg, *J. Amer. Chem. Soc.*, 1956, **78**, 6285; (b) McQuillin, *J.*, 1955, 528; Howe and McQuillin, *J.*, 1955, 2423.

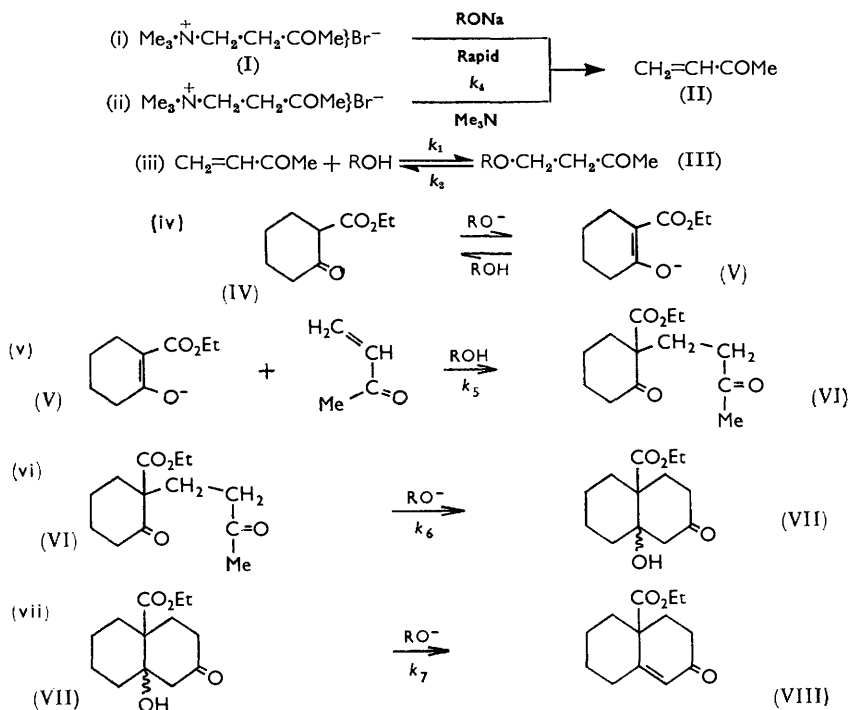
⁷ (a) Woodward, Sondheimer, Taub, Heusler, and MacLamore, *J. Amer. Chem. Soc.*, 1952, **74**, 4223; (b) Johnson, Ackerman, Eastham, and De Walt, *ibid.*, 1956, **78**, 6302; (c) Dreiding and Tomasowski, *ibid.*, 1955, **77**, 411.

⁸ Albright and Snyder, *J. Amer. Chem. Soc.*, 1959, **81**, 2239.

⁹ Doucet, *Compt. rend.*, 1943, **216**, 198.

¹⁰ I.G. Farbenind., *Fr. P.* 847,407; *Chem. Abs.*, 1941, **35**, 5511; Puetzer, Nield, and Barry, *J. Amer. Chem. Soc.*, 1945, **67**, 872; Muoata and Arai, *J. Chem. Soc. Japan*, 1953, **56**, 638.

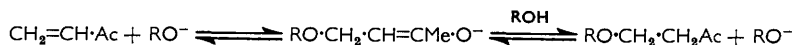
¹¹ Cf. Pepper, *Quart. Rev.*, 1954, **8**, 88; Marvel and Levesque, *J. Amer. Chem. Soc.*, 1939, **60**, 380.



determined the rate of equilibration in both directions starting from (a) butenone and (b) methoxy- and ethoxy-butanone. Individual reactions obeyed pseudo-first-order



kinetics and gave reasonably concordant values for a second-order constant k_{eq} (see Table 1) characteristic of each alkoxide in establishing the equilibria:



From these values and the equilibrium value $C = [\text{CH}_2=\text{CHAc}]/[\text{RO}\cdot\text{CH}_2\text{CH}_2\text{Ac}]$, values for the second-order constants k_1 and k_2 for the forward and the back reaction were computed.

From the rate of disappearance of butenone released from a quaternary metho-salt by an excess of sodium alkoxide the following values were derived for k_{eq} (l. mole⁻¹ min.⁻¹)

TABLE 1.

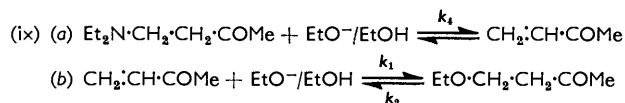
Second-order rate constants k_1, k_2 (l. mole⁻¹ min.⁻¹) at 19°: $\text{CH}_2\text{CHAc} \xrightleftharpoons[k_2]{k_1} \text{RO}\cdot\text{CH}_2\text{CH}_2\text{Ac}$; derived from the second-order constant for equilibration,

Base	(a)	(b)	k_1	k_2	10°C *
MeO ⁻	22.5, 22.3	24.4	23.3	0.119	0.525
EtO ⁻	93.1, 95.0	92.1	91.8	1.29	1.38
Pr ⁱ O ⁻	187, 191	—	183.1	5.9	3.1

* $C = [\text{CH}_2=\text{CHAc}]/[\text{RO}\cdot\text{CH}_2\text{CH}_2\text{Ac}]$ at equilibrium; (a) and (b) refer to measurements starting with butenone and alkoxybutanone, respectively.

defined as above: ${}^+\text{Me}_3\text{N}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{COMe Br}^-/\text{MeO}^-$ 21; ${}^+\text{Et}_2\text{MeN}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{COMe I}^-/\text{EtO}^-$ 107. These values are in fair agreement with those derived from more direct measurement of the butenone-alcohol reaction, and they support the sequence (i) and (iii) for decomposition of these quaternary salts by alcoholic alkoxides. Unless, therefore, alkylation is very fast the effective source of butenone in alcoholic solution will be the derived alkoxybutanone.

