152. *The Effect of Varying the Cation in Some Organic Reactions requiring an Alkaline Medium.*

By O. L. Brady and J. Jakobovits.

In the methylation of lactam–lactim tautomerides in alkaline media with methyl sulphate the nature on the alkali appreciably alters the ratio of *O*- to *N*-methylation, the most marked difference being between sodium hydroxide and a tetra-alkylammonium hydroxide.

In the Reimer–Tiemann reaction, with sodium hydroxide the ratio of *ortho*- to *para*-substitution is approximately 2 : 1, with cæsium hydroxide 1 : 1, and with methyltriethylammonium hydroxide 1 : 2.

Kinetic studies have been made of the hydrolysis of a number of esters. With methyl sulphate, in 0·1N-alkali in aqueous methyl alcohol, change of alkali has little effect; but with ethyl sulphate in 1N-alkali in aqueous methyl alcohol, passing from sodium hydroxide to methyltriethylammonium hydroxide approximately doubles the rate constant.

The hydrolyses of alkali alkyl phthalates $C_6H_4(CO_2M)CO_2R$, where M is Na or $NMeEt_3$, with the corresponding alkali hydroxide MOH show no difference in rate constants in aqueous solution, but in aqueous methyl alcohol the hydrolysis when M = Na has a rate constant about ten times that found when $M = NMeEt_3$.

An explanation of these results is suggested depending on formation of co-ordination complexes.

It has long been known that use of sodium and silver salts often gives different products in the alkylation of compounds capable of tautomerism, *e.g.*, in the methylation of isatin, cyanides, and nitrites, but the fact that these reactions are often, of necessity, carried out in hetereogenous media, with the solid salt, has deterred speculation on the causes of the different directions in which they proceed. A classical example of the effect of a change of metal within the same group of the Periodic Table is the Kolbe–Schmidt reaction, in which sodium phenoxide heated under pressure with carbon dioxide gives sodium salicylate but potassium phenoxide under similar conditions gives a large proportion of potassium *p*-hydroxybenzoate (Kolbe, *J. pr. Chem.*, 1874, [ii], **10**, 95; Brunner, *Annalen*, 1907, **351**, 326; Tijmstra Bz, *Ber.*, 1905, **38**, 1375; Johnson, *J. Amer. Chem. Soc.*, 1933, **55**, 3029). Neogi (*J.*, 1906, **89**, 1900; 1914, **105**, 2371; 1916, **109**, 701) found that when a sodium alkyl sulphate was fused with sodium nitrite the ratio of the yields of alkyl nitrite and nitroparaffin was 0·36 : 1, whereas it was 1·9 : 1 when the potassium salts were used. Here again solid salts were employed.

Graebe (*Annalen*, 1905, **340**, 244) noted that dry potassium benzoate gave, with methyl sulphate, a better yield of methyl benzoate than was obtained from sodium benzoate, and that potassium benzoate was methylated by potassium methyl sulphate more readily than by sodium methyl sulphate. Ullmann (*Ber.*, 1900, **33**, 2774; *Annalen*, 1902, **327**, 104) found that phenols were methylated equally well in sodium hydroxide or potassium hydroxide solution or in the form of the solid sodium or potassium phenoxide. Klemenc (*Monatsh.*, 1917, **38**, 553) found that, in the methylation with methyl sulphate of quinol and resorcinol in aqueous alkali, potassium hydroxide gave a much smaller yield than sodium hydroxide, suggested that the former hydrolysed methyl sulphate faster than did the latter, and confirmed this by measuring the rate constants of the heterogeneous hydrolysis of methyl sulphate by N-alkali at 11°, finding $k_{\mathrm{KOH}}/k_{\mathrm{NaOH}} = 1{\cdot}25$.

These reactions were carried out in a heterogeneous medium and might be accounted for by different rates of diffusion of methyl sulphate into the alkaline solutions, or by greater solubility of methyl sulphate in potassium hydroxide solution, as well as by a specific effect of the cation.

Walden and Centnerszwer (*Z. Elektrochem.*, 1909, **15**, 310) however, measured the rate constants of the reaction

$$\mathrm{Me_2SO_4 + MCNS = MeCNS + MeMSO_4}$$

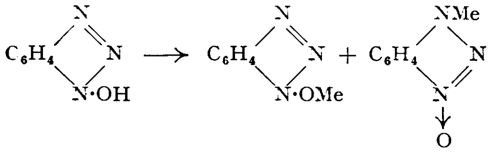
where M = Na or K, in homogeneous methyl alcoholic solution and found for 0·5N-solution $k_{\mathrm{K}}/k_{\mathrm{Na}} = 1{\cdot}14$, for 0·25N-solution 1·06, and for 0·125N-solution 1·34.

Other reactions are recorded in which the rate constants with different alkalis appear to be unchanged; for example, Meyer (*Z. anorg. Chem.*, 1921, **115**, 212) could not detect an appreciable difference in the rate constants for the hydrolysis of ethyl acetate by the hydroxides of lithium, sodium, potassium, rubidium, and cæsium in approximately N./10-solution. It will be shown later, however, that this is too low a concentration to show an effect of variation in the cation.

Reimer and Tiemann (*Ber.*, 1876, **9**, 824) state that, contrary to experience in the Kolbe–Schmidt reaction, in their synthesis of hydroxy-aldehydes the proportion of *ortho*- and *para*-derivatives is unaffected by changing from sodium hydroxide to potassium hydroxide; and Walden (*Ber.*, 1899, **32**, 1833), for the hydrolysis of α-chlorosuccinic acid by 0·4N-alkali, found that the rotation of the malic acid obtained differed considerably according to the alkali used (LiOH +100°; NaOH +150°; KOH +425°; RbOH +440°; aq. $\mathrm{NH_3}$ +460°).

