Intramolecular Nucleophilic Assistance in Reactions of Acetals

By **E. Anderson**, Chemistry Department, University of Leicester, Leicester
B. Capon,* Chemistry Department, University of Glasgow, Glasgow W.2

The hydrolyses of 4-aminobutyraldehyde diethyl acetal, 2-pyridylmethylaminoacetaldehyde diethyl acetal, succinaldehydic acid dimethyl acetal, and D-*threo*-teturonic acid dimethyl acetal are not appreciably faster than those of analogous acetals without the potential neighbouring groups, which indicates that there is no intramolecular nucleophilic assistance in the former reactions. The cyclisation of 2-carboxybenzaldehyde diethyl acetal to 3-ethoxyphthalide is about three times faster than the hydrolysis of terephthalaldehydic acid diethyl acetal in aqueous buffers, which also indicates the absence of significant nucleophilic assistance. In 82% w/w aqueous dioxan the pH*–rate profile for the cyclisation of 2-carboxybenzaldehyde diethyl acetal at 60° is sigmoid and at pH* 9·46 the rate is 3000 times that for the hydrolysis of terephthalaldehydic acid diethyl acetal. Therefore under these conditions the carboxylate group provides nucleophilic assistance for the acid-catalysed rupture of the acetal bond.

Hydrolysis of 2-(*o*-carboxyphenyl)-1,3-dioxolan proceeds *via* an intermediate, probably 3-(2-hydroxyethyl)-1,3-dioxolan, in aqueous solution at a rate approximately ten times that for the hydrolysis of 2-(*p*-carboxyphenyl)-1,3-dioxolan. Hydrolysis of 3-(2-hydroxy-1,1,2,2-tetramethylethoxy)phthalide is too fast for it to be detectable as an intermediate in the hydrolysis of 2-(*o*-carboxyphenyl)-4,4,5,5-tetramethyl-1,3-dioxolan. In water the latter reaction is about ten times faster than hydrolysis of the *para*-isomer and in 50% w/w aqueous dioxan it is about fifty times faster. Under these conditions the reaction probably involves intramolecular nucleophilic catalysis.

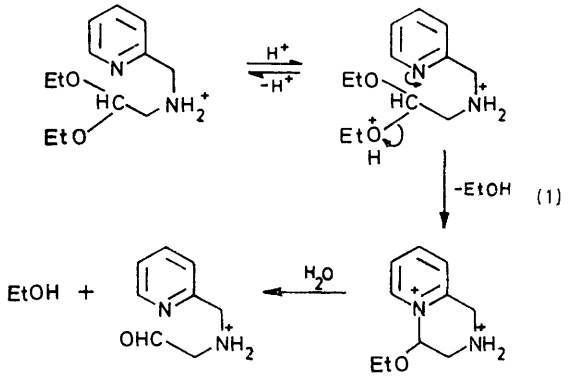
The hydrolyses of *o*-carbamoylbenzaldehyde diethyl acetal and 2-(*o*-carbamoylphenyl)-1,3-dioxolan yield 3-hydroxyphthalimidine. These reactions proceed *via* an intermediate which was tentatively identified as *o*-carbamoylbenzaldehyde.

THE possibility that the hydrolysis of glycosides catalysed by enzymes sometimes involves nucleophilic catalysis by functional groups of the latter [1] has stimulated interest in nucleophilic catalysis in the non-enzymic hydrolysis of acetals and glycosides.[2,3] Nucleophilic assistance has been demonstrated to occur in the cyclisation of glucose dimethyl acetal to yield a mixture of furanosides,[3] but this does not result in nucleophilic catalysis as the subsequent hydrolysis of the furanosides is relatively slow. We now report a search for true nucleophilic catalysis and a more comprehensive survey of the structural requirements which favour nucleophilic assistance.

RESULTS AND DISCUSSION

4-Aminobutyraldehyde Diethyl Acetal.—The pK_a value of the amino-group of this compound would be expected to be *ca.* 10, so that an appreciable concentration of the un-ionised form would only be present at high pH values. At pH 9 hydrolysis was very slow but at pH 5·83 (phosphate buffer; $I = 0{\cdot}1$M) and 65° a measurable rate of formation of ethanol was observed with $k_{obs} = 1{\cdot}35 \times 10^{-5}$ s^{-1}. This was very similar to the estimated rate constant (10^{-5} s^{-1}) for the hydrolysis of butyraldehyde diethyl acetal and since 2 equiv. of ethanol were liberated there appears to be no nucleophilic assistance.

2-Pyridylmethylaminoacetaldehyde Diethyl Acetal.—The pK_a of the pyridine group would be expected to be *ca.* 5—6 and of the aliphatic amino-group *ca.* 10. At pH *ca.* 5 there is therefore the possibility of participation as shown in equation (1), but since at pH 5·02 and 60° in acetate buffer ($I = 0{\cdot}2$M) the rate constant (determined by g.l.c. estimation of ethanol) is $5{\cdot}30 \times 10^{-5}$ s^{-1}, *cf.* $3{\cdot}31 \times 10^{-5}$ s^{-1} for 4-pyridylmethylaminoacetaldehyde diethyl acetal, this presumably does not occur.



Succinaldehydic Acid Dimethyl Acetal (I).—The kinetics of hydrolysis of this acetal in aqueous buffers of pH 3·95—4·81 show no evidence for intramolecular nucleophilic assistance (Table 1). Thus at pH 3·95 the reaction is slightly slower than the hydrolysis of

TABLE 1

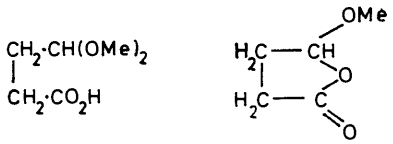
The kinetics of hydrolysis of succinaldehydic acid dimethyl acetal at 30·0° in acetate buffers ($I = 0{\cdot}1$M)

pH	$10^5 k_{obs}$ s^{-1}
3·95 [a]	3·49
3·95	3·60 [b]
4·18	1·12
4·31	0·905
4·48	0·275
4·81	0·220

[a] k_{obs} For the hydrolysis of butyraldehyde dimethyl acetal under these conditions is $4{\cdot}0 \times 10^{-5}$ s^{-1}. [b] Determined gas chromatographically.