Mannich *et al.*¹² made use of base-catalysed decomposition of the β -alkylamino-ketone rather than the quaternary salt method. We have found that the most carefully redistilled diethylaminobutanone shows appreciable absorption at 219 $\text{m}\mu$, and after reaction with ethanolic sodium ethoxide gave 4-ethoxybutan-2-one. Decomposition of the amino-butanone therefore takes the course (ix):



In very dilute solution the first stage (ix) (a) is essentially irreversible, and from the rate data of Table I it was possible to derive for k_4 the approximate value, 82.3 l. mole⁻¹ min.⁻¹ at 18.6°.

The equilibrium of ethyl 2-oxocyclohexanecarboxylate (IV), $\lambda_{\text{max.}}$ 256 $\text{m}\mu$, with the enolate ion (V), $\lambda_{\text{max.}}$ 283 $\text{m}\mu$, was examined over a range of concentrations. With a greater than ten-fold excess of sodium isopropoxide in isopropyl alcohol the absorption intensity at 283 $\text{m}\mu$ reached a constant value and conversion of ethyl 2-oxocyclohexanecarboxylate into its enolate ion was presumed to be complete. The derived value of $\epsilon = 15,550$ was taken as the molar extinction coefficient of the enolate ion in isopropyl alcohol and, as applicable to a first approximation, also in methanol and ethanol. Using this value gave the following approximate values for $K = [\text{Enolate ion}]/[\text{Keto-ester}][\text{RO}^-]$:

RO ⁻	MeO ⁻	EtO ⁻	Pr ⁱ O
K (l. mole ⁻¹)	<i>ca.</i> 10	7.4×10^2	10^5

From calibration curves of ϵ at 286 $\text{m}\mu$ against alkoxide concentration the appropriate enolate-ion concentration could be derived.

Alkylation of ethyl oxocyclohexanecarboxylate was followed, depending on the base used and relative concentration of keto-ester and base, by the change in absorption at 256 $\text{m}\mu$ due to the enol, and/or by that at 283 $\text{m}\mu$ due to the enolate ion. When butenone is used, alkoxide ion catalyses both the alkylation (v) and the alcohol addition (iii). With the relatively weaker bases, which are less effectively removed in the equilibrium (iv), reaction (iii) becomes more important. This effect, due to difference of base strength, could be demonstrated. Use of equal concentrations ($3 \times 10^{-2}\text{M}$) of butenone, ethyl 2-oxocyclohexanecarboxylate, and sodium methoxide in methanol led to rapid and almost complete removal of butenone, whilst only 0.18 equiv. of the keto-ester reacted in the first 9 minutes, as judged by change in absorption at 219 and 256 $\text{m}\mu$. With butenone and ethyl 2-oxocyclohexanecarboxylate (each $1.83 \times 10^{-2}\text{M}$) in isopropyl alcohol with a catalytic proportion ($0.79 \times 10^{-3}\text{M}$) of sodium isopropoxide, alkylation became the principal reaction for which a second-order rate constant, $k_5 = 180$ l. mole⁻¹ min.⁻¹ at 20°, could be derived. The alkylation step (v) was, however, more conveniently examined by using the alkoxybutanone in combination with the corresponding sodium alkoxide, both in sufficient excess to maintain the equilibrium (iii), and by ensuring that the concentration of butenone did not alter appreciably during the experiment; thus the kinetics of the reaction became of pseudo-first-order. The rate of reaction was then proportional to the concentration of enolate ion ($\lambda_{\text{max.}}$ 283 $\text{m}\mu$). There is here also the advantage that with an excess of base reaction may be followed by change in absorption at 283 $\text{m}\mu$; at 256 $\text{m}\mu$ there is overlap

¹² Mannich, Koch, and Borkowsky, *Ber.*, 1937, **70**, 355; Mannich and Fourneau, *Ber.*, 1938, **71**, 2090.

with the band of λ_{max} 237 $\text{m}\mu$ due to the product (VIII) whose intensity increases progressively. It is, of course, necessary to correct for overlap of the 256 and the 283 $\text{m}\mu$ band envelopes.

The results in Table 2 were obtained in this way. The values of k_p refer to the second-order rate constant for the alkylation (v) derived from the observed pseudo-first-order constants, the known equilibrium concentration of butenone (Table 1), and the appropriate enolate-ion concentration. The last factor introduces some uncertainty, but the value 172 $\text{l. mole}^{-1} \text{ min.}^{-1}$ for the isopropoxybutanone-sodium isopropoxide reaction is in fair agreement with that derived above from direct measurement of the reaction with butenone ($k_5 = 180 \text{ l. mole}^{-1} \text{ min.}^{-1}$).

