625. *Anionotropic Systems. Part IV.* The Kinetics of the Rearrangement of 3-Hydroxy-3 : 5-dimethylhex-4-en-2-one. The Effect of an Acetyl Group on Anionotropic Mobility.*

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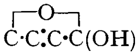
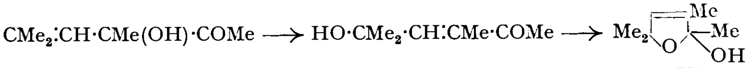
A kinetic study has been made of the acid-catalysed rearrangement of the α-hydroxy-βγ-ethylenic ketone (I) to the γ-hydroxy-αβ-ethylenic ketone (II) and of the cyclisation of the latter to the dihydrohydroxyfuran (III).

The anionotropic change $\text{C:C·C(OH)·C:O} \longrightarrow \text{C(OH)·C:C·C:O}$ exhibits mechanistic features analogous to those found with other allyl alcohols, except for effects arising from the strong solvation of the acetyl group in aqueous solvents, but the mobility of the system is the lowest yet encountered and provides a measure of the strong electron-attracting properties of the acetyl group.

The cyclisation reaction $\text{C(OH)·C:C·C:O} \longrightarrow$  C·C:C·C(OH) has a rate similar to that of the rearrangement in 40% aqueous dioxan, but shows quite a different dependence on solvent composition, being accelerated by increasing dioxan content. A mechanism for the cyclisation reaction is discussed which accounts for the solvent dependence in terms of the effects of the solvation of the acetyl group on the equilibrium between the *cis*- and the *trans*-form of the oxonium ion (II*a*).

IN the preceding Part,* the anionotropic rearrangement of 3-hydroxy-3 : 5-dimethylhex-4-en-2-one (I) to 5-hydroxy-3 : 5-dimethylhex-3-en-2-one (II) and the subsequent cyclisation of the latter to the dihydrohydroxyfuran (III) were described. In the present communication, a quantitative investigation of these reactions is reported.



(I) (II) (III)

The rate measurements were carried out spectrometrically, by following the appearance and subsequent disappearance of the intense absorption band at 2290 Å associated with the conjugated (C:C·C:O) system present in the keto-alcohol (II). The progress of the two consecutive reactions is evident from a plot of the extinction coefficient at 2290 Å against time (Fig. 1). Under favourable conditions, with 40% aqueous dioxan as reaction medium, the absorption intensity rises to a maximum value corresponding to about 50% of (II) and the slope of the rising, left-hand part of the curve is rather steeper than that of the falling right-hand part, showing that the rate of rearrangement is slightly faster than the cyclisation under these conditions. In order to obtain results comparable with previous data on allied reactions, however, some of the kinetic measurements were made

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* Part III, preceding paper.

with 60 and 80% aqueous dioxan solvents, in which cyclisation is about as fast as, or even faster than, rearrangement, so that the concentration of the rearranged keto-alcohol (II) rarely reached more than about 30% of the total. The rearrangement was therefore followed in detail over the first third of the reaction, and first-order rate constants (k_R) were calculated by taking the actual value of $\varepsilon_{max.}$ of the conjugated keto-alcohol (II) as the end-point, and were extrapolated to zero time (see Experimental). Approximate rate constants (k_C) for the cyclisation could be derived from the decrease of k_R as the reaction progresses, or from the falling branch of the curves of ε against time, but were more conveniently determined separately, a pure sample of the rearranged keto-alcohol (II) being used.