The effect of varying the cation has now been investigated further, first, on the products of methylation of tautomeric compounds, secondly on the proportion of *ortho*- : *para*-substitution in the Reimer–Tiemann reaction, and thirdly on the hydrolysis of esters.

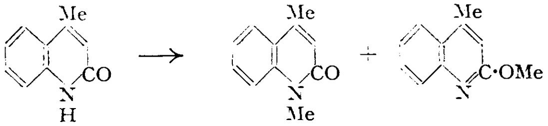
In studying methylation it was necessary to choose a compound, stable to alkali, which gave reasonable amounts of the isomeric methyl derivatives. Such was found in 1-hydroxybenztriazole which with methyl sulphate in 2N-alkli gave two methyl derivatives (Brady and Reynolds, *J.*, 1928, 198; 1931, 1273). The ratio *O*-Me/*N*-Me formed in 2N-MOH was LiOH 1·12, NaOH 0·97, KOH 1·02, RbOH 1·17, CsOH 1·26, and $\mathrm{NMeEt_3{\cdot}OH}$ 1·53. Although the accuracy of the results is not sufficient to dogmatise on the effect of the change from one alkali-metal to another the difference between sodium hydroxide and methyltriethylammonium hydroxide seems well outside the limit of experimental error, and probably the difference between sodium hydroxide and cæsium hydroxide is also significant.



Since sodium hydroxide and methyltriethylammonium hydroxide gave the greatest difference, in subsequent experiments the hydroxides of cæsium and rubidium were not always used on account of the lengthy task of continually recovering the limited amounts of the materials.

Lithium hydroxide could not always be employed owing to the sparing solubility of lithium salts, which crystallised out and altered the conditions of the experiment.

2-Hydroxylepidine can be methylated by methyl iodide in methyl alcohol in the presence of alkali methoxide. With sodium methoxide, the ratio *N*-Me/*O*-Me is 4·5, with potassium methoxide is 10·8, and with $NMeEt_3$·OMe is ∞ . In the last case no trace of the *O*-Me compound, but 82% of the *N*-Me compound, was obtained.



The improvement in technique afforded by the determination of aldehydes by dinitro phenylhydrazine has enabled us to show the effect of change of alkali in the Reimer–Tiemann reaction where the original authors failed (*loc. cit.*). In 15N-alkali the *ortho-para*-ratio was NaOH 2·08, KOH 1·24, CsOH 0·98, and $NMeEt_3$·OH 0·52. In 2N-alkali the difference almost disappeared, the ratio being NaOH 0·90, KOH 0·91, and $NMeEt_3$·OH 0·86. In 15N-lithium hydroxide the ratio was 0·9 but, as much lithium phenoxide crystallised out, the concentration in solution was low.

The yields of aldehyde in the Reimer–Tiemann reaction were of the usual low order (Armstrong and Richardson, *J.*, 1933, 496) and the results would not be credible were they not so remarkable and repeatable within reasonable limits. On changing from sodium hydroxide to methyltrimethylammonium hydroxide the product changes from *o*-/*p*- = 2 : 1 to *o*-/*p*- 1 : 2.

The experiments so far described did not admit of very accurate measurements, so a kinetic investigation has been made of the hydrolysis of esters by various alkalis in homogeneous media, with the following results :

Hydrolysis of Me_2SO_4 *in* 50% *v*/*v aqueous* MeOH *at* 0°.

Alkali.	Concn., N.	10^3k_2, sec.$^{-1}$.
NaOH	0·1000	2·61
KOH	0·1022	2·57
$NMeEt_3$·OH	0·1037	2·52

The differences are within the experimental error, so at this concentration of alkali no effect is observed.

Methyl sulphate in aqueous methyl alcohol is decomposed much too rapidly by stronger alkalis for kinetic measurements to be made, so the less reactive ethyl sulphate was substituted, with results as follows :

Hydrolysis of Et_2SO_4 *in* 90% *v*/*v aqueous* MeOH *at* 0°.

Alkali.	Concn., N.	10^5k_2, sec.$^{-1}$.
NaOH	1·0328	7·5
KOH	1·0328	9·5
$NMeEt_3$·OH	1·0534	16·9

Owing to the difficulty in obtaining accurate results in kinetic measurements at these concentrations, it would be unwise to place too much reliance on the difference between sodium and potassium hydroxides, but the difference between sodium and methyltriethylammonium hydroxides is too large to be due to experimental error.

The use of methyl alcohol as a solvent introduces possible complications, so esters were investigated which could be hydrolysed in homogeneous aqueous solution.

The hydrolysis of methyl methanesulphonate in 1·026N-aqueous sodium hydroxide at 25° gave $k_2^{25} = 5·5 \times 10^{-4}$ sec.$^{-1}$ and in 1·026N-aqueous methyltriethylammonium hydroxide gave $k_2^{25} = 9·4 \times 10^{-4}$ sec.$^{-1}$.

The alkali alkyl phthalates *o*-$RO_2C·C_6H_4·CO_2M$ (R = alkyl, M = Na, K, or $NMeEt_3$) at 25° or 0°, in both water and 90% methyl alcohol, were hydrolysed with the corresponding alkali hydroxide; for comparison ethyl acetate was hydrolysed in 90% methyl alcohol at 0°. The rate constants are given in Table I. In 0·1N-alkali no effect is observable, even in aqueous methyl alcohol. In N-alkali the effects are not marked in aqueous solutions, except in the case

TABLE I.