TABLE 2.

Rate constants ($\text{l. mole}^{-1} \text{ min.}^{-1}$) for reaction of ethyl 2-oxocyclohexanecarboxylate sodioenolate with butenone at 20°.

	Base	MeO ⁻	EtO ⁻	Pr ¹ O
k_5		52.5, 57.7	118, 119	172, 180

These values for k_5 are much larger than those for k_2 (Table 1), so that in the absence of a large excess of alkoxide base the rate of formation of butenone by elimination is likely to be rate-determining.

Ethyl 2-oxocyclohexanecarboxylate and butenone in isopropyl alcohol with a catalytic amount of sodium isopropoxide gave in good yield a product, $\text{C}_{13}\text{H}_{20}\text{O}_4$, which was chromatographed on alumina and gave physical constants in agreement with values recorded by Dreiding *et al.*⁷ This material gave a bis-2,4-dinitrophenylhydrazone, but in the infrared region showed absorption at 3578, 3528, 3401 (OH), and 1707 cm.^{-1} (C=O), indicating that it behaves as a mixture of compounds (VI) and (VII).^{*} With this material the dehydration stages (vi) and (vii) could be followed by the increasing absorption due to (VIII) (λ_{max} 237 $\text{m}\mu$, ϵ 13,300). For sodium isopropoxide-isopropyl alcohol the reaction was kinetically of the pseudo-first order and gave satisfactory values for a second-order rate constant (Table 3). With sodium methoxide-methanol and sodium ethoxide-ethanol, however, the experimental results indicated two consecutive steps for which appropriate rate constants were derived (Table 3).

TABLE 3.

Reactions: (VI) $\xrightarrow[k_6]{\text{RO}^-}$ (VII) $\xrightarrow[k_7]{\text{RO}^-}$ (VIII). Second-order rate constants
($\text{l. mole}^{-1} \text{ min.}^{-1}$) at 20°.

	Base	MeO ⁻	EtO ⁻	Pr ¹ O
k_6		9.3×10^{-2}	1.80	—
k_7		1.86×10^{-2}	0.27	9.8, 9.65

This behaviour can be understood in terms of the equilibria (x) concerned in the dehydration stage. The rate-determining factors will evidently be the concentration of enolate ions (XI) and (XIII). The stages (a), (c), and (d) all involve proton transfers which in the presence of strong bases should be rapid and we are inclined to identify k_6 and k_7 provisionally with steps (b) and (e).

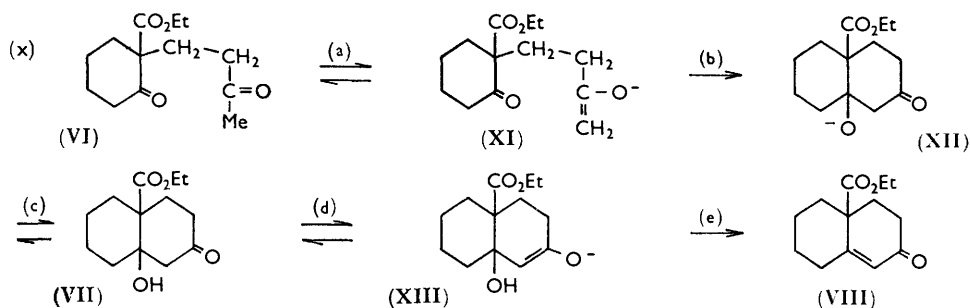
The rate data for the different steps in the reaction sequence (i) to (vii) may be summarised as in Table 4.

The alcohol solvents used were carefully purified and dried and the strengths of alkoxide solutions were estimated by titration. Contact of solutions with the atmosphere was minimised, but with concentrations of the order of 10^{-3}M the effective alkoxide concentration may have been somewhat smaller than was estimated. The derived second-order rate constants, especially for the stronger bases, may therefore be a little low. With

* An alternative ketol structure may be noted.¹³

¹³ Johnson, Korst, Clement, and Dutta, *J. Amer. Chem. Soc.*, 1960, **82**, 614.

this qualification, however, the trend of the figures suggests a reasonably sound basis for discussion of the reaction sequence concerned.



The relatively slow dehydration stage agrees with the not infrequent isolation of the diketone and/or hydroxy-ketone product.^{3a,6b,7b} Experimentally it is reflected in the common device of finally refluxing the mixture, or carrying out the dehydration as a separate stage.^{3,4,6,7} The differences in rate reflect the reported differences¹⁴ in base strength: pK_{auto} MeOH 16.7, EtOH 19.1, at 25°; by choice of conditions the nature of the product may be determined.

TABLE 4.
Second-order rate constants (l. mole⁻¹ min.⁻¹).

Reaction	(iii) $k_{\text{eq}}, 19^\circ$	(v) $k_{\text{e}}, 20^\circ$	(vi) $k_{\text{e}}, 20^\circ$	(vii) $k_{\text{e}}, 20^\circ$
Base: MeO ⁻	22.7	55	9.3×10^{-2}	1.86×10^{-2}
EtO ⁻	93.4	118	1.8	0.27
PrO ⁻	189	172	9.7	

Addition such as (iii) or (v) involves both a proton removal and a proton addition stage. The relatively minor effect of changes in base strength and solvent on the rates of these reactions is therefore not unreasonable.