The Anionotropic Rearrangement.—The kinetic features of the rearrangement (I) ⟶ (II) are essentially analogous to those observed in the anionotropy of other substituted allyl alcohols (cf. Braude, *J.*, 1948, 794; *Ann. Reports*, 1949, **46**, 114). In aqueous dioxan–hydrochloric acid, the rate constants are approximately proportional to the acid concentration at low acidities and decrease with increasing dioxan content of the medium, being lower by factors of 2—3 in 60%, compared with those in 40%, aqueous dioxan. The plots of log k_R for 40 and 60% dioxan–0·1M-hydrochloric acid against $1/T$ gave straight lines in the 75—90° range, and the Arrhenius energies of activation are 25 and 19 kcal./mole respectively (Table 1). Measurements were also made at 95°, but, although reproducible values were obtained, they fall appreciably below the Arrhenius plots (Fig. 2). A similar deviation above 90° was observed in the rearrangements of 1-ethynyl-3-methylallyl alcohol (hex-2-en-5-yn-3-ol) and its acetate in the same media (Braude, *loc. cit.*, 1948). This effect is most probably due to a partial breakdown of the hydrogen-bonded " structure " of

FIG. 1. *Rearrangement of* (I) *in* 40% *aqueous dioxan*–0·1M-*hydrochloric acid at* 80°.

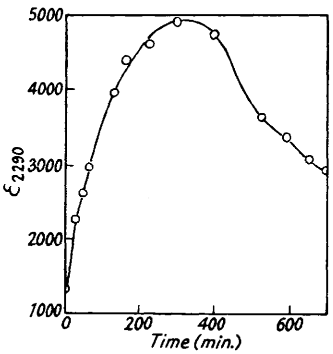


FIG. 2. *Arrhenius plots for the rearrangement of* (I) *in* 40% *and* 60% *aqueous dioxan*–0·1M-*hydrochloric acid.*

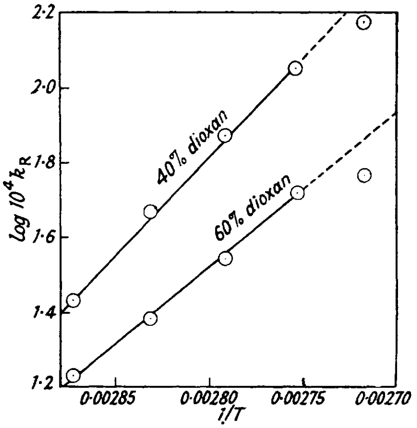
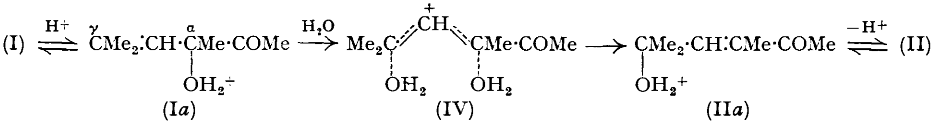


TABLE 1. *First-order rate constants* (k_R *in* min.$^{-1}$) *for the rearrangement* (I) ⟶ (II) *in aqueous dioxan–hydrochloric acid.* c_A = *acid concn.* (*mole/l.*).

	(*a*) *In* 40% *aqueous dioxan* †				(*b*) *In* 60% *aqueous dioxan* †			
t	c_A	c_{ROH}	10^4k_R	k_R/c_A	c_A	c_{ROH}	10^4k_R	k_R/c_A
75°	0·1	0·13	27·5	0·0275	0·1	0·13	16·9	0·0169
80	0·1	0·13	46·5	0·0465	0·1	0·13	24·3	0·0243
85	0·1	0·13	74·5	0·0745	0·1	0·13	34·7	0·0347
					0·1	1·3	33·5	0·0335
					0·2	0·13	71·5	0·0357
90	0·1	0·13	113	0·113	0·1	0·13	52	0·052
					0·2	0·13	110	0·055
95	0·1	0·13	150 *	0·150	0·1	0·13	58 *	0·058
	E_{Arr} = 24·6 kcal./mole.				E_{Arr} = 19·3 kcal./mole.			