Water.		90% Methyl alcohol.	
Alkali (+)-sec.-*octyl phthalate at* 25°.			
1·026N-NaOH	$6{\cdot}2 \times 10^{-6}$	—	—
1·026N-$NMeEt_3$·OH	$6{\cdot}95 \times 10^{-6}$	—	—
Alkali sec.-*butyl phthalate at* 25°.			
1·026N-NaOH	$1{\cdot}8 \times 10^{-4}$	1·047N-NaOH 0·985N-KOH	$1{\cdot}4 \times 10^{-5}$ $1{\cdot}1 \times 10^{-5}$
1·026N-$NMeEt_3$·OH	$1{\cdot}8 \times 10^{-4}$	1·077N-$NMeEt_3$·OH	$0{\cdot}092 \times 10^{-5}$
Alkali methyl phthalate at 25°.			
1·005N-NaOH	$4{\cdot}33 \times 10^{-3}$	0·9847N-NaOH	$1{\cdot}25 \times 10^{-4}$
1·026N-$NMeEt_3$·OH	$3{\cdot}5 \times 10^{-3}$	1·108N-$NMeEt_3$·OH	$0{\cdot}14 \times 10^{-4}$
Alkali methyl phthalate at 0°.			
1·005N-NaOH	$5{\cdot}0 \times 10^{-4}$	—	—
1·026N-$NMeEt_3$·OH	$5{\cdot}0 \times 10^{-4}$	—	—
Ethyl acetate at 0°.			
—	—	1·0328N-NaOH	$1{\cdot}66 \times 10^{-4}$
—	—	1·0328N-KOH	$1{\cdot}66 \times 10^{-4}$
—	—	1·0328N-$NMeEt_3$·OH	$1{\cdot}17 \times 10^{-4}$

of methyl methanesulphonate where $k^{25}_{\text{Am}}/k^{25}_{\text{NaOH}} = 1{\cdot}7$ (k_{Am} refers to the quaternary ammonium base), but in 90% methyl alcohol in the hydrolysis of ethyl sulphate $k_{\text{Am}}/k_{\text{NaOH}} = 2{\cdot}2$, of alkali *sec.*-butyl phthalate $k^{25}_{\text{Am}}/k^{25}_{\text{NaOH}} = 0{\cdot}066$ and of alkali methyl phthalate $k^{25}_{\text{Am}}/k^{25}_{\text{NaOH}} = 0{\cdot}112$.

The most significant fact is that in the same solvent methyltriethylammonium hydroxide hydrolyses ethyl sulphate more rapidly, but an alkali alkyl phthalate less rapidly, than does sodium hydroxide. It seems impossible to suppose that the difference in rate constants is due simply to variation of hydroxyl-ion concentrations in the solutions, and one must seek an explanation in the nature of the compound hydrolysed.

The first difference in nature of the substance hydrolysed is that whereas the esters of carboxylic acids on alkaline hydrolysis normally undergo acyl–oxygen fission (see Day and Ingold, *Trans. Faraday Soc.*, **1941**, **37**, 689, for a summary of the evidence) methyl methanesulphonate on aqueous alkaline hydrolysis undergoes alkyl–oxygen fission by a bimolecular mechanism (Ader, University of London Ph.D. Thesis, "Mechanism of Sulphonic Ester Hydrolysis," **1949**), and ethyl sulphate on interaction with alcohol in the presence of water and sodium hydroxide undergoes mainly an alkyl–oxygen fission (Lauder and Green, *Nature*, **1946**, **157**, 767).

In aqueous methyl alcoholic solutions both hydroxyl and methoxyl ions will exist: $MOH \rightleftharpoons M^+ + HO^-$; $HO^- + HOMe \rightleftharpoons H_2O + MeO^-$. In acyl–oxygen fission attack by MeO^- does not lead to a change in the acid titre:

$$R'{\cdot}CO_2R + MeO^- \rightleftharpoons R'{\cdot}CO_2Me + RO^-$$

but with alkyl–oxygen fission the titre changes:

$$O_2S(OEt)_2 + MeO^- \longrightarrow O_2S(O^-)(OEt) + EtOMe$$

An explanation might be suggested, therefore, that in a solution of methyltriethylammonium hydroxide in 90% methyl alcohol the methoxyl-ion concentration is higher than in a corresponding solution of sodium hydroxide, and vice versa for the hydroxyl-ion concentration. This would account for the slower action of the ammonium base on the carboxylic esters and might account for its more rapid action on ethyl sulphate. If this were the explanation one would expect a similar change of the same order in the rate constant of the hydrolysis of ethyl acetate, but in this case a decrease of only 30% is observed whereas in the phthalates there is a factor of ten.

In experiments using methyl alcohol as a solvent a complication may arise when a different alcohol is produced from the ester, since the rate constant may be a composite figure representing the following reactions:

$$R'{\cdot}CO_2R + HO^- \longrightarrow R'{\cdot}CO_2H + RO^-$$
$$R'{\cdot}CO_2R + MeO^- \rightleftharpoons R'{\cdot}CO_2Me + RO^-$$
$$R'{\cdot}CO_2Me + HO^- \longrightarrow R'{\cdot}CO_2H + MeO^-$$

This might be the case for the hydrolysis of alkali *sec.*-butyl phthalate in methyl alcohol, but not for the hydrolysis of alkali methyl phthalate in methyl alcohol. Since, however, the rate constant for the hydrolysis of sodium *sec.*-butyl phthalate by sodium hydroxide is approximately one-tenth of that of sodium methyl phthalate by sodium hydroxide and the rate constant for the hydrolysis of methyltriethylammonium *sec.*-butyl phthalate by methyltriethylammonium hydroxide is also approximately one-tenth of that of methyltriethylammonium methyl phthalate, it can be assumed that this complication plays but a small part in the difference between the rate constants obtained with sodium hydroxide and methyltriethylammonium hydroxide. It seemed desirable, in the first instance, to confine these experiments to one solvent alcohol, to avoid ambiguities caused by possible variation in the alkoxyl : hydroxyl ratio in changing from one alcohol to another, or by different facilities of various alcohols for forming co-ordination compounds.