So far as yield is concerned, the present results show that with a sensitive reagent such as butenone the advantage of a stronger base in maintaining a reasonable enolate concentration may be offset by greater losses by polymerisation. Results¹⁵ for the alkylation of ethyl methylacetoacetate with the methiodide of 2-diethylaminomethylcyclohexanone are illustrative: with a 0.5 mol. excess of base, yields were for EtO⁻ 39–42%, PrO⁻ 41%, t-BuO⁻ 15%. Similarly, for the ethyl 2-oxocyclohexanecarboxylate–butenone reaction recorded yields are (a) by the metho-salt method² with EtO⁻ in 0.17 equivalent excess, 50%, (b) on use of diethylaminobutanone¹⁶ with EtO⁻, 1.1 equivalents, 33%, and (c) on use of Triton B as catalyst,^{7c} 91%. Acceptable yields (45–57%) are recorded^{7a} for ethyl vinyl ketone with potassium t-butoxide in small amount (~0.1 equiv.) and a relatively acidic ketone. t-Butoxide has not, however, been widely used as a catalyst. With less acidic ketones, where strong base is necessary for enolisation, sodamide, excess of which will be largely insoluble, or sodium methoxide or ethoxide has generally been used. Survey of the reported yields in a large number of cases indicates no correlation with the effective excess of base. The use of a homogeneous reaction system appears to be a more important factor;⁶ release of butenone in high local concentration at the surface of the insoluble metho-salt will assist polymerisation.

EXPERIMENTAL

Materials.—Methyl, ethyl, and isopropyl alcohol were purified by successive treatment under reflux with sodium hydroxide, calcium hydride (for drying), and sulphanic acid (to remove

¹⁴ Hammett, "Physical Organic Chemistry," McGraw-Hill, New York, 1940, p. 250.

¹⁵ Logan, Marvell, La Pore, and Bash, *J. Amer. Chem. Soc.*, 1954, **76**, 4127.

¹⁶ McQuillin and Robinson, *J.*, 1941, 586.

ammonia), followed by distillation. The products showed pH 7 in aqueous solution and transmission at 219μ was 85—90%.

4-Dimethylaminobutan-2-one was prepared (b. p. $70^\circ/40 \text{ mm.}$) as directed by Wilds and Shunk.⁴ The methobromide was prepared from the base (3 g.) in acetone (25 c.c.) by passing in methyl bromide generated from dimethyl sulphate and potassium bromide. The product which was precipitated recrystallised from alcohol as a *hemihydrate*, m. p. 140° (Found: C, 38.4; H, 8.0. $\text{C}_7\text{H}_{16}\text{ONBr}\cdot 0.5\text{H}_2\text{O}$ requires C, 38.4; H, 7.8%).

4-Diethylaminobutan-2-one, b. p. $78^\circ/48 \text{ mm.}$, gave a methiodide, m. p. 86° (from acetone) (Found: equiv., by titration against AgNO_3 , 285.6. Calc. for $\text{C}_{10}\text{H}_{22}\text{IN}$: equiv., 285.0).

But-3-en-2-one was obtained from the commercially available product by drying (K_2CO_3 , followed by Na_2SO_4) and distillation through a column, or by a modification of Hagemeyer's method.¹⁷ 4-Diethylaminobutan-2-one (71.5 g.) in dry bromobenzene (1 l.) was treated with dry hydrogen chloride, and the butenone formed on heating distilled through an 18 in. column (top temperature 90°) and refractionated (after drying); it had b. p. $80\text{--}81^\circ$.

Ethyl 2-oxocyclohexanecarboxylate b. p. $106^\circ/11 \text{ mm.}$, was prepared as directed by Snyder, Brooks, and Shapiro¹⁸ and carefully refractionated.

4-Methoxybutan-2-one.—But-3-en-2-one (14 g.) was added during 15 min. to a solution of sodium (0.1 g.) in methyl alcohol (100 c.c.), and after a further 5 min. the solution was brought to pH 6—7 by addition of methyl-alcoholic hydrogen chloride. Fractionation gave 4-methoxybutan-2-one (14.6 g.), b. p. 138° , $66^\circ/50 \text{ mm.}$ (Found: C, 58.8; H, 10.3. Calc. for $\text{C}_5\text{H}_{10}\text{O}_2$: C, 58.8; H, 9.8%). The 2,4-dinitrophenylhydrazone formed yellow plates, m. p. 114° , from alcohol (Found: C, 46.8; H, 5.1. $\text{C}_{11}\text{H}_{14}\text{N}_4\text{O}_5$ requires C, 46.8; H, 4.9%).

4-Ethoxybutan-2-one, b. p. $74^\circ/50 \text{ mm.}$, was obtained (71%) by a similar method (Found: C, 62.1; H, 10.6. Calc. for $\text{C}_8\text{H}_{16}\text{O}_2$: C, 62.0; H, 10.3%), and gave a 2,4-dinitrophenylhydrazone, m. p. 87° (from alcohol) (Found: C, 48.9; H, 5.9. $\text{C}_{12}\text{H}_{16}\text{N}_4\text{O}_5$ requires C, 48.7; H, 5.5%).