[1] *Cf.* B. Capon, *Chem. Rev.*, 1969, **69**, 433.
[2] (*a*) C. Speck, D. J. Rynbrandt, and I. H. Kochevov, *J. Amer. Chem. Soc.*, 1965, **87**, 4979; (*b*) T. H. Fife, *ibid.*, p. 271.
[3] B. Capon and D. Thacker, *J. Amer. Chem. Soc.*, 1965, **87**, 4199; *J. Chem. Soc.* (*B*), 1967, 1322.

butyraldehyde dimethyl acetal. Also the spectrophotometrically determined rate constant is equal within experimental error to the gas-chromatographically determined constant. Since the former is a measure of the rate of formation of free aldehyde and the latter is a measure of the rate of formation of methanol this result indicates that γ-methoxy-γ-butyrolactone (II) is never an intermediate present at appreciable concentration. However if it were an intermediate it would probably be hydrolysed more rapidly than it is formed since the rate constant for the hydrolysis of



(I) (II)

γ-ethoxy-γ-butyrolactone ($k_{obs} = 5{\cdot}02 \times 10^{-4}$ s^{-1} at pH 4·00 and 30°) [2b] is considerably larger than that for hydrolysis of the acetal ($k_{obs} = 3{\cdot}6 \times 10^{-5}$ s^{-1} at pH 3·95 and 30°). Therefore, our results do not exclude γ-methoxy-γ-butyrolactone as an intermediate but they do show that, if it is, there can be little intramolecular nucleophilic assistance for its formation.

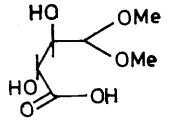
D-threo-*Teturonic Acid Dimethyl Acetal* (III).—This compound was investigated because it was thought that the introduction of hydroxy-groups should favour a nucleophilically assisted reaction of the acetal and that a substituted chain would cyclise more readily than an unsubstituted one. However the rate constant for hydrolysis at pH 2·84 is slightly less than that for hydrolysis

TABLE 2

The kinetics of hydrolysis of D-*threo*-teturonic acid dimethyl acetal at 70·0° in chloroacetate buffer of pH 2·84 (I = 0·2M)

	$10^4 k_{obs}$/s^{-1}
D-*threo*-Teturonic acid dimethyl acetal	2·71
D-Glyceraldehyde dimethyl acetal	3·00

of D-glyceraldehyde dimethyl acetal (see Table 2). Clearly there is no nucleophilic assistance.



(III)

Phthalaldehydic Acid Diethyl Acetal.—The greater rigidity of this compound should favour nucleophilic assistance but the increased stability of the carbonium ion should favour the unassisted reaction and hence reduce the possibility of observing a nucleophilically assisted reaction.

The first product to be formed from phthalaldehydic acid diethyl acetal in aqueous buffers of pH 3·50—5·83 is 3-ethoxyphthalide. This reaction is 12 and 15·5 times faster than the hydrolysis of the acetal group of 2-methoxycarbonylbenzaldehyde diethyl acetal at pH values 3·95 and 5·04, respectively, and 2—3·5 times faster than the hydrolysis of terephthalaldehydic acid acetal (see Table 3). These results provide little

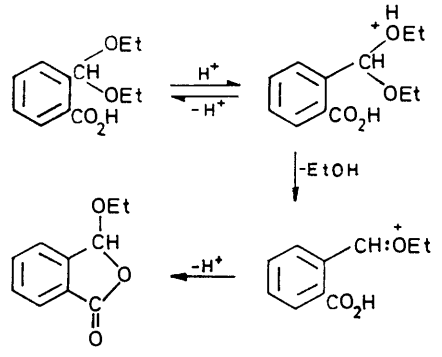
TABLE 3

The kinetics of hydrolysis of 2-carboxybenzaldehyde diethyl acetal and related compounds in aqueous formate and acetate buffers at 25° (I = 0·1M)

pH	$10^4 k_{obs}$/s^{-1} [a]	$10^4 k_{obs}$/s^{-1} [b]	$10^4 k_{obs}$/s^{-1} [c]
3·50 [d]	156		
3·85 [d]	115		
3·93	63·2	5·14	27·1
4·08	53·9		22·2
4·31	39·2		
4·48	20·1		
4·83	10·3		
5·04	8·32	0·55	
5·83	3·23		0·90

[a] 2-Carboxybenzaldehyde diethyl acetal. [b] 2-Methoxycarbonylbenzaldehyde diethyl acetal. [c] 4-Carboxybenzaldehyde diethyl acetal. [d] Formate buffers.

evidence for nucleophilic assistance and the 3-ethoxyphthalide may be formed by intramolecular capture of a carbonium ion as shown in equation (2). The pK_a



(2)

of phthalaldehydic acid diethyl acetal is probably *ca.* 3·6 and so it should be mainly ionised in the pH range studied. This would account for the approximately linear dependence of log k_{obs} on −pH.

When phthalaldehydic acid diethyl acetal reacts in

TABLE 4

The kinetics of hydrolysis of 2-carboxybenzaldehyde diethyl acetal in 82% w/w dioxan–water at 60·0° in acetate and formate buffers

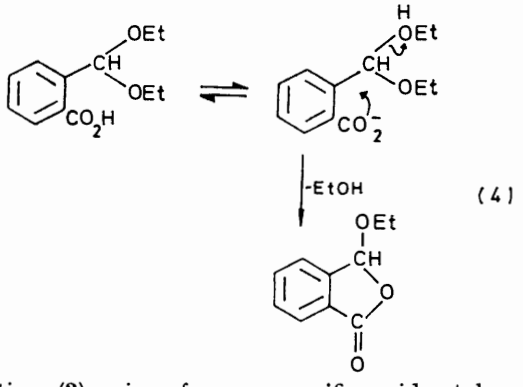
pH	$10^3 k_{obs}$/s^{-1}	$10^3 k_{calc}$/s^{-1} [a]
8·73 [b]	3·36	3·36
9·46 [b,c]	3·10	3·16
9·93	3·03	2·78
10·43	2·00	1·77
10·67	1·23	1·27
10·82	0·930	0·998
10·99	0·721	0·737
11·13	0·476	0·564
11·33	0·360	0·377
11·43	0·282	0·306
11·48	0·266	0·275

[a] Calculated from the expression $k_{calc} = (k_1 + k_2 \times 10^{-pH^*})/(1 + K_a/10^{-pH^*})$ with $k_1 = 3{\cdot}80 \times 10^{-3}$ s^{-1} (s.d. 6·68%); $k_2 = -2{\cdot}08 \times 10^5$ l mol^{-1} s^{-1} (s.d. 87·1%), $K_a = 4{\cdot}25 \times 10^{-11}$ mol l^{-1} (s.d. 11·8%). The value of k_2 is not well defined (*i.e.* zero within experimental error) as it does not make a sufficiently large contribution in the pH* range studied. [b] Formate buffers. [c] k_{obs} For hydrolysis of *para*-isomer is $1{\cdot}01 \times 10^{-6}$ s^{-1}.