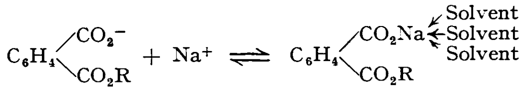
It might be held that different solvation of the cations would have an influence. The primary solvation would be in the order $Na^+ > K^+ \gg MeEt_2N^+$ (cf. Bockris, *Quart. Reviews*, **1949**, **3**, **173**), and if water molecules solvated the cations more readily than methyl alcohol molecules the concentration of HO^- compared with MeO^- in 90% methyl alcohol would be reduced more by Na^+ than by $MeEt_3N^+$ owing to the removal of water in the equilibrium $HO^- + HOMe \rightleftharpoons MeO^- + H_2O$, but this would decrease the rate of hydrolysis by sodium hydroxide compared with that by methyltriethylammonium hydroxide. If, on the other hand, there was preferential solvation by methyl alcohol, a greater increase in HO^- concentration would result from Na^+ than from $MeEt_3N^+$, but owing to the high proportion of methyl alcohol the difference would probably be very small. Further, solvation would not surmount the difficulty of explaining an opposite effect of the cations in the hydrolysis of ethyl sulphate and methyl methanesulphonate.

Neither of these explanations can be used to account for the differences observed in the alkylation of tautomerides and in the Reimer–Tiemann reaction in which alteration in the orientation of substitution is observed.

An explanation, which covers all cases and can be extended to numerous other reactions where a difference is observed between the alkali hydroxides, concerns the ease with which the different cations can form stable covalent links with the organic compound under investigation.

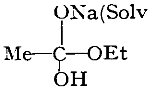
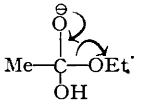
Other evidence leads to the conclusion that, with the alkali metals, the tendency to form stable covalent bonds decreases from sodium to cæsium ; the nitrogen in the tetra-alkylammonium ion, having already a completed octet of electrons, is unlikely to form other stable covalent bonds.

In the case of the half esters of phthalic acid a solution of the tetra-alkylammonium salt may, therefore, be regarded as being almost completely ionised, but a solution of the sodium salt will consist of the equilibrium mixture :

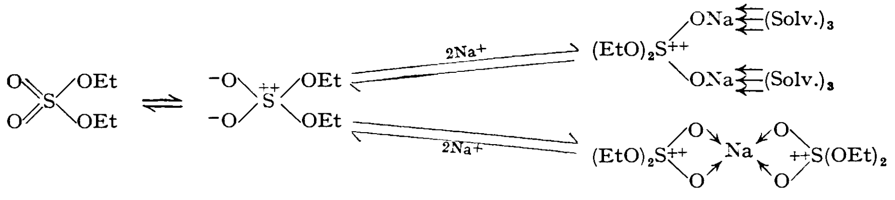


$$C_6H_4\begin{cases}CO_2^-\\CO_2R\end{cases} + Na^+ \rightleftharpoons C_6H_4\begin{cases}CO_2Na\leftarrow(\text{Solvent})_3\\CO_2R\end{cases}$$

The compound undergoing hydroysis in the two cases will therefore not be the same. In view of the negative charge on the carboxyl group in the ion this will hydrolyse less rapidly than the sodium co-ordination compound. The equilibrium in the sodium salt would move to the right on passing from an aqueous to an alcoholic medium and to the left on reduction of concentration of the reactants in the solvent. The experimental rate constants are in accordance with these considerations.

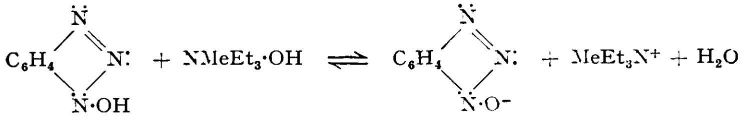
In ethyl acetate a much smaller effect would be expected although it might still exist, for in the transition state  $Me{-}C(ONa(Solv.)_3)(OH){-}OEt$ would be less likely to give the acid than  $Me{-}C(O^-)(OH){-}OEt$.

In ethyl sulphate the sodium ions can accept electrons from the co-ordinately linked oxygens and from the solvent, thus :



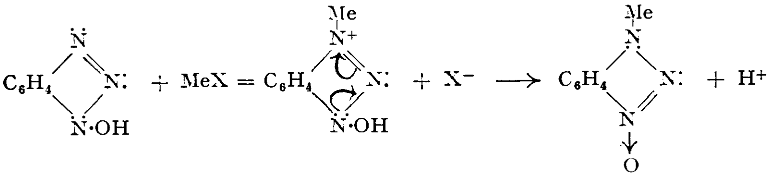
Any such tendency to neutralise the negative charge on oxygen will enhance the positive charge on sulphur which would favour alkyl–oxygen fission, but in view of the tendency of the sulphur atom to increase its octet the hydroxyl ion will be strongly attracted to the S^{++} centre. If only one hydroxyl ion attacks, the sulphur atom will still bear a positive charge and there will be little tendency for acyl–oxygen fission to occur with escape of EtO^-; this might be expected only if two hydroxyl ions attacked at the same time, but such a termolecular reaction would be very slow. The sodium complex is accordingly less easily attacked by sodium hydroxide than by the tetra-alkylammonium hydroxide.

We turn now to the methylation of tautomeric compounds; in solutions of 1-hydroxybenztriazole in tetra-alkylammonium hydroxide the undissociated compound (I) and the ion

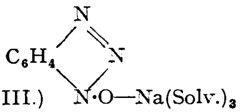


(I.) (II.)

(II) will be present. In (I) attack will occur at the oxygen atom, leading to the formation of 1-methoxylbenztriazole, but in (I) attack at nitrogen will be favoured, followed by elimination of a proton owing to electron withdrawal by the N^+, leading to the formation of 3-methylbenztriazole 1-oxide.