4-Isopropoxybutan-2-one was obtained (12—20%) by a similar method, with b. p. $78^\circ/50 \text{ mm.}$ (Found: C, 64.5; H, 10.6. $\text{C}_7\text{H}_{10}\text{O}_2$ requires C, 64.6; H, 10.8%) [2,4-dinitrophenylhydrazone, m. p. 58° (from alcohol or light petroleum) (Found: C, 49.9; H, 6.1. $\text{C}_{13}\text{H}_{18}\text{N}_4\text{O}_5$ requires C, 50.2; H, 5.8%)].

4-Ethoxybutan-2-one from 4-Diethylaminobutan-2-one.—4-Diethylaminobutan-2-one (11.5 g.) was added to a solution from sodium (0.2 g.) in dry ethyl alcohol (100 c.c.). After 15 min. the volume of the solution was reduced to 50 c.c. *in vacuo* at 20° and after adjustment of pH to 6—7 the residue was fractionated. 4-Ethoxybutan-2-one (6.2 g.), b. p. 150° , was obtained and gave a 2,4-dinitrophenylhydrazone, m. p. 86° .

Ethyl 2-Oxo-1-3'-oxobutylcyclohexanecarboxylate.*—Ethyl 2-oxocyclohexanecarboxylate (8.8 g., 0.0518 mole) in dry isopropyl alcohol (75 c.c.) was treated successively with sodium isopropoxide in isopropyl alcohol (0.1M; 10 c.c.) and but-3-en-2-one (3.5 g., 0.05 mole). After 2 hr. further sodium isopropoxide solution (0.1M; 10 c.c.) was added and after 3 hr. the solution was brought to pH 6.5 by means of dry hydrogen chloride in isopropyl alcohol and concentrated. Fractionation of the residue gave the product (9.7 g.), n_D^{20} 1.4710, b. p. $116^\circ/2 \text{ mm.}$, and a small residue.

This material (2 g.), when placed on alumina (50 g.) and eluted with 1 : 9 benzene—light petroleum, gave 70 mg. of material showing absorption at 237μ , followed by ethyl 2-oxo-1-3'-oxobutylcyclohexanecarboxylate (1.42 g.), eluted by 1 : 1 benzene—light petroleum (Found: C, 65.1; H, 8.5. Calc. for $\text{C}_{13}\text{H}_{20}\text{O}_4$: C, 65.0; H, 8.4%) [bis-2,4-dinitrophenylhydrazone, m. p. 159° (from alcohol) (Found: C, 49.9; H, 4.9. $\text{C}_{25}\text{H}_{28}\text{N}_8\text{O}_{10}$ requires C, 50.0; H, 4.7%)].

Ethyl 1,2,3,4,4a,5,6,7-Octahydro-7-oxonaphthalene-4a-carboxylate.—Ethyl 2-oxo-1-3'-oxobutylcyclohexanecarboxylate (5 g.) in ethyl alcohol (25 c.c.) was treated with sodium ethoxide in ethyl alcohol (0.1M; 10 c.c.). The course of reaction was followed by measuring the absorption of samples at 237μ . After 2.5 hr. further sodium ethoxide (0.1M; 10 c.c.) was added. After 4 hr. the absorption had become constant. The solution, brought to pH 7 by addition of ethanolic hydrogen chloride and distilled, gave the octahydro-ester (3.1 g.), b. p. $112^\circ/2 \text{ mm.}$, n_D^{20} 1.5003 (lit.,¹⁹ n_D^{25} 1.5043), further purified by chromatography on alumina and

* This is a mixed product in equilibrium with the hydroxy-ester (VII).

¹⁷ Hagemeyer, *J. Amer. Chem. Soc.*, 1949, **71**, 1119.

¹⁸ Snyder, Brooks, and Shapiro, *Org. Synth.*, Coll. Vol. II, p. 531.

¹⁹ Dauben, Tweit, and Maclean, *J. Amer. Chem. Soc.*, 1955, **77**, 48.

elution with 1:9 benzene-light petroleum (Found: C, 70.3; H, 8.3. Calc. for $C_{13}H_{18}O_3$: C, 70.3; H, 8.1%).

Reaction of Ethyl 2-Oxocyclohexanecarboxylate with 4-Ethoxybutan-2-one.—Ethyl 2-oxocyclohexanecarboxylate (17 g.) was added to a solution from sodium (2 g.) in ethyl alcohol (150 c.c.), followed, with ice-cooling, by 4-ethoxybutan-2-one (11.6 g.). After 1 hr. the solution was refluxed for 3 hr. The product, on distillation, gave ethyl 2-oxocyclohexanecarboxylate (1.1 g.), followed by material (8.1 g.), b. p. 175—176°/10 mm., which was hydrolysed and decarboxylated with aqueous-alcoholic potassium hydroxide to 1,2,3,4,4a,5,6,7-octahydro-2-oxonaphthalene, b. p. 102—103°/4 mm., n_D^{20} 1.5238 [2,4-dinitrophenylhydrazone, m. p. 168° (lit.,² n_D^{20} 1.5241; 2,4-dinitrophenylhydrazone, m. p. 168°)].

Ultraviolet Absorption.—This was measured on a Hilger Uvispec instrument.