buffers in 82% w/w aqueous dioxan the product is also 3-ethoxyphthalide. The pH*–rate profile for this reaction has a sigmoid portion and follows equation (3) (see Table 4). At pH* 9·46 this reaction is *ca.* 3000

$$\text{Rate} = k_{obs}[\text{total substrate}] = k_1\,[\text{un-ionised form}] + k_2\,[\text{un-ionised form}] \times 10^{-pH^*} \quad (3)$$

times faster than the hydrolysis of terephthalaldehydic acid diethyl acetal, which suggests that the carboxylate group participation is a rate-determining step. The most likely origin of the rate enhancement is nucleophilic assistance to the departure of the protonated ethoxy-group, as shown in equation (4). There is no nucleophilic catalysis as the hydrolysis of 3-ethoxyphthalide is slow. On this formulation the k_1 term of

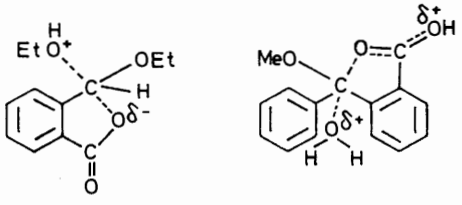


(4)

equation (3) arises from a specific acid-catalysed reaction of the acetal with the ionised carboxy-group. The second-order constant for this process, k_2^*, would be related to k_1 by the equation $k_2^* = k_1/K_a = (3{\cdot}31 \times 10^{-3})/(3{\cdot}52 \times 10^{-11}) = 9{\cdot}42 \times 10^7$ l mol^{-1} s^{-1}. This is $3{\cdot}24 \times 10^4$ times greater than the second-order constant for the hydrolysis of terephthalaldehydic acid acetal.

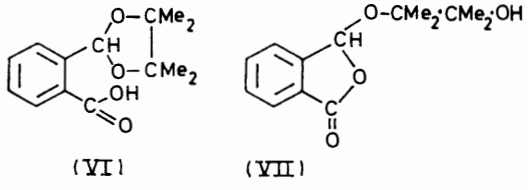
The detection of a nucleophilically assisted reaction in aqueous dioxan but not in water could arise from an increase in the rate of the nucleophilically assisted reaction or a decrease in the rate of the non-assisted reaction. At present it is not possible to pronounce definitely on this point. In aqueous dioxan the contribution of the term k_2[un-ionised form] $\times 10^{-pH^*}$ of equation (3) to the total rate is greatly reduced because the un-ionised form is present at much higher values of pH* than it is of pH in aqueous solution. This alone should make the term k_1[un-ionised form] more easily detectable. If k_1 were the same in water as it is in 82% dioxan the contribution of the term k_1[un-ionised form] to the total rate in water would be negligible. Therefore there is no evidence that k_1 or k_2^* has increased on going from water to dioxan.

The transition state for the nucleophilically catalysed reaction must be as (IV). If this has carbonium ion character there can be no stabilisation by conjugation with the ring as the p orbital on the aldehydic carbon atom must be orthogonal to the π system. This should be reflected in the effect of substituents on the rate of this reaction but this has not been investigated. It is interesting that Weeks and Zuorick have concluded that the transition state for the hydrolysis of 3-methoxy-3-phenylphthalide is (V) and that the reaction is bimolecular.[4] Although this reaction is not the exact microscopic reverse of the hydrolysis of phthalaldehydic acid diethyl acetal there is an obvious similarity between the transition states (IV) and (V).

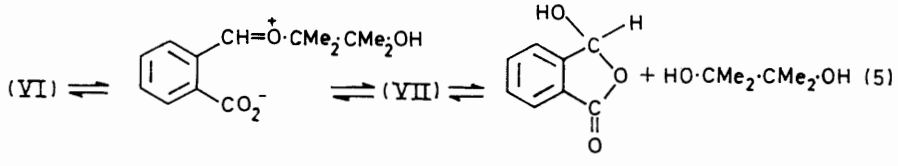


(IV) (V)

2-(o-*Carboxyphenyl*)-1,3-*dioxolan*.—The hydrolysis of this compound was not studied in detail. At 45° in an aqueous acetate buffer of pH 4 the reaction is complex with the increase in absorbance at 300 nm showing an induction period. This is consistent with conversion of the dioxolan into 3-(2-hydroxyethoxy)phthalide



(VI) (VII)



followed by conversion of this into the anion of phthalaldehydic acid, since of these three species only the anion of phthalaldehydic acid absorbs at 300 nm.

2-(o-*Carboxyphenyl*)-4,4,5,5-*tetramethyl*-1,3-*dioxolan* (VI).—No intermediate was detected spectrophotometrically in the hydrolysis of this compound under any of the conditions employed. 3-(2-Hydroxy-1,1,2,2-tetramethylethoxy)phthalide (VII) was too insoluble in

[4] D. P. Weeks and G. W. Zuorick, *J. Amer. Chem. Soc.*, 1969, **91**, 477.

aqueous buffers for reliable kinetic data to be obtained with the apparatus available, but if a stock solution in dioxan was injected into a buffer with pH 3—5 at 65·0° the initially turbid solution cleared within 4—5 min to give a solution whose u.v. spectrum was identical with that of phthalaldehydic acid at the same pH. Therefore it seems that hydrolysis of the phthalide (VII) is fast under these conditions and it would not be detectable if it were an intermediate in the hydrolysis of the dioxolan (VI). The hydrolysis of dioxolan (VI) is 7—15 times faster than that of its *para*-isomer (see Table 5) and hence there is possibly weak intramolecular nucleophilic catalysis.

TABLE 5

The kinetics of hydrolysis of 2-(*o*- and *p*-carboxyphenyl)-4,4,5,5-tetramethyl-1,3-dioxolan in aqueous acetate and formate buffers at 69·0° (I = 0·1M)

pH	10^4k_{obs}/s^{-1} (*ortho*)	10^4k_{obs}/s^{-1} (*para*)
0·1M-HCl		58·6
3·13 [a]	14·4	0·869
3·30 [a]	8·24	
3·72	5·64	0·442
3·98	3·20	0·217
4·01	2·98	
4·40	2·00	
4·90	1·06	

[a] Formate buffers.