Brady and Reynolds (*loc. cit.*) showed that in the absence of alkali and solvent 1-hydroxybenztriazole suffered only *N*-methylation, and Brady and Day (*J.*, 1923, **123**, 2258) showed that in the substituted hydroxybenztriazoles (*e.g.*, the nitro-compounds) the more acidic the compound, and consequently the less hydrolysed its salts in aqueous solution, the greater the preponderance of *O*-alkylation.

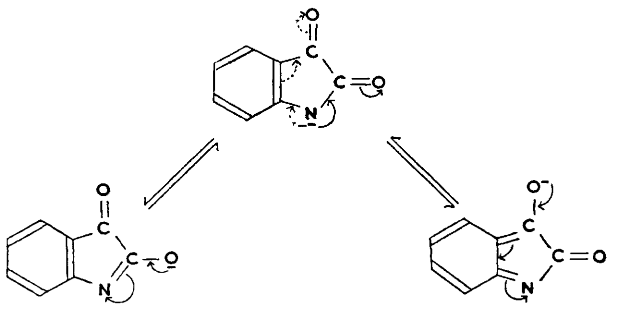


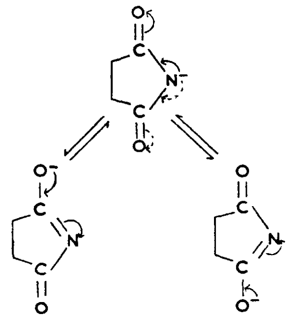
(III.)

In the presence of sodium hydroxide the solution will contain a third species (III), in which attack at nitrogen will be favoured; so the proportion of *N*-methylation increases. The proportion of (III) falls on passing from sodium to cæsium, so the proportion of *N*-methylation also falls.

A methyltriethylammonium hydroxide solution of 2-hydroxylepidine, which, on our argument, should contain essentially ions only, gave, on methylation, only the *N*-methyl compound.

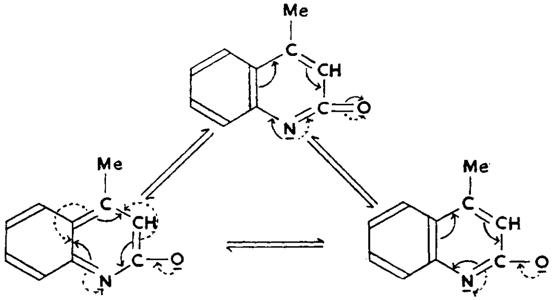
No explanation seems to have been advanced for the *N*- rather than the *O*-alkylation of the sodium salts of lactam–lactim tautomerides such as isatin, phthalimide, and 2-hydroxypyridine. In isatin and the cyclic imides an electron pair on a negatively charged nitrogen can move in two directions, *viz.*:





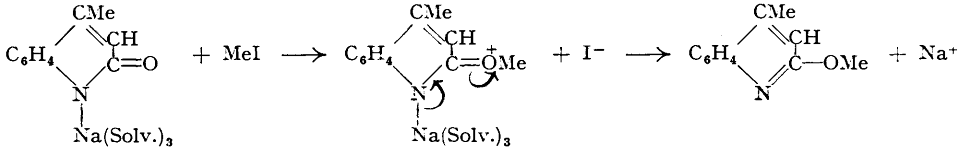
but, in the mesomeric ions produced, the electron pair on the negatively charged oxygen can move only in one direction. It seems reasonable, therefore, to suppose that the ion with the negative charge associated with nitrogen contributes more than do the ions with the negative charges associated with oxygen to the structure of the resonance ion and, consequently, that the nitrogen atom will be attacked by an electrophilic reagent such as Me^+. A similar explanation can be offered for the exclusive *C*-alkylation of, *e.g.*, ethyl sodiomalonate.

The case of 2-hydroxylepidine or 2-hydroxypyridine is more complex. When the negative charge is on nitrogen the electron pair can again move in two directions, whilst in the ions with the charge associated with oxygen the electron pair can move only in one direction, but the latter ions are interconvertable by electron shift within the benzenoid ring, thus :



It is noteworthy that the ion of hydroxybenztriazole, which becomes alkylated on oxygen, does not exhibit this peculiarity, nor does the oximino-ion $R{\cdot}CH{=}N{-}O^-$, which also becomes alkylated on oxygen (Brady and Goldstein, *J.*, 1926, 2403; Brady and Jackson, unpublished).

As the negative charge on the 2-hydroxylepidine ion is associated mainly with the nitrogen atom, *N*-alkylation is explicable in tetra-alkylammonium hydroxide solution, but in sodium hydroxide solution, owing to the tendency to form a co-ordination compound, some *O*-methylation can occur by the following mechanism :

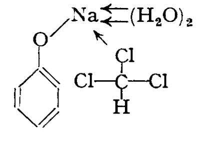


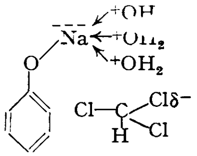
In the Reimer–Tiemann reaction the significant stage is entry of the $-CHCl_2$ into the nucleus

$$C_6H_5{\cdot}OM + CHCl_3 + M^+ + HO^- = MO{\cdot}C_6H_4{\cdot}CHCl_2 + M^+ + Cl^- + H_2O$$

In the presence of 15N-tetra-alkylammonium hydroxide no un-ionised phenol would be present and no co-ordination compound, so that the only reacting species would be the phenoxide ion. In these circumstances substitution yields approximately 2 parts of *p*- to 1 of *o*-compound; the preponderance of *para*-substitution is in accordance with expectation in view of the strong electromeric effect of the negative pole. When 15N-sodium hydroxide is employed a different state of affairs can exist: either chloroform or solvent molecules or both can co-ordinate with the sodium :

(IV.)