But-3-en-2-one in methanol gave the following values:

[Butenone] (10^{-4} mole/l.)	1.8	3.6	4.8	7.2	
ϵ at 219 $m\mu$	3600	3592	3590	3540	Mean 3580

In ethanol and isopropyl alcohol the mean values of ϵ at 219 $m\mu$ were 3620 and 3630, respectively.

Ethyl 2-oxocyclohexanecarboxylate ($1.58 \times 10^{-4}M$) in ethanolic sodium ethoxide solution gave the following results (0.5 cm. cell):

Initial $[EtO^-]$ ($10^{-2}M$)	0	0.94	1.84	3.74	5.58
Absorbance at 283 $m\mu$	0.096	0.562	0.708	0.901	1.008
Enolate (%)	0	41.1	53.9	71.0	80.4
10^2K (l. mole $^{-1}$)	—	7.97	6.66	6.75	7.53

In this Table, enolate % = percentage of the keto-ester converted into the sodium enolate, calculated from the absorption at 283 $m\mu$ by using $\lambda_{max} = 15,550$.

$$K = [\text{sodioenolate}]/[\text{Keto-ester}][RO^-].$$

Similarly, K for methanol-sodium methoxide = ~ 10 , and for isopropyl alcohol-sodium isopropoxide = $\sim 10^5$.

Reaction of Diethylmethyl-3-oxobutylammonium Halides with Sodium Alkoxides.—Results were as follows: (a) Quaternary iodide in excess in methanol: [Iodide] = $5.14 \times 10^{-2}M$. NaOMe = $3.8 \times 10^{-2}M$. Temp. 20°.

Min.	1	2	3	5	20
10^{-2} [Butenone] *	4.32	4.83	5.03	5.12	5.14

* Mole l. $^{-1}$, estimated by absorption at 324 $m\mu$.

A similar rapid release of butenone followed by a slower release was observed with an excess of trimethyl-3-oxobutylammonium bromide and sodium ethoxide in ethanol.

(b) Alkoxide in excess in methanol: [Iodide] = $5.14 \times 10^{-2}M$. [NaOMe] = $6 \times 10^{-2}M$. Temp. 19°.

Min.	3	4.5	5.5	8.5	10.5	12.5	14	16	32	60
Absorbance at 324 $m\mu$	0.239	0.270	0.217	0.137	0.098	0.073	0.059	0.042	0.008	0.008
10^2 [Butenone] *	3.01	2.33	1.87	1.18	0.845	0.629	0.509	0.362	0.069	0.069
k (min. $^{-1}$)	0.181	0.180	0.188	0.178	0.178	0.177	0.175	0.178	—	—

Excess of NaOMe = 0.86×10^{-2} mole l. $^{-1}$, whence $k_2 = 21.1$ l. mole $^{-1}$ min. $^{-1}$.

* As previous Table. † Pseudo-first-order rate constant for the reaction of butenone with sodium methoxide obtained from $k = (2.303/t) \log [(d_0 - d_\infty)/(d_t - d_\infty)]$.

When an excess of the corresponding bromide in ethanol was used with an excess of sodium ethoxide at 20°, $k_2 = 107$ l. mole $^{-1}$ min. $^{-1}$.

Reaction of Trimethyl-3-oxobutylammonium Bromide with Triethylamine.—The bromide ($3 \times 10^{-4}M$) and amine ($2 \times 10^{-2}M$) in ethanol at 18.6° gave the following results:

Min.	5	10	15	20	30	40	50	60	70	∞
10^4 [Butenone]	0.57	0.945	1.263	1.540	1.920	2.27	2.55	2.76	2.85	3.00
10^2k (min. $^{-1}$)	4.23	3.78	3.67	3.60	3.41	3.54	3.79	4.21	4.28	—

Base-catalysed Equilibration between But-3-en-2-one and 4-Alkoxybutan-2-ones in Alcoholic Solution.—The change in absorption at 219 $m\mu$ was measured on a solution of either but-3-en-2-one or a 4-alkoxybutan-2-one on the addition of sodium alkoxide. For the former reaction

the first-order rate constant k and the second-order rate constant k_{eq} were calculated as for the reaction between quaternary salts and an excess of alkoxide. For the alkoxybutanones, Guggenheim's method²⁰ was used, since it was difficult to obtain the alkoxybutanones free from butenone. The reaction of 4-methoxybutan-2-one ($6.7 \times 10^{-2}M$) with sodium methoxide ($3.8 \times 10^{-3}M$) in methanol at 19° (0.5 cm. cell) illustrates this:

Time (t) (min.)	2	3	4	5	6	8	9	10	11	12
A = Absorbance at t min.	0.279	0.315	0.345	0.369	0.386	0.430	0.447	0.464	0.478	0.491
B = Absorbance at ($t = 18$) min.	0.560	0.567	0.573	0.577	0.581	0.588	0.591	0.596	0.599	0.602
$B - A$	0.281	0.252	0.228	0.208	0.195	0.158	0.144	0.132	0.122	0.111
$-\log(B - A)$	0.551	0.599	0.642	0.682	0.710	0.801	0.842	0.879	0.914	0.959

The graph of $-\log(B - A)$ against t is a straight line of slope 0.04. $k = 2.303 \times 0.04 = 0.092 \text{ min.}^{-1}$. $k_{eq} = k/[\text{Alkoxide}] = 24.2 \text{ l. mole}^{-1} \text{ min.}^{-1}$.