The hydrolysis of dioxolan (VI) was also studied in 50% w/w dioxan–water at 95° (see Table 6). The limited kinetic data approximately fit a rate law of the form $k_{obs} = k_1$[undissociated form] with $k_1 = 1·44 \times 10^{-4}$ s^{-1} and ${}_sK_a = 1·79 \times 10^{-6}$M; the measured ${}_sK_a$ value at 25° is $1·48 \times 10^{-6}$M. The hydrolysis of 3-(2-hydroxy-1,1,2,2-tetramethylethoxy)phthalide (VII) is

TABLE 6

The kinetics of hydrolysis of 2-(*o*-carboxyphenyl)-4,4,5,5-tetramethyl-1,3-dioxolan in 50% w/w dioxan–water at 95° (I = 0·05M)

pH*	5·03 [a]	5·30	5·46	5·70	6·00
10^5k_{obs}/s^{-1}	11·7	10·9	10·0	6·9	5·3
10^5k_{calc}/mol^{-1} s^{-1} [b]	12·1	10·6	9·52	7·61	5·18

[a] k_{obs} For *para*-isomer is $2·5 \times 10^{-6}$ s^{-1}; k_{obs} for *para*-isomer in 0·004M-$HClO_4$ is $3·16 \times 10^{-4}$ s^{-1}. [b] Calculated from the expression $k_{calc} = k_1/(1 + K_a/10^{-pH*})$ with $k_1 = 1·44 \times 10^{-4}$ s^{-1} and $K_a = 1·79 \times 10^{-6}$ mol l^{-1}.

rapid under these conditions and so it would not be detectable if it were an intermediate. The hydrolysis of the dioxolan (VI) is *ca.* 44 times faster than the hydrolysis of the *para*-isomer at pH* 5·03, and was estimated to be *ca.* 150 times faster at pH* 5·83, the half-neutralisation point. These larger rate enhancements, coupled with the above demonstrated tendency of acetals of phthalaldehydic acid to be converted into 3-alkoxyphthalides, suggest that we have here an example of nucleophilic catalysis with hydrolysis of the dioxolan (VI) passing through the phthalide (VII). The reason that this rate enhancement is smaller than that found for the hydrolysis of phthalaldehydic acid diethyl acetal is probably because the reaction was studied in 50 instead of 82% aqueous dioxan. It is possible that the rate enhancement found with the dioxolan (VI) arises from intramolecular capture by the carboxylate group of a reversibly formed carbonium ion [5] as shown in equation (5). At present it is not possible to distinguish this mechanism from a concerted displacement.

It is interesting that an *A*2 mechanism has been proposed for the hydrolysis of 4,4,5,5-tetramethyl-2-phenyldioxolan. Also weak general acid catalysis was found in the hydrolysis of 2-(*p*-methoxyphenyl)-4,4,5,5-tetramethyldioxolan and tentatively interpreted as arising from a combination of nucleophilic catalysis by formate ion and specific acid catalysis.[6] Therefore it seems that hydrolysis of 2-aryl-4,4,5,5-tetramethyldioxolans is sensitive to inter- and intramolecular catalysis.

o-*Carbamoylbenzaldehyde Diethyl Acetal* (VIII).—In aqueous buffers of pH *ca.* 4 this compound yields 3-hydroxyphthalimidine (XI), the cyclic form of the amide of phthalaldehydic acid. The reaction is first order and slower than hydrolysis of *p*-carbamoylbenzaldehyde diethyl acetal (Table 7). Nucleophilic

TABLE 7

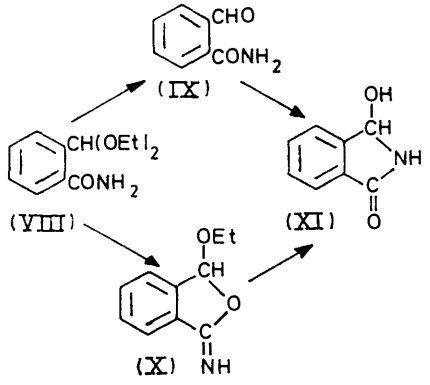
The kinetics of hydrolysis of *o*- and *p*-carbamoylbenzaldehyde diethyl acetal in aqueous buffers at 25·0° (I = 0·1M)

pH	10^4k_{obs}/s^{-1} (*ortho*)	10^4k_{obs}/s^{-1} (*para*)
3·93	4·40	7·19
4·00	4·09	6·04
4·08	3·80	5·07

assistance by the amide group is not important under these conditions. At higher acidities the situation is more complex. At 25° in a chloroacetate buffer of pH 2·99 and ionic strength of 0·1M the absorbance at 254 nm increases to a maximum and then slowly decreases. Repeated scans of the u.v. spectrum during this process show that an intermediate with a broad maximum at 255·5 nm is formed. The half-life for the formation of this intermediate (2·5 min) is similar to that for the hydrolysis of *p*-carbamoylbenzaldehyde diethyl acetal and so again the rate of reaction of the *ortho*-compound is not enhanced. Similar behaviour was observed when the reaction of *o*-carbamoylbenzaldehyde diethyl acetal (VIII) was studied in 95% dioxan–water at 25° containing perchloric acid. The u.v. spectrum of the intermediate is quite unlike that of 3-ethoxyphthalimidine and hence this structure can be ruled out. Therefore, two pathways were considered with compounds (IX) and (X) as intermediates. The evidence presented in the Experimental section supports structure (IX), 2-carbamoylbenzaldehyde. The formation and disappearance of a low field singlet at δ 10·35 p.p.m. in the n.m.r. spectrum of a reacting solution is not easy to interpret unless the

[5] *Cf.* B. Capon and D. Thacker, *J. Chem. Soc.* (*B*), 1967, 185.
[6] T. H. Fife, *J. Amer. Chem. Soc.*, 1967, **89**, 3228; T. H. Fife and L. H. Brod, *ibid.*, 1970, **92**, 1681.

intermediate is (IX). It is also reasonable that this compound should be converted into 3-hydroxyphthalimidine when attempts are made to isolate it. Therefore we favour the pathway in which (IX) is an intermediate.



2-(o-*Carbamoylphenyl*)-1,3-*dioxolan*.—The absorbance at 254 nm of a hydrolysing solution of this acetal at pH 2·99 and 45° also increases and then decreases. The time to reach half the maximum absorbance (12 min) was similar to the half-life for the hydrolysis of the *para*-isomer under the same conditions (13·5 min). The u.v. spectrum of the intermediate appears to be similar to that in the hydrolysis of *o*-carbamoylbenzaldehyde diethyl acetal. As there appears to be no rate enhancement this reaction was not investigated further. The failure of the neighbouring amide group to provide assistance is not surprising since it is about 10^6 times less basic than the carboxylate group.

EXPERIMENTAL

4-*Aminobutyraldehyde Diethyl Acetal*.—3-Chloropropionaldehyde diethyl acetal was converted into the nitrile by treatment with sodium cyanide in dimethyl sulphoxide;[7] b.p. 86—87° at 6·0 mmHg (lit.,[8] 34° at 5·0 mmHg), $\nu_{max.}$ (neat), 2220m (C≡N str.), 1190, 1120, and 1050 cm^{-1} (acetal C–O–C str.). The nitrile was treated twice with sodium in ethanol to yield the amine, b.p. 81—81·5° at 9 mmHg (lit.,[9] 83—83·7 at 10 mmHg), $\nu_{max.}$ (neat) 3375m, 3290m, 3280s (NH str.), 1120, 1050, and 1000 cm^{-1} (acetal C–O–C str.), δ (neat) 1·1 (m, 8H), 1·3—1·6 (m, 4H), 2·51 (d, 2H), 3·0—3·7 (m, 4H), and 4·4 p.p.m. (t, 1H).