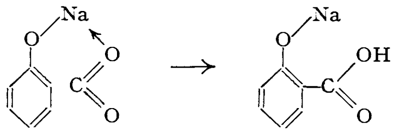




(V.)

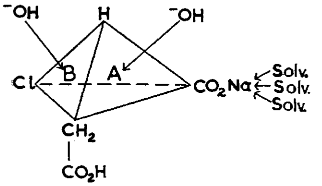
In either case the chloroform is presented to the *ortho*-position since in (V) the positive charges on the solvent molecules will tend to attract the lone electrons on the chlorine. On passing from sodium hydroxide to potassium hydroxide and cæsium hydroxide the extent of co-ordination will decrease and the amount of *ortho*-substitution decreases.

Ingold (*Ann. Reports*, 1926, **23**, 142) has suggested a similar explanation of the nuclear alkylation of phenols through their salts in non-ionising solvents where the substituent enters exclusively at the *ortho*-position. The same idea has been invoked in the Kolbe–Schmidt reaction which has been shown to involve, probably, direct substitution at nuclear carbon and not intermediate formation of sodium phenyl carbonate (Tijmstra Bz, *Ber.*, 1905, **38**, 1375; Johnson, *J. Amer. Chem. Soc.*, 1933, **55**, 3029).



The above authors state no reasons for the difference in behaviour between sodium and potassium phenoxide, but it could be caused by a reduced stability of the potassium co-ordination compound.

When the Reimer–Tiemann reaction is carried out in less concentrated solutions, *e.g.*, in 2N-alkali, the *ortho–para* ratio, when tetra-alkylammonium hydroxide is used, corresponds to the substitution of the phenoxide ion plus that of free phenol formed by hydrolysis. When 2N-sodium hydroxide is used, only a small amount of co-ordination compound is formed, so that the *ortho–para* ratio is not appreciably altered.



If the view put forward is correct a number of other phenomena are capable of a similar explanation. In the Walden inversion previously mentioned, if co-ordination compounds are formed at the carboxyl group attached directly to the asymmetric carbon atom, steric hindrance might well hinder the approach of the hydroxyl ion to face *A* as required for inversion, and approach to face *B* involving no inversion would be favoured. The increase in inversion found by Walden (*loc. cit.*) was in the order LiOH $<$ NaOH $<$ KOH $<$ RbOH $<$ NH_4OH, that is, as the probability of co-ordination compound formation decreased.

EXPERIMENTAL.

Preparation of Alkalis.—Solutions of sodium hydroxide and potassium hydroxide were made up with the usual precautions to avoid all but small amounts of carbonate, diluted with water or methyl alcohol, and checked against standardised hydrochloric acid. Rubidium and cæsium hydroxides were prepared from the sulphates and barium hydroxide. Methyltriethylammonium hydroxide solutions were prepared by shaking a weighed amount of the iodide with the solvent and 1·3 equivalents of silver oxide for 10—20 hours until a filtered test portion gave no precipitate with nitric acid and silver nitrate; the precipitate was allowed to settle, and the solution siphoned off, titrated with hydrochloric acid, and the strength adjusted. Precautions were taken to avoid contamination with carbon dioxide.

Methylation of 1-*Hydroxybenztriazole.*—The hydroxybenztriazole was prepared *via o*-nitrophenylhydrazine. 1-Methoxybenztriazole and 3-methylbenztriazole 1-oxide were prepared for test of the analytical method (Brady and Reynolds, *J.*, 1928, 196).

The hydroxybenztriazole (1·5 g.; 0·011 mol.) was dissolved in 2N-aqueous alkali (6 c.c.), and redistilled methyl sulphate (1·1 c.c.; 0·011 mol.) added. The mixture was thoroughly shaken for 10 minutes whereupon the solid ethers began to separate, and after 50 minutes were repeatedly extracted with chloroform. The combined extracts were dried (Na_2SO_4), the solvent was removed, and the residue dried in an evacuated desiccator. The relative amounts of *O*- and *N*-methyl derivatives were determined by Zeisel and Herzig–Meyer estimations. As the amounts of silver iodide formed did not correspond to the total quantity of the mixed *N*- and *O*-methyl compound employed, determinations were carried out with the pure derivatives. The *O*-methyl compound gave an almost theoretical yield of silver iodide, but the *N*-methyl compound gave approx. 61%. This determination was reproducible within 1%; the loss is probably caused by migration of some of the methyl into the benzene nucleus on heating of the hydriodide. In column 6 of Table II a correction has been applied to the content of *N*-methyl compound which is calculated from $(1 + 39/61)$ time the actual weight of silver iodide. The total amount of methyl compounds (column 7 of Table II) then varies from 87 to 100%, with an average of 93%.

Methylation of Hydroxylepidine.—2-Hydroxylepidine was prepared by the method of Laver and Kaslow (*Org. Synth.*, **24**, 68); the *O*- and *N*-methyl derivatives were prepared for comparison (Knorr, *Annalen*, 1886, **236**, 97; Knorr and Autrick, *Ber.*, 1884, **17**, 2876). A Zeisel estimation for the pure *O*-methyl compound gave a 98% yield of methyl iodide, and a Herzig–Meyer estimation for the *N*-methyl compound a 95% yield.

The hydroxylepidine (3 g.) was added to 2N-alkali methoxide (9 c.c.) in methyl alcohol (slightly more than 1 equiv.) together with methyl iodide (2·3 c.c.; 1·5 equivs.), and the whole heated under reflux for 30 minutes; a further 3 c.c. of the methoxide solution and 1 c.c. of methyl iodide were then added, and heating was continued for a further 90 minutes. The solution was diluted with water and made strongly alkaline with aqueous sodium hydroxide. The methylation products were extracted with ether, the extract was dried (Na_2SO_4), the solvent removed, and the solid residue dried in a vacuum-desiccator. The yield of crude ethers was about 80% of the theoretical. The quantities of *O*- and *N*-methyl derivatives were determined as before. The results are given in Table III.