By a similar method, k_{eq} for ethanol-4-ethoxybutan-2-one was determined. The results in Table 5 were obtained.

TABLE 5.

Reactants and temp.	Catalyst concn. ($10^{-2}M$)	k (min.^{-1})	k_{eq} ($\text{l. mole}^{-1} \text{ min.}^{-1}$)
Butenone-MeOH-NaOMe at 18.6°	1.86	0.414	22.3
	0.93	0.210	22.6
	2.6	0.584	22.5
Butenone-EtOH-NaOEt	0.323	0.315	97.5
	0.148	0.139	93.9
Butenone-Pr ⁱ OH-NaOPr ⁱ at 19°	0.125	0.234, 0.239	189
4-Methoxybutan-2-one-MeOH-NaOMe at 19°	0.38	0.092	24.2
4-Ethoxybutan-2-one-EtOH-NaOEt at 19°	0.072	0.0663	92.1

From these experiments the following equilibrium values $C = [\text{Butenone}]/[\text{Alkoxybutenone}]$ follow: MeOH-NaOMe 0.525×10^{-2} ; EtOH-NaOEt 1.38×10^{-2} ; PrⁱOH-NaOPrⁱ 3.1×10^{-2} .

Reaction of Ethyl 2-Oxocyclohexanecarboxylate with Butenone and Sodium Alkoxides.—(a) Keto-ester, butenone, and NaOMe each $3 \times 10^{-2}M$ in methanol at 20°. (A , 256 $m\mu$, and A 219 $m\mu$ = absorbance at 256 and 219 $m\mu$, respectively.)

Time (min.)	0	3.25	5.25	9.0
A , 256 $m\mu$	0.674	0.640	0.622	0.560
A , 219 $m\mu$	0.873	0.359	0.267	0.066

The principal reaction is the formation of 4-methoxybutan-2-one.

(b) Keto-ester and butenone each $1.83 \times 10^{-2}M$; NaOPrⁱ $0.79 \times 10^{-3}M$ in isopropyl alcohol; 20°.

Time (min.)	0	2	4	7	9	14
A , 256 $m\mu$	0.792	0.596	0.448	0.302	0.235	0.122
10^3k		14.2	14.3	13.8	13.5	13.4

The equilibrium (iv) (p. 105) is rapidly established and $K \approx 10^5$, so that in the presence of excess of ethyl 2-oxocyclohexanecarboxylate the concentration of the enolate ion is approximately constant and equal to 0.79×10^3M . k is the pseudo-first-order rate constant and k_5 is the derived second-order rate constant.

$$\begin{aligned}
 -d[\text{Keto ester}]/dt &= -d[\text{butenone}]/dt \\
 &= k_5[\text{enolate ion}][\text{butenone}] \\
 &= k[\text{butenone}].
 \end{aligned}$$

Therefore, $k_5 = k/[\text{enolate ion}]$,

whence $k_5 = 180 \text{ l. mole}^{-1} \text{ min.}^{-1}$.

Reaction of Ethyl 2-Oxocyclohexanecarboxylate with Alkoxybutanones and Sodium Alkoxides.—Measurements of absorbance were made at 283 $m\mu$, with a comparison cell containing an alkoxybutanone-sodium alkoxide-alcohol solution of the same concentration as the reaction mixture. The alkoxybutanone was in large excess and the alkoxide was of sufficient concentration to keep the butenone concentration approximately constant by maintaining the equilibrium between butenone and alkoxybutenone.

²⁰ Guggenheim, *Phil. Mag.*, 1926, 1, 538.

Keto-ester 1.84×10^{-4} M. Methoxybutanone 5.4×10^{-2} M.Sodium methoxide 11.4×10^{-2} M in methanol. 20°.

Time (min.)	0	5	10	15	20	25	30	40	50	60	80	100
A , 283 $m\mu$	0.890	0.841	0.797	0.758	0.717	0.683	0.645	0.582	0.525	0.471	0.381	0.282
A' , 283 $m\mu$	0.872	0.824	0.781	0.742	0.702	0.669	0.632	0.570	0.514	0.460	0.372	0.275
10^3k		1.112	1.11	1.07	1.08	1.061	1.072	1.062	1.056	1.067	1.071	1.076

 A , 283 $m\mu$ = absorbance observed at 283 $m\mu$, 0.5 cm. cell. A' , 283 $m\mu$ = absorbance corrected for overlap of 256 $m\mu$ band due to residual keto-ester. k (mean) = 1.075×10^{-2} min.⁻¹.

Fraction of keto-ester as enolate ion = 0.73.

Fraction of methoxybutanone as butenone = 0.525×10^{-2} .Whence $k_s = 1.075 \times 10^{-2}/0.73 \times 0.525 \times 10^{-2} \times 5.4 \times 10^{-2} = 52.2$ l. mole⁻¹ min.⁻¹.

The following results were obtained by a similar method.