* Omitted in the evaluation of E_{Arr}. † For details of solvent composition, see Experimental.

the solvent on approaching the boiling point, and a consequent decrease in the acidity function (cf. Braude and Stern, *Nature*, 1948, **161**, 169; *J.*, 1948, 1976).



$$\text{(I)} \overset{\text{H}^+}{\rightleftharpoons} \overset{\gamma}{\text{C}}\text{Me}_2\text{:CH·}\underset{\text{OH}_2^+}{\overset{\alpha}{\text{C}}}\text{Me·COMe} \xrightarrow{\text{H}_2\text{O}} \text{Me}_2\underset{\text{OH}_2}{\text{C}}\overset{+}{\cdots\text{CH}\cdots}\underset{\text{OH}_2}{\text{C}}\text{Me·COMe} \longrightarrow \underset{\text{OH}_2^+}{\text{C}}\text{Me}_2\text{·CH:CMe·COMe} \overset{-\text{H}^+}{\rightleftharpoons} \text{(II)}$$

(I*a*) (IV) (II*a*)

There is no reason to doubt that the anionotropic rearrangement of (I) proceeds by the same mechanism as that of other allyl alcohols under similar conditions, namely, bimolecular attack by a solvent water molecule at the γ-carbon atom of the oxonium ion (I*a*) (Braude, *loc. cit.*). The expression (IV) represents the *transition state* in which the migration of the positive charge is half-completed and which should be clearly differentiated from the solvated form of an allyl cation *intermediate* (cf. Dewar, *Ann. Reports*, 1951, **48**, 123). One noteworthy point of difference, however, between the rearrangement of (I) and of other allyl alcohols previously studied is that, in the present case, the energy of activation is lower in 60% than in 40% aqueous dioxan (cf. Braude and Stern, *J.*, 1947, 1096). This may be explained in terms of the aqueous solvation of the carbonyl group which will be much more marked than that of other less highly polar conjugating groups such as aryl, alkenyl, etc. The acetyl group has a strongly retarding influence on the rearrangement (see below) which will be much reduced by solvation, as can be seen by considering the extreme hydrated form $\cdot\text{CMe(OH)}_2$. This hydrated form is not readily detected in the keto-alcohols themselves, the ultra-violet-light absorption of which shows little dependence on the water content of the medium, but will be greatly enhanced in the oxonium ions (I*a*; II*a*) owing to the effect of the positive charge (cf. the formation of stable hydrates by aldehydes and ketones, *e.g.*, chloral, containing strongly electron-attracting groups). Now, the equilibrium $\cdot\text{CMe:O} \overset{\text{H}_2\text{O}}{\rightleftharpoons} \cdot\text{CMe(OH)}_2$ in the oxonium ion (I*a*) will be displaced to the left with increase in temperature, and it will be so displaced more rapidly in the less aqueous solvent which is less highly associated (cf. Braude and Stern, *loc. cit.*, 1948) and will give rise to the larger heat of solvation. Thus, the temperature dependence of the solvation equilibrium will be superimposed on the other factors contributing to the observed energy of activation. Since the unsolvated species will be the less reactive, the rates will increase *less* rapidly with temperature than they would in the absence of solvation, *i.e.*, the observed energies of activation will be smaller and more markedly so in the less aqueous solvent.

The main interest of the rate data for the rearrangement attaches to a comparison of the mobility of the system with that of analogues containing different conjugating substituents. Table 2 shows that the rate of rearrangement of the keto-alcohol (I) is slower by several powers of ten than that of analogues containing aryl or alkenyl substituents in place of the acetyl group. It is well established that anionotropy is facilitated by electron-donating and retarded by electron-attracting substituents, and the exceptionally low mobility of (I) provides a quantitative measure of the strong electron-attracting properties of the carbonyl group. Qualitatively, these are well established, *e.g.*, from the predominant *meta*-direction of the electrophilic substitution of aryl ketones, but the only other quantitative evidence appears to come from the dissociation of α-keto-acids (Böeseken, Hansen, and Bertram, *Rec. Trav. chim.*, 1916, **35**, 313) and from nucleophilic substitution reactions (Conant and Hussey, *J. Amer. Chem. Soc.*, 1925, **47**, 488; Bunnett

TABLE 2.