TABLE II.

2N-Alkali.	Expt.	Wt. (g.) of crude methyl compounds from 1·5 g. of triazole.	OMe, %.	NMe, %, found.	NMe, %, corr.	Total OMe and NMe, %.	Ratio, OMe/NMe.	Mean.
LiOH	*a*	1·03	50·0	27·6	45·2	95·2	1·10	1·12
			49·8	26·9	44·1	93·9	1·13	
	b	1·01	50·7	27·6	45·2	95·9	1·12	
			50·7	26·9	44·1	94·8	1·14	
NaOH	*a*	1·00	48·2	31·7	51·9	100·1	0·93	0·97
	b	1·06	47·9	29·9	49·0	96·9	0·98	
	c	1·09	48·0	28·7	47·0	95·0	1·02	
	d	1·10	47·6	30·9	50·6	98·2	0·94	
KOH	*a*	1·28	46·3	28·7	47·0	93·3	0·99	1·01
	b	1·40	48·3	30·0	49·2	97·5	0·98	
	c	1·35	49·0	28·8	47·2	96·2	1·04	
			48·4	28·3	46·4	95·8	1·04	
RbOH	—	—	46·9	24·6	40·0	86·9	1·17	1·17
CsOH	*a*	1·30	49·0	24·3	39·8	88·8	1·23	1·26
			49·2	24·1	39·5	88·7	1·24	
	b	1·22	52·6	25·2	41·3	93·9	1·27	
			51·4	23·8	39·0	90·4	1·32	
$NMeEt_3{\cdot}OH$	*a*	1·35	54·5	21·0	34·4	88·9	1·58	1·53
			55·8	21·6	35·4	91·2	1·64	
	b	1·20	53·7	22·9	37·5	91·2	1·43	
			57·5	24·1	39·5	97·0	1·46	

TABLE III.

Alkali.	Expt.	OMe, %.	NMe, %.	Ratio, NMe/OMe.	Mean.	Alkali.	Expt.	OMe, %.	NMe, %.	Ratio, NMe/OMe.	Mean
NaOH	*a*	12·7	52·3	4·12	4·5	KOH	*a*	7·6	82·1	10·8	10·8
	b	21·5	75·7	3·52		$NMeEt_3{\cdot}OH$	*a*	0	82·6	∞	∞
	c	12·6	71·0	5·63							
	d	15·5	66·5	4·78							

In two qualitative experiments using the tetra-alkylammonium hydroxide no *O*-methyl compound was obtained.

Reimer–Tiemann Reaction.—Phenol (3 g.) was dissolved in approx. 15N-alkali (10 c.c.) under a reflux condenser and warmed at 50—60°. Chloroform (3 c.c.) was then added with vigorous shaking which was continued for 15 minutes. The mixture was then heated on a water-bath for 30 minutes. After cooling, the solution, which contained solid, was diluted until the solid dissolved, and then acidified with hydrochloric acid and distilled in steam, about 600 c.c. of distillate being collected. The distillate was transferrred to a graduated flask, concentrated hydrochloric acid added (200 c.c.), and the volume made up to 1000 c.c. with water; 50-c.c. lots were removed, and an equal volume of a solution of 2 : 4-dinitrophenylhydrazine hydrochloride was added. This reagent was prepared by suspending 2 : 4-dinitrophenylhydrazine (4 g.) in dilute hydrochloric acid (25 c.c.), adding concentrated hydrochloric acid (20 c.c.) with shaking and then a further 2 l. of 2N-acid. After being kept overnight the solution was filtered from the small amounts of undissolved material. The precipitated dinitrophenylhydrazone was kept for an hour to coagulate, filtered through a sintered-glass crucible, washed 3 times with 2N-hydrochloric acid, dried for 2 hours at 110°, and weighed. The residue from the steam-distillation was filtered whilst hot, cooled, and made up to 1 l. by concentrated hydrochloric acid (200 c.c.) and water. The *p*-hydroxybenzaldehyde was determined as above in 50-c.c. portions. Similar experiments were performed using 2N-alkali. The results are shown in Table IV.

Kinetic Experiments.—Methyl sulphate was repeatedly shaken with water until the aqueous layer was free from sulphate, dried (Na_2SO_4), and twice distilled at 6—7 mm., the portion boiling at 45—47° being collected. Ethyl sulphate was similarly purified, the fraction boiling at 57·5—60° being collected. *sec.*-Butyl hydrogen phthalate and methyl hydrogen phthalate were prepared by the standard method. We are indebted to Dr. J. Kenyon for a specimen of (+)-*sec.*-octyl hydrogen phthalate and to Dr. G. Ader for one of methyl methanesulphonate.

As an example of the technique employed the hydrolysis of methyl sulphate with an equivalent quantity of 0·1N-sodium hydroxide in 50% (v/v) aqueous methyl alcohol at 0° is described.

The methyl sulphate (*ca.* 0·5 c.c.; 1 mol.) was run into a thin, weighed, glass bulb, which was sealed and re-weighed. An amount of the 0·1N-sodium hydroxide solution exactly equivalent (1 mol.) to the methyl sulphate was cooled to 0° and the bulb crushed beneath its surface. After mixing, the solution was transferred to a stoppered flask, cooled in ice–water well stirred with a mechanical stirrer in a large lagged beaker. For experiments at 25° a thermostat was used. From time to time portions (5 c.c.)

of the solution were removed, the reaction was stopped by running the mixture into an equivalent of 0·1N-hydrochloric acid, and the acid formed during hydrolysis titrated against 0·05N-barium hydroxide (bromocresol-purple as indicator). The rate constants were calculated from the usual second-order equation, with results given in Table V.