Succinaldehydic Acid Dimethyl Acetal, Cyclohexylammonium Salt.—Methyl succinaldehydate[10] was converted into its dimethyl acetal by treatment with trimethyl orthoformate in acidic methanol; b.p. 80—81° at 11 mmHg (lit.,[11] 79—81·5° at 11 mmHg). The ester was hydrolysed by shaking with exactly 1 equiv. of 0·4N-barium hydroxide until a neutral, homogeneous solution was obtained. One equiv. of cyclohexylammonium sulphate was added, the precipitated barium sulphate was removed by centrifuging, and the aqueous solution was freeze-dried to give the *cyclohexylammonium salt*, which was recrystallised from methanol–ether; m.p. 77—79°, $\nu_{max.}$ (Nujol) 1620m (NH_3^+ bend), 1540s (CO_2^-), 1150s, and 1050s cm^{-1} (acetal C–O–C str.) (Found: C, 58·2; H, 9·95; N, 5·55. $C_{12}H_{25}NO_4$ requires C, 58·3; H, 10·2; N, 5·7%).

Butyraldehyde Dimethyl Acetal.—This was prepared from butyraldehyde and acidic methanol and purified by fractional distillation through a spinning band column; b.p. 114—114·2° at 750 mmHg.

2-*Pyridylmethylaminoacetaldehyde Diethyl Acetal*.—This was bought from the Aldrich Chemical Co. and purified by distillation; b.p. 123—124° at 0·4 mmHg.

4-*Pyridylmethylaminoacetaldehyde Diethyl Acetal*.—This was bought from the Aldrich Chemical Co. and purified by distillation; b.p. 123—125° at 0·4 mmHg.

D-threo-*Teturonic Acid Dimethyl Acetal, Cyclohexylammonium Salt*.—The methyl ester dimethyl acetal[12] was converted into the cyclohexylammonium salt as described for succinaldehydic dimethyl acetal methyl ester. It was recrystallised from methanol but was very hygroscopic; $\nu_{max.}$ (Nujol), 3400 (OH str.) 1600br (OH def., NH_3 def., and CO_2^- str.), 1125s, 1060s, and 1000s cm^{-1} (acetal C–O–C str.); δ (pyrimidine) 0·83—2·0 (m, 11H), 2·33br (s, r), 3·47 (s, 6H), and 4·41—5·08 p.p.m. (m, 3H). A satisfactory analysis could not be obtained.

D-*Glyceraldehyde Dimethyl Acetal*.—The sample prepared by Dr. D. Thacker[3] was used.

2-*Carboxybenzaldehyde Diethyl Acetal, Cyclohexylammonium Salt*.—Methyl 2-formylbenzoate[13] was treated with triethyl orthoformate in ethanol containing a trace of hydrochloric acid to yield its *diethyl acetal*, which was purified by distillation; b.p. 104—105°/0·3 mmHg, $\nu_{max.}$ (neat) 1715s (ester C=O), 1270s (ester C–O), 1100s, 1050s, and 1015s cm^{-1} (acetal C–O–C str.), δ ($CDCl_3$) 1·20 (t, *J* 7 Hz), 3·51 (q, 4H, *J* 7 Hz), 3·85 (s, 3H), 6·20 (s, 1H), and 7·21—7·97 p.p.m. (m, 4H) (Found: C, 65·2; H, 7·6. $C_{13}H_{18}O_4$ requires C, 65·5; H, 7·6%).

The acetal ester was converted into the *cyclohexylammonium salt* by the method described above; m.p. 191—192° (from methanol–ether), $\nu_{max.}$ (Nujol), 1625m (NH_3^+ bend), 1520 (CO_2^- str.), 1115, 1080, 1045, and 1020 cm^{-1} (acetal C–O–C str.), δ (CD_3·SO·CD_3) 1·05 (t, *J* 6 Hz) superimposed on a broad absorption at 0·50—3·17 (20H in all), 3·50 (two overlapping q, 4H, *J* 6 Hz), 6·27 (s, 1H), and 7·17—7·87 p.p.m. (m, 4H) (Found: C, 66·75; H, 8·85; N, 4·35. $C_{18}H_{29}NO_4$ requires C, 66·8; H, 9·0; N, 4·3%).

Terephthalaldehydic Acid Diethyl Acetal, Cyclohexylammonium Salt.—Ethyl terephthalaldehydate diethyl acetal was prepared by treating ethyl terephthalaldehydate with triethyl orthoformate in acidic methanol; b.p. 110—112° at 0·3 mmHg, $\nu_{max.}$ (neat) 1722s (C=O str. of ester), 1260s (C–O str. of ester), 1110s, 1050s, 1020m (acetal C–O–C str.) and 760m cm^{-1} (*p*-substituted benzene), δ (neat) apparent q consisting of two overlapping t at 1·18 and 1·30 p.p.m. both with *J* 7 Hz (9H), 3·52 (q, *J* 7 Hz, 4H), 4·25 (q, *J* 7 Hz, 2H), 5·50 (s, 1H), AA'BB' system with signals at 7·47, 7·60, 7·97, and 8·10 p.p.m. (4H) (Found: C, 66·7; H, 7·95. $C_{14}H_{20}O_4$ requires C, 66·6; H, 8·0%).

This was converted into the *cyclohexylammonium salt* by the method given above; m.p. 117—120°, $\nu_{max.}$ (KBr)

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2960 (CH_2 str.), 3220—2500m (NH_3^+ str.), 1618 (NH_3^+ def.), 1540 (CO_2^-), 1400 (CH_2 def.), 1120, 1060, and 1020 cm^{-1} (acetal C–O–C str.), δ (CD_3·SO·CD_3; 60° 1·16 (t, *J* 7 Hz, 1H) superimposed on broad absorption 0·3—2·2 p.p.m. (m, 17H), 3·60 (q, *J* 7 Hz, 4H), 5·55 (s, 1H), AA'XX' system centred on 7·75 p.p.m. (4H) (Found: C, 66·7; H, 8·8; N, 4·3%).