	$\text{Me·CO·CMe(OH)·CH:CMe}_2$	$\text{Ph·CMe(OH)·CH:CMe}_2$	$\text{CHMe:CH·CMe(OH)·CH:CMe}_2$
k'_{R} [1] ………	0·00027 [2]	7·4 [3]	37·00 [3]
	$\text{Me·CO·CO}_2\text{H}$	$\text{Ph·CO}_2\text{H}$	$\text{CHMe:CH·CO}_2\text{H}$
10^5K [4] ……	320	6·3	2·04

[1] Specific rate constants ($k_{\text{R}}/c_{\text{A}}$; min.$^{-1}$) for 60% aqueous dioxan–hydrochloric acid at 30°. [2] Extrapolated from measurements at higher temperatures. [3] Braude and Timmons, *J.*, 1950, 2000; Braude and Coles, *J.*, 1952, 1425; and unpublished work. [4] Dissociation constants in water at 25°.

and Zahler, *Chem. Reviews*, 1951, **49**, 308) in which the acetyl group exerts a facilitating influence. Thus, pyruvic acid is a much stronger acid than benzoic or crotonic (Table 2).

A plot of log (k_R/c_A) for the anionotropic rearrangements of a more extended series of substituted allyl alcohols $CMeR'{:}CH{\cdot}CRX{\cdot}OH$ against the logarithms of the dissociation constants of the acids $X{\cdot}CO_2H$ reveals (Fig. 3) an approximately inverse relationship of the type first established by Hammett (*Chem. Reviews*, 1935, **17**, 125; cf. Burkhardt, Ford, and Singleton, *J.*, 1936, 17) for substituted phenyl derivatives. (The data are taken from Braude and Stern, *J.*, 1947, 1096; Braude and Fawcett, *J.*, 1950, 800; 1952, 4158; and Table 2.) Since the degree of alkyl substitution is not the same in each alcohol, the specific rate constants have been "normalised" by adding or subtracting an appropriate increment when R or R' = Me. It is notable that, in the present instance, the correlation extends over a rate range of 10^8 and includes not only X = phenyl, *m*- and *p*-substituted phenyl, and 2-naphthyl, but also X = vinyl, propenyl, and acetyl. On the other hand, the correlation does not include X = *o*-tolyl, 1-naphthyl, 9-anthryl and 9-phenanthryl, 2-thienyl and 2-furyl, and ethynyl and hexynyl; in each of these cases the carboxylic acid is weaker than would be predicted from the anionotropic mobility of the allyl alcohol if the straightforward relationship held. The four "abnormal" benzenoid groups all contain *o*-substitutents or their equivalent; evidently, steric inhibition to electronic interaction between X and the side-chain reduces the stability of the carboxylate ions $X{\cdot}CO_2^-$ relative to the undissociated acids $X{\cdot}CO_2H$ much more seriously than it does that of oxonium ions (*e.g.*, I*a*) relative to the alcohols (*e.g.*, I). This is quite understandable, since charge-resonance involving X will be much more marked in the carboxylate ions than in the oxonium ions, and analogous steric "*ortho*"-effects have been observed in other reactions (Hammett, *loc. cit.*; Burkhardt *et al.*, *loc. cit.*). The deviation from the linear relation of the five-membered heterocyclic and acetylenic derivatives similarly indicates that these groups, unlike ethylenic and acetyl groups, do not readily partake in charge-resonance involving the accommodation of a negative charge, in agreement with previous conclusions (Braude and Stern, *loc. cit.*, 1947; Braude and Fawcett, *loc. cit.*, 1952).