Reactants + Et 2-oxocyclohexanecarboxylate	k_s (l. mole ⁻¹ min. ⁻¹)
Methoxybutanone and NaOMe in MeOH at 20°	52.2, 57.7
Ethoxybutanone and NaOEt in EtOH at 20°	118, 119
Isopropoxybutanone and NaOPr ⁱ in Pr ⁱ OH	172

Comparative Rates of Reaction of 4-Diethylamino-, 4-Methoxy-, and 4-Isopropoxy-butan-2-one with Ethyl 2-Oxocyclohexanecarboxylate.—For substituted butanone 2.68×10^{-2} M, keto-ester 2.5×10^{-2} M, and NaOPrⁱ 0.86×10^{-2} M in PrⁱOH at 20°, absorbances at 256 $m\mu$ were:

Time (min.)	0	15	30	45	60
Diethylaminobutanone	0.915	0.864	0.790	0.723	0.676
Methoxybutanone	0.915	0.893	0.883	0.872	0.864
Isopropoxybutanone	0.915	—	0.904	0.901	0.899

Cyclodehydration of Ethyl 2-Oxo-1-3'-oxobutylcyclohexanecarboxylate.—The ester, dissolved in the appropriate alcohol, was treated (thermostat) with the corresponding sodium alkoxide and the progress of the reaction was followed by means of the absorption at 237 $m\mu$ due to ethyl 1,2,3,4,4a,5,6,7-octahydro-7-oxonaphthalene-4a-carboxylate (VIII).

(i) Propan-2-ol solution. Ester 1.85×10^{-4} M. NaOPrⁱ 8.73×10^{-3} M. 20°.

Time (min.)	1.5	4	12	18	20	25	33	61
A , 237 $m\mu$	0.129	0.336	0.748	0.911	0.950	1.019	1.099	1.161
10^3k (min. ⁻¹)	7.88	8.55	8.62	8.54	8.53	8.42	8.88	

Mean $k = 8.53 \times 10^{-3}$ min.⁻¹. k = first-order rate constant calculated from $k = (2.303/t) \log [d_\infty/(d_\infty - d_t)]$.The second-order rate constant $k_{6,7} = k/[\text{alkoxide}] = 9.8$ l. mole⁻¹ min.⁻¹.By using 4.36×10^{-3} M-sodium isopropoxide, $k_{6,7}$ was found to be 9.65 l. mole⁻¹ min.⁻¹.(ii) Ethanol solutions. Ester 1.83×10^{-4} M. NaOEt 0.1M 20°.

Time (min.)	5	10	12	15	22	24	32	35	42	47	62	66	220
A , 237 $m\mu$	0.074	0.170	0.210	0.282	0.420	0.465	0.607	0.661	0.753	0.822	0.948	0.980	1.217
Conv.* (obs.)	6.1	14.9	17.2	23.1	34.5	38.1	49.7	54.2	61.8	67.5	77.7	80.3	100
„ (calc.)	4.4	13.2	16.9	22.6	35.4	38.8	50.3	54.2	62.2	66.9	77.9	80.2	

* Conv. = conversion (%) into product (VIII).

For a consecutive reaction: $A \xrightarrow{k'_6} B \xrightarrow{k'_7} C$, if $[A_0]$ is the initial concentration and $[A]$, $[B]$, and $[C]$ are the concentrations at time t , then $d[C]/dt = k'_7\{[A_0] - [A] - [C]\}$ or in the later stages when $[A]$ is small $d[C]/dt = k'_7\{[A_0] - [C]\}$, whence graphically the first-order constant $k'_7 = 0.027$ min.⁻¹. At the point of inflexion (t_{int}), we have $\ln k'_7/k'_6 = t_{\text{int}}(k'_7 - k'_6)$. By inspection $t_{\text{int}} \gg 17$ min., whence $k'_6 \ll 4k'_7$. In the expression $[C]/[A_0] = 1 + [k'_7 \exp(-k'_6 t) - k'_6 \exp(-k'_7 t)]/(k'_6 - k'_7)$, if t is chosen such that $k'_7 t \ll 1$, then $k'_6 t \ll 4$ and $k'_7 \exp(-k'_6 t)$ is relatively small, and $[C]/[A_0] = 1 - [k'_6 \exp(-k'_7 t)]/(k'_6 - k'_7)$. By substituting the known value of k'_7 and experimental values of $[C]/[A_0]$, the following values of the pseudo-first-order rate constant k'_6 were obtained:

Time (min.)	35	42	47	62	66
k'_6 (min. ⁻¹)	0.179	0.183	0.20	0.170	0.183

whence k'_6 (mean) = 0.181 min.⁻¹.

The agreement with the experimental values is indicated by comparison of Conv. (obs.) with Conv. (calc.).

Experiments in propan-2-ol indicate that the rates of reaction are also proportional to the concentration of alkoxide ion. Since the ethoxide ion is 0.1M, the second-order rate constants, k_6 and k_7 , in ethanol are therefore 1.81 and 0.27 l. mole⁻¹ min.⁻¹, respectively.

In a second experiment with 4.01×10^{-3} M-ester and with the same concentration of sodium ethoxide at 20°, the conversions into product (VIII) at various times were almost identical with those in the above experiment, giving the same values for k_6 and k_7 .

(iii) Methanol solution. 20°.

By a similar method, $k_6 = 9.3 \times 10^{-2}$ l. mole⁻¹ min.⁻¹; and $k_7 = 1.86 \times 10^{-2}$ l. mole⁻¹ min.⁻¹.

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