2-(2-*Carboxyphenyl*)-1,3-*dioxolan*, *Cyclohexylammonium Salt*.—A solution of methyl 2-formylbenzoate, ethylene glycol, and a small amount of toluene-*p*-sulphuric acid in toluene was refluxed in a Dean–Stark apparatus until the theoretical quantity of water had distilled over. The crude product was converted into the *cyclohexylammonium salt* by the method given above and recrystallised from methanol–ether; m.p. 173—174°, $\nu_{max.}$ (KBr) 3200—2500 (CH_2 and $^+NH_3$ str.), 1630 ($^+NH_3$ bend), 1560 (CO_2^- str.), 1375 (CH_2 scissoring), 1110, 1070 (C–O–C str. of dioxolan ring), and 750 cm^{-1} (*o*-disubstituted benzene), δ (CD_3·SO·CD_3) 0·67—2·17 (m, 14H), 3·91 (d, 4H, *J* 3 Hz), and 5·33—7·74 p.p.m. (m, 5H) (Found: C, 65·5; H, 8·2; N, 4·85. $C_{16}H_{23}NO_4$ requires C, 65·5; H, 7·9; N, 4·8%).

2-(4-*Carboxyphenyl*)-1,3-*dioxolan*.— 2-(4-Methoxycarbonylphenyl)-1,3-dioxolan [14] (1·0 g) was shaken with 0·1M-sodium hydroxide (75 ml) until a homogeneous mixture was obtained. This was cooled in ice, covered with ether, vigorously stirred, and acidified to pH 3·0 with 0·1M-hydrochloric acid. The ether layer was separated, dried, and evaporated *in vacuo* to yield 2-(4-*carboxyphenyl*)-1,3-*dioxolan* which was recrystallised from ether; m.p. 168—169°, $\nu_{max.}$ (Nujol) 1690 (C=O), 1295 (C–O of CO_2H), 1073, 1020 (C–O–C str. of dioxolan ring), and 850 cm^{-1} (*p*-substituted benzene), δ ($CDCl_3$) 4·10br (s, 4H), 5·08 (s, 1H), AA'XX' system with signals at 7·27, 7·40, 7·55, and 7·68 (4H), and 11·12 p.p.m. (s, 1H, disappeared on shaking with D_2O) (Found: C, 61·8; H, 5·35. $C_{10}H_{10}O_4$ requires C, 61·85; H, 5·2%).

2-(2-*Carboxyphenyl*)-4,4,5,5-*tetramethyl*-1,3-*dioxolan*.—*o*-Bromobenzaldehyde was converted into the corresponding *tetramethyldioxolan* by the standard method; [6] b.p. 112—113° at 1·0 mmHg, m.p. 67—68° [from light petroleum (b.p. 40—60°)], δ 1·25, 1·30 (12H), 6·21 (s, 1H), 6·93—7·66 (m, 4H), and 11·95 (s, 1H) p.p.m. (s, 1H) (Found: C, 54·85; H, 5·95; Br, 28·25. $C_{13}H_{17}BrO_2$ requires C, 54·75; H, 6·0; Br, 28·0%).

This compound could not be converted into the Grignard reagent in ether and the reaction only went to 50% completion in tetrahydrofuran. The reaction solution was decanted from the unchanged magnesium and diethyl carbonate was added. In contrast to a control preparation of ethyl *o*-toluate, where the reaction is extremely exothermic, this reaction was very slow. The mixture was heated under reflux overnight and worked up by using saturated ammonium chloride solution to decompose the magnesium complexes. The crude product was fractionally distilled under reduced pressure, but it proved impossible to separate the desired product from unchanged bromodioxolan.

The i.r. spectrum showed a typical aromatic ester carbonyl absorption at 1720 cm^{-1} and the n.m.r. spectrum a typical ethyl ester triplet and quartet at δ 1·21 and 4·26 p.p.m. (*J* 7 Hz). It was estimated from the integrated spectrum and g.l.c. that the distilled product contained *ca.* 70% of the required ester.

The crude ester (2·5 g) was shaken with sufficient 1M-carbonate-free sodium hydroxide solution to react with the estimated amount of ester present until the mixture was neutral to Brilliant Orange indicator paper (pH 9—9·5). The residual material was removed with ether and the resultant clear solution was cooled to 0°, acidified with 0·1M-hydrochloric acid to pH 3·2, and rapidly extracted with ether. The extract was dried to yield the required *acid* (30% overall), which was recrystallised from benzene; m.p. 67—68°, $\nu_{max.}$ (CCl_4) 3520—2800 (C–H and O–H), 1700 (C=O), 1460, 1400 (asymm. and sym. C–H deformation of methyl groups), 1300, 1150 (C–O stretching of ester group), 1100, 1060, and 1000 cm^{-1} (dioxolan ring C–O–C stretch), δ ($CDCl_3$) 1·25 and 1·31 (12H), 6·75 (s, 1H), 7·1—8·17 (m, 4H), and 10·31 p.p.m. (s, 1H, disappears on shaking with D_2O) (Found: C, 67·05; H, 7·25. $C_{14}H_{18}O_4$ requires C, 67·2; H, 7·25%).

This compound can be made more easily from the reaction of phthalaldehyde acid and pinacol as described below.

2-(4-*Carboxyphenyl*)-4,4,5,5-*tetramethyl*-1,3-*dioxolan*.—Methyl 4-formylbenzoate was converted into the *tetramethyldioxolan* by the standard procedure; [6] m.p. 53—54° (from light petroleum), $\nu_{max.}$ (CCl_4) 2980 and 2950 (asymm. CH_3 str.), 2865 (symm. CH_3 str.), 2865 (symm. CH_3 str.), 1720 (C=O), 1430 (asymm. CH_3 deformation), 1380 and 1370 (*gem* CH_3), 1273 and 1260 (ester C–O str.), 1110, 1080, and 1020 cm^{-1} (dioxolan C–O–C str.), δ ($CDCl_3$) 1·20, 1·28 (12H), 3·88 (s, 3H), 6·02 (s, 1H), 7·52—8·15 (AA'BB', 4H), and 11·95 p.p.m. (s, 1H) (Found: C, 68·0; H, 7·6. $C_{15}H_{20}O_4$ requires C, 68·2; H, 7·6%).

The ester was converted into the *acid* by saponification with sodium hydroxide and acidification; m.p. 168—170° (from cyclohexane), $\delta_{max.}$ (KBr) 3500—2800 (OH and CH str.), 1700 (C=O str.), 1450 (asymm. CH_3 def.), 1290 (asymm. ester C–O str.), 1150 (symm. ester C–O str.), 1080, 1020 (dioxolan C–O–C str.), and 860 cm^{-1} (*p*-substituted aromatic), δ ($CDCl_3$) 1·25 and 1·30 (12H), 6·05 (1H), 7·55—8·25 (AA'BB'), and 10·32 p.p.m. (s, 1H, removed on shaking with D_2O) (Found: C, 67·0; H, 7·35%).