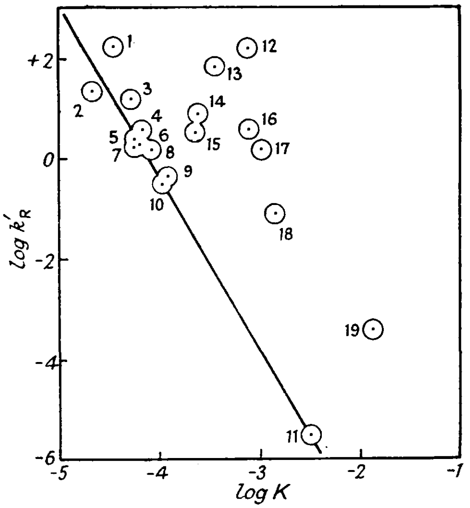


FIG. 3. *Plot of the logarithms of the specific rate constants* (k'_R) *for the rearrangements of* $CHMe{:}CH{\cdot}CHX{\cdot}OH$ *in* 60% *aqueous dioxan against the logarithms of the dissociation constants* (k) *of* $X{\cdot}CO_2H$ *in water.* X = (1) p-*methoxyphenyl,* (2) *propenyl,* (3) p-*tolyl,* (4) 2-*naphthyl,* (5) m-*tolyl,* (6) *phenyl,* (7) *vinyl,* (8) p-*fluorophenyl,* (9) p-*chlorophenyl,* (10) p-*bromophenyl,* (11) *acetyl,* (12) 2-*furyl,* (13) 2-*thienyl,* (14) 9-*anthryl,* (15) 1-*naphthyl,* (16) o-*tolyl,* (17) 9-*phenanthryl,* (18) *hex*-1-*ynyl,* (19) *ethynyl.*

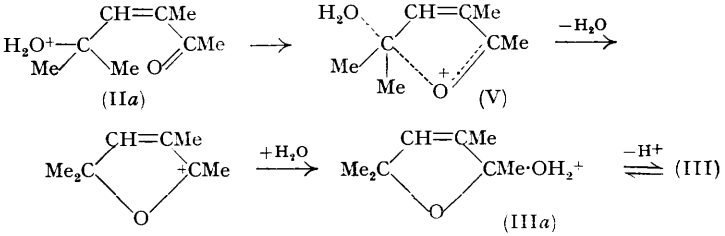
The Cyclisation Reaction.—Although cyclisation reactions of the type (II) ⟶ (III) are well known (for references, see Part II, *loc. cit.*), hardly any kinetic measurements have been reported. In the case of saturated γ-hydroxy-ketones, the furan derivatives have been shown to exist in equilibrium with the open-chain forms (cf. Hurd and Saunders, *J. Amer. Chem. Soc.*, 1952, **74**, 5324). In the present system, cyclisation is essentially complete (>95%) under the conditions examined. At the higher concentrations used in preparative experiments (Part III, *loc. cit.*), cyclisation is accompanied by extensive self-etherification of the dihydrohydroxyfuran (III); this is probably absent under the conditions of the kinetic runs, since the rate of etherification in analogous cases decreases rapidly with concentration (cf. Braude, Fawcett, and Newman, *J.*, 1950, 793). In any case, etherification will have no effect on the measured rates of cyclisation, since the extinction coefficients of (III) and the corresponding diether will be practically identical.

The cyclisation of (II), like the anionotropic rearrangement by which (II) is formed, is acid-catalysed, but exhibits a very different dependence on medium composition. The rate constants are rather more than doubled on increase of the acid concentration from 0·1 to 0·2M and *increase* markedly with decreasing water concentration; the relative rates in 40, 60, and 80% aqueous dioxan are in the ratio 1 : 3 : 10 (Table 3). The energies of activation for 40 and 60% aqueous dioxan–0·1M-hydrochloric acid are *ca.* 30 and 23 kcal./mole, respectively; as in the rearrangement of (I) (see above), and no doubt owing to the same cause, the rate constants at 95° fall considerably below the plots of log k against $1/T$, and were neglected.