3-(2-*Hydroxy*-1,1,2,2-*tetramethylethoxy*)*phthalide*.—Phthalaldehydic acid (0·03 mol), pinacol (0·03 mol), toluene-*p*-sulphonic acid (1 mg), and toluene (10 ml) were heated under reflux in a Dean–Stark apparatus. Immediately after the stoicheiometric amount of water had collected (5 min) the solution was allowed to cool, and a quantitative yield of 2-(2-carboxyphenyl)-4,4,5,5-tetramethyl-1,3-dioxolan, identical with that prepared above, crystallised. This is one of the few examples of a reaction of phthalaldehydic acid yielding a 'normal' derivative. The reaction was repeated using benzene as solvent and refluxing for several h. Samples were withdrawn every h and the i.r. spectrum was recorded. The acid carbonyl absorption at 1700 cm^{-1} decreased and a new absorption at 1785 cm^{-1}, typical of a γ-lactone, appeared and increased. When the reaction was complete (*ca.* 7 h) the solution was cooled and the product crystallised in 60% yield; m.p. 242—243°. The same product could be obtained by sublimation of the initially formed acid at 180°; $\nu_{max.}$ (KBr) 3500 (OH str.) and 1780 cm^{-1} (lactone carbonyl), δ ($CDCl_3$) 1·53 and 1·60 (12H, methyl groups of aliphatic chain moved 12—15 Hz downfield compared to the corresponding dioxolan), 6·75 (s, 1H), and 7·50—8·18 p.p.m. (m, 4H).

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o-*Carbamoylbenzaldehyde Diethyl Acetal*.—*o*-Bromobenzaldehyde was converted into the *diethyl acetal* by treatment with triethyl orthoformate (Found: C, 51·5; H, 5·7; Br, 31·3. $C_{11}H_{15}BrO_2$ requires C, 51·0; H, 5·8; Br, 20·8%). The bromine atom was replaced by a cyano-group, which was hydrolysed to give the *amide*, m.p. 104—104·5° [from ether–light petroleum (b.p. 40—60°)], $\nu_{max.}$ (Nujol) 3350, 3160, 1645, 1620, 1595, 1575, 1115, 1060, and 1020 cm^{-1}, δ ($CDCl_3$) 1·17 (t, *J* 7 Hz, 6H), 3·8 (q, *J* 7 Hz, 4H), 5·77 (s, 1H), 7·05 (s, 2H), and 7·0—7·7 p.p.m. (m, 4H) (Found: C, 64·75; H, 7·65; N, 6·3. $C_{12}H_{17}NO_3$ requires C, 64·55; H, 7·7; N, 6·3%).

p-*Carbamoylbenzaldehyde Diethyl Acetal*.—*p*-Cyanobenzaldehyde was converted into the diethyl acetal, which was hydrolysed to the amide,[15] m.p. 104—105° (from benzene), $\nu_{max.}$ (Nujol) 3370, 3165, 1650, 1622, 1571, 1215, 1195, 1075, and 850 cm^{-1}, δ ($CDCl_3$) 1·23 (t, *J* 7 Hz, 6H), 3·60 (q, *J* 7 Hz, 4H), 5·53 (s, 1H), 6·67 (s, 2H), and 7·71 p.p.m. (AA'BB', 4H) (Found: C, 64·2; H, 7·35; N, 6·25%).

2-(o-*Carbamoylphenyl*)-1,3-*dioxolan*.—*o-Bromobenzylidene dibromide* was prepared in 95% yield by the photobromination of *o*-bromotoluene in carbon tetrachloride;[16] b.p. 100—102° at 1·0 mmHg (Found: C, 25·75; H, 1·7; Br, 72·8. $C_7H_5Br_3$ requires C, 25·6; H, 1·5; Br, 72·9%). This compound (0·5 mol) was added cautiously to a stirred solution of sodium methoxide (1·0 mol) in methanol (600 ml) which was heated under reflux overnight. The neutral solution was filtered and the methanol was evaporated to give an oil which was dissolved in chloroform. This solution was washed several times with water, dried, and evaporated *in vacuo* to give an oil which was distilled to give o-*bromobenzaldehyde dimethyl acetal* (90%), b.p. 96° at 0·5 mmHg, $\nu_{max.}$ (neat) 2920, 2800, 1105, 1075, 1015, and 750 cm^{-1}, δ (neat) 4·91 (s, 6H), 5·55 (s, 1H), and 6·83—7·83 p.p.m. (m, 4H) (Found: C, 46·9; H, 4·9; Br, 34·7. $C_9H_{11}BrO_2$ requires C, 46·8; H, 4·8; Br, 34·6%).

o-Bromobenzaldehyde dimethyl acetal (0·1 mol) was converted into 2-(o-*bromophenyl*)-1,3-*dioxolan* (50%) by the standard procedure; b.p. 90—92° at 0·2 mmHg, $\nu_{max.}$ 1121, 1085, 1020, and 750 cm^{-1} (Found: C, 47·1; H, 4·05; Br, 34·9. $C_9H_9BrO_2$ requires C, 47·2; H, 4·0; Br, 34·9%). This was converted[7] into 2-(o-*cyanophenyl*)-1,3-*dioxolan*, b.p. 122° at 0·6 mmHg, m.p. 30—31° [from light petroleum (b.p. 40—60°)], $\nu_{max.}$ (melt) 2220, 1120, 1000, and 760 cm^{-1}. δ ($CDCl_3$) 4·10 (m, 4H), 5·98 (s, 1H), and 7·16—7·86 p.p.m. (m, 4H) (Found: C, 68·5; H, 5·25; N, 7·05. $C_{10}H_9NO_2$ requires C, 68·6; N, 5·2; N, 8·0%). 2-(o-*Carbamoylphenyl*)-1,3-*dioxolan* was prepared from the nitrile by the standard procedure; m.p. 131—132° (from methylene chloride), $\nu_{max.}$ (Nujol) 3480, 3380, 3200, and 1615 cm^{-1} δ ([$^2H_6$]acetone) 4·00 (m, 4H), 6·22 (2, 1H), 6·9 (s, 2H), and 7·25—2·80 p.p.m. (m, d) (Found: C, 62·2; H, 5·8; N, 7·25. $C_{10}H_{11}NO_3$ requires C, 62·2; H, 5·7; N, 7·25%).

2-(p-*Carbamoylphenyl*)-1,3-*dioxolan*.— *p*-Cyanobenzaldehyde was converted into the dioxolan, the cyano-group of which was hydrolysed give the *amide*, m.p. 158—158·5° (from methylene chloride), $\nu_{max.}$ 3485, 3180, 1645, 1028, and 850 cm^{-1}, δ ([$^2H_6$]acetone) 4·05 (m, s), 5·83 (s, 1H), and 7·50—7·96 p.p.m. (AA'BB', 4H) (Found: C, 61·8; H, 5·85, N, 7·1%).