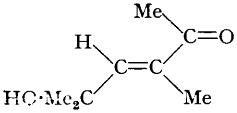
TABLE 3. *First-order rate constants* (k_C *in* min.$^{-1}$) *for the cyclisation* (II) ⟶ (III) *in aqueous dioxan–hydrochloric acid. Keto-alcohol concentration* ca. 0·0043 *mole/l. throughout* (*for meaning of symbols, see Table* 1).

t	c_A	10^4k_c (40% dioxan)	10^4k_c (60% dioxan)	10^4k_c (80% dioxan)	t	c_A	10^4k_c (40% dioxan)	10^4k_c (60% dioxan)
75°	0·1	16·5	68	—	90°	0·1	97	235
80	0·1	30	115	—		0·2	—	680
85	0·1	51	170	2030	95	0·1	105	255
	0·2	—	515	—				

A plausible mechanism for the cyclisation involves the oxonium ion (II*a*) which is the intermediate product of the rearrangement. The next step will be an electrophilic attack at the carbonyl oxygen by the γ-carbon atom, rendered partially positive by the attachment of a proton to the neighbouring hydroxyl group. The γ-carbon atom and the two oxygen atoms can take up an approximately linear arrangement in the transition state, depicted in (V). Finally, the resulting cyclic carbonium ion rapidly captures a solvent water molecule to give the conjugate acid (III*a*) of the dihydrohydroxyfuran, or a dihydrohydroxyfuran molecule to give the corresponding diether (cf. Part III, *loc. cit.*).



It will be noted that, independently of the details of the intermediate steps, the cyclisation requires a *cis*-arrangement of the –COMe and –CMe_2·OH groups about the ethylenic double bond. The actual orientation of the groups in the keto-alcohol (II), as isolated, is not certain, but it is clear that the geometrical isomers will be readily interconvertible in acid solution owing to the presence of a small concentration of oxonium ions formed by addition of a proton at the *carbonyl*-oxygen atom and charge-resonance in the resulting $C{=}C{-}C{=}OH^+ \longleftrightarrow {}^+C{-}C{=}C{-}OH$ system. Now, there are four possible arrangements of the *cis*- and *trans*-isomers in which the conjugated system is uniplanar, namely the *trans-s-trans* (*a*), *trans-s-cis* (*b*), *cis-s-trans* (*c*), and *cis-s-cis* (*d*) conformations. Of these, (*d*) is obviously the most conducive to cyclisation, while (*a*) is probably the most stable thermodynamically, since the transoid arrangement of a conjugated system is normally favoured (Aston *et al.*, *J. Chem. Phys.*, 1946, **14**, 67; Braude *et al.*, *J.*, 1949, 1890; 1952, 1419), and since uniplanarity in (*c*) is, moreover, opposed by steric hindrance. If the *trans-s-trans*-conformation (*a*) predominates in solution, the rate of cyclisation will depend directly on the small equilibrium concentration of the *cis-s-cis* conformation (*d*), and the very marked accelerating effect of decreasing the water content of the medium may be explained in the following way. In the more aqueous solvent, the acetyl group will be extensively solvated by water molecules (cf. p. 3140), and conformation (*a*) will be stabilised additionally with respect to (*d*). As the water concentration is decreased, however, external solvation of the acetyl group will become incomplete and the *cis-s-cis* conformation (*d*) will gain in relative stability, since the distance between the hydroxyl-hydrogen atom and the carbonyl-oxygen atom is here sufficiently small for *internal* solvation of the acetyl group. Thus, the proportion of (*d*) and the rate of cyclisation will increase with decreasing water content of the medium. This interpretation is also in accord with the marked decrease in the energy of activation of the cyclisation on changing from 40% to 60% dioxan.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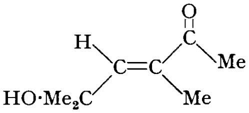
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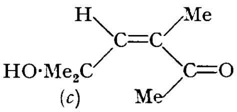
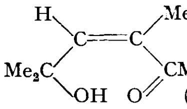

(*c*)


(*d*)

EXPERIMENTAL

The keto-alcohols were those described in Part III (*loc. cit.*). The reaction media described as "40, 60, and 80%" aqueous dioxan were made up by mixing 40·5, 60·8, and 81·0 ml. of dioxan with appropriate volumes of aqueous hydrochloric acid and water to give 100 ml. of solution. The kinetic measurements were carried out by the method previously described, with a Beckman photo-electric spectrophotometer, Model DU (cf. Braude and Fawcett, *J.*, 1950, 800). In the rearrangement of (I), where the first-order rate constants decrease as the reaction progresses, the plots of k against time were approximately linear and the values of k for $t = 0$ were obtained graphically by extrapolating the plots. The values thus obtained were reproducible within ±2%. Most of the data in Tables 1 and 3 are based on duplicate runs. Six typical runs are reproduced below.

(i) Rearrangement of (I) in 40% dioxan–0·1M-HCl, at 75°. $c_{\text{ROH}} = 0{\cdot}00607$.

Time (min.) ...	0	32·4	44·0	54·2	63·7	74·2	85·2	95·7	107	119	—
10^{-1} ε (2290 Å)	93	171	198	220	238	260	271	289	303	332	1130
10^4k (min.$^{-1}$) ...	27·0 *	24·3	24·3	24·4	34·7	23·5	22·2	21·9	21·1	21·9	—

(ii) Rearrangement of (I) in 60% dioxan–0·1M-HCl, at 75°. $c_{\text{ROH}} = 0{\cdot}00608$.

Time (min.) ...	0	16·1	20·0	24·2	30·3	34·9	39·6	47·7	52·2	56·3	—
10^{-1} ε (2290 Å)	93	116	117	121	122	133	134	137	140	142	1130
10^4k (min.$^{-1}$) ...	16·9 *	15·3	13·8	12·2	10·0	11·8	11·1	9·8	9·4	9·2	—

(iii) Rearrangement of (I) in 40% dioxan–0·1M-HCl, at 85°. $c_{\text{ROH}} = 0{\cdot}00565$.

Time (min.) ...	0	5·9	8·9	12·2	13·9	15·5	17·4	19·2	21·1	—
10^{-1} ε (2290 Å)	99	142	155	182	192	203	212	221	228	1130
10^4k (min.$^{-1}$) ...	74·5 *	74·5	65·6	69·5	68·6	68·7	66·6	66·1	64·6	—

* Extrapolated.

(iv) Cyclisation of (II) in 40% dioxan–0·1M-HCl, at 75°. $c_{\text{ROH}} = 0{\cdot}00437$.

Time (min.) ...	0	160	230	284	299	337	372		2800
10^{-1} ε (2290 Å)	983	825	757	629	684	673	633		242
10^4k (min.$^{-1}$) ...	—	14·9	16·5	17·6	17·2	16·0	17·1	(Mean)	16·5

(v) Cyclisation of (II) in 60% dioxan–0·1M-HCl, at 75°. $c_{\text{ROH}} = 0{\cdot}00325$.

Time (min.) ...	0	51·2	58·7	76·4	85·5	94	103		990
10^{-1} ε (2290 Å)	1020	764	710	655	614	593	563		124
10^4k (min.$^{-1}$) ...	—	64	66	71	71	69	68	(Mean)	68

(vi) Cyclisation of (II) in 40% dioxan–0·1M-HCl, at 85°. $c_{\text{ROH}} = 0{\cdot}00458$.

Time (min.) ...	0	49	65	72	80	88	101	113	144		1400
10^{-1} ε (2290 Å)	1040	853	807	788	753	747	714	687	617		226
0^4k (min.$^{-1}$) ...	—	51·7	49·9	50·7	53·3	50·0	50·1	49·8	50·2	(Mean)	50·7

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