3-*Hydroxyphthalimidine*.—This was prepared by the reduction of phthalimide with magnesium and ammonium chloride in methanol;[17] m.p. 171—172° (lit.,[17] 178°), $\nu_{max.}$ (KBr) 3350, 3180, 3075, 1705, 1615, and 1060 cm^{-1}.

3-*Ethoxyphthalimidine*.—This was prepared by the method of Dunet and Willemart;[18] m.p. 104—104·5° (from aqueous ethanol) (lit.,[17] 108°), $\nu_{max.}$ (KBr) 3300—3000, 1710, 1620, 1605, and a complex of 8 sharp symmetrical peaks centred on 1090 and 750 cm^{-1}, δ ($CDCl_3$) 1·18 (t, *J* 7 Hz, 3H), 3·51 (q, *J* 7 Hz, 2H) 5·79 (s, 1H), and 7·18—7·91 p.p.m. (m, 4H). The signal of the NH system was not observed.

Attempted Characterisation of the Intermediate in the Hydrolysis of 2-Carbamoylbenzaldehyde Diethyl Acetal.—Three methods were used: isolation, following the reaction by n.m.r. spectroscopy, and following the reaction by i.r. spectroscopy.

Isolation. As the acetal is not very soluble in water it was necessary to use acetone–water as the hydrolytic medium. An aqueous buffer of pH 2·5 was mixed with an equal volume of the acetal (*ca.* 10%). The reaction was followed by t.l.c. and when all the acetal had reacted the mixture was poured into a large excess of water and extracted with a variety of organic solvents. However no product was ever found in the organic phase. The same procedure was repeated but the reaction mixture was neutralised and freeze-dried. The only organic material that was isolated was 3-hydroxyphthalimidine.

Following the reaction by n.m.r. spectroscopy. A solution of the acetal in [$^2H_6$]acetone–deuterium oxide (1 : 1) was made up in a dry box. [^2H]Trifluoroacetic acid (2 μl) was added and the pH (apparent) read from the meter (2·7). The solution was transferred to an n.m.r. tube and cooled to 0°. The spectrum was scanned every few min. The acetal proton resonance at δ 6·1 p.p.m. disappeard rapidly (half-life 5—6 min) and was replaced by a new resonance at δ 10·3 p.p.m. This resonance disappeared during *ca.* 25 min and a new resonance at δ 6·1 p.p.m. appeared. At the resolution used there was no change in the signals of the ethoxy-groups, but there were significant, though not readily interpretable, changes in the aromatic region. The spectrum after completion of the reaction was identical with that of a synthetic mixture of 3-hydroxyphthalimidine and ethanol in the molar ratio 1 : 2. The former was also shown to be present by t.l.c. This evidence suggests that the intermediate is 2-carbamoylbenzaldehyde with the signal at δ 10·3 p.p.m. being that of the aldehyde proton.

Following the reaction by i.r. spectroscopy. A solution of pH(apparent) 3·0 in dioxan–deuterium oxide (1 : 1) containing phosphoric acid was used. The solution was introduced quickly into an RIIC ' disposable cell ' of path length 0·1 mm. with silver chloride windows. After *ca.* 3 min the absorption at 1635 cm^{-1} had been replaced by an absorption at 1690—1670 cm^{-1}, which was in turn replaced by an absorption at 1705 cm^{-1} characteristic of 3-hydroxyphthalimidine. It is difficult to identify the intermediate from these results as so little is known about the position of the amide I band in aqueous solution and its dependence on structure.

Standardisation of the Glass Electrode in Aqueous Dioxan.

[15] A. I. Vogel, ' A Text Book of Practical Organic Chemistry,' 3rd edn., Longmans, London, p. 798.
[16] E. L. Eliel and D. E. Rivard, *J. Org. Chem.*, 1952, **17**, 1252.
[17] A. Dunet and A. Willemart, *Bull. Soc. chim. France*, 1948, 1045.
[18] A. Dunet and A. Willemart, *Bull. Soc. chim. France*, 1948, 887.

—An operational pH scale, pH*,[19] was established in aqueous dioxan by making use of the $_{s}pK_{a}$ values of acids that had been determined conductimetrically. For dioxan–water (1 : 1) the values determined for benzoic acid by Dunsmore and Speakman [20] were used. For this solvent the meter reading after calibration against aqueous buffers is not significantly different from pH*. For 82% dioxan–water the values of $_{s}pK_{a}$ determined by Harned [21] were used. It was necessary to apply a correction of +2·50 to the meter reading. Over the range pH* 8·5—11·0 the response of the electrode was linear to within the accuracy of the measurements. The response of the high temperature electrode (Radiometer type G 202BH) in 82% dioxan at 60° is not very satisfactory. It was therefore necessary to check the pH* values at 25° and to correct to 60° using the temperature coefficients [22] of the $_{s}pK_{a}$ values.

Kinetic Measurements.—By gas chromatographic estimation of ethanol or methanol. A Perkin-Elmer F11 flame ionisation instrument was used with a Honeywell–Brown recorder equipped with a disc integrator. The packing was 10% Carbowax 400 on 100—200 Celite or (more satisfactorily) Poropak Q. Below 65° the reaction mixture was contained in a graduated flask sealed with a serum cap and above 65° in sealed ampoules. The mixture was neutralised with solid sodium carbonate and 0·5 μl of the neutralised solution was injected into the chromatogram. The mixtures contained n-propanol as an internal standard. Rate constants were calculated from the integrated first-order rate equation using a linear least-squares method.

Spectrophotometric method. A Unicam SP 800 or a Hilger–Gilford spectrophotometer was used. Buffer (3 ml) was placed in the cell and stock solution (30 μl) was added from a Hamilton syringe. The absorbances at convenient time intervals were read from the chart and rate constants were calculated from the integrated first-order rate equations using a linear least-squares method. The method of sealed bulbs was used for reactions at temperatures higher than 60°.

Polarimetric method. A Perkin-Elmer 141 polarimeter was used with light of wavelength 360 nm. The change in rotation with time was recorded on a strip-chart recorder and first-order rate constants were calculated as already described.

We thank the M.R.C. for financial support.

[1/1619 *Received, September 6th,* 1971]

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[21] H. S. Harned and L. D. Fallon, *J. Amer. Chem. Soc.*, 1939, **61**, 2377.
[22] *Cf.* R. A. Robinson and R. H. Stokes, 'Electrolyte Solutions,' Butterworths, London, revised edn., 1965, p. 538.