TABLE IV.

Alkali:	15N.				2N.			
	ortho-, %.	*para-*, %.	*ortho-* : *para-*.	Mean.	*ortho-*, %.	*para-*, %.	*ortho-* : *para-*.	Mean.
NaOH	12·95	6·38	2·03	2·08	5·06	5·69	0·89	0·90
	9·38	4·03	2·33		4·52	5·02	0·90	
	10·95	4·94	2·21		4·11	4·52	0·91	
	10·25	5·56	1·85					
	8·84	4·44	1·99					
KOH	11·41	9·46	1·21	1·24	4·15	4·73	0·877	0·91
	12·24	9·71	1·26		4·86	5·25	0·923	
	10·79	8·55	1·26		4·90	5·25	0·931	
CsOH	7·35	7·64	0·96	0·98				
	8·19	8·05	1·01					
$NMeEt_3$·OH	3·90	6·43	0·61	0·52	2·16	2·43	0·87	0·86
	3·86	6·76	0·57		1·39	1·63	0·85	
	2·62	6·60	0·40					

TABLE V.

Time, secs., $\times 10^{-2}$.	Titration figures, c.c. (four expts.).				$10^3 k_2^0$, sec.$^{-1}$ (four expts.).			
6	1·4	1·4	1·4	1·4	2·70	2·70	2·70	2·70
12	2·35	2·45	2·35	2·35	2·51	2·70	2·51	2·51
18	3·0	3·2	3·1	3·1	2·36	2·61	2·48	2·48
24	3·8	—	4·05	3·8	2·51	—	2·81	2·51
30	4·45	4·5	4·5	4·45	2·63	2·71	2·71	2·68
36	4·9	4·85	4·8	4·9	2·63	2·60	2·55	2·63
42	5·15	5·1	5·2	5·0	2·50	2·48	2·56	2·56
54	5·8	5·7	5·7	5·9	2·53	2·43	2·43	2·65
66	6·4	6·4	6·5	6·25	2·65	2·66	2·77	2·50
78	6·65	6·7	6·95	6·8	2·51	2·58	2·87	2·71
144	8·0	8·0	8·1	8·2	2·75	2·75	2·90	3·11
258	—	8·7	—	—	—	2·60	—	—
864	10·1	10·05	10·2	10·0				
				Mean:	2·57	2·62	2·66	2·61

Overall mean $k_2^0 = 2·61 \times 10^{-3}$ sec.$^{-1}$.

With 0·1022N-KOH, the overall mean $k_2 = 2·57 \times 10^{-3}$ sec.$^{-1}$ with maximum deviations of +0·23 and −0·14.

With 0·1037N-$NMeEt_3$·OH the overall mean $k_2 = 2·52 \times 10^{-3}$ sec.$^{-1}$ with maximum deviations of +0·10 and −0·17.

TABLE VI.

Time, secs., $\times 10^{-2}$.	Titration figures, c.c. (2 expts.).		$10^5 k_2^0$, sec.$^{-1}$ (2 expts.).	
9	0·85	0·9	7·36	8·13
18	1·55	1·65	8·60	8·7
27	1·95	2·2	7·33	8·6
36	2·4	2·7	7·25	8·5
45	2·8	2·9	7·15	7·5
54	3·5	3·35	8·28	7·7
90	4·25	4·55	6·63	7·4
124·5	5·3	5·4	6·98	7·15
166·2	6·2	5·95	7·13	6·71
364	10·2	10·4		
		Mean:	7·41	7·70

The hydrolysis of ethyl sulphate was investigated at 0° with 1·5 equivalents of alkali in 90% (v/v) aqueous methanol. With 1·0328N-sodium hydroxide the results given in Table VI were obtained.

The deviation from the mean k_2^0 is as much as 16% but, as the concentrations were high and appreciable errors were likely owing to volume changes in mixing and to separation of solid sodium ethyl sulphate during the reaction, it was considered that the results were as satisfactory as could be expected.

With 1·0328N-potassium hydroxide the mean $k_2^0 = 9·5 \times 10^{-5}$ sec.$^{-1}$ with maximum deviations of +0·6 and −0·5, and with 1·0534N-$NMeEt_3$·OH $k_2^0 = 16·9 \times 10^{-5}$ sec.$^{-1}$ with maximum deviations of +1·2 and −1·8.

The maximum value for sodium hydroxide was k_2^0 8·7, and the minimum for potassium hydroxide was 9·0; it is thus uncertain whether there is any appreciable difference between these two alkalis, but the minimum for methyltriethylammonium hydroxide was k_2^0 15·1, which is about 1·75 times the maximum for sodium hydroxide and beyond the limit of experimental error.

Methyl methanesulphonate was added to an equivalent quantity of 1·026N-alkali and the reaction carried out in a thermostat at 25°. Portions (2 c.c.) were removed at intervals, run into ice-cold water (20 c.c.), and titrated against 0·0989N-hydrochloric acid (bromocresol-purple). Results are in Table VII.

TABLE VII.

1·026N-NaOH.			1·026N-NMeEt$_3$·OH.		
Time, secs., $\times 10^{-2}$.	Titre.	$10^4 k_2^{25}$, sec.$^{-1}$.	Time, secs., $\times 10^{-2}$.	Titre.	$10^4 k_2^{25}$, sec.$^{-1}$.
3·6	16·3	5·08	3·8	14·7	(8·35)
7·3	14·0	5·30	7·35	11·6	9·30
11	12·3	5·34	11	9·7	9·35
14·6	10·8	5·58	14·65	8·3	9·40
18·45	9·8	5·45	18·55	7·2	9·44
24	8·4	5·62	24	6·1	9·38
33	6·95	5·61	32·95	4·8	9·57
51	5·15	5·63	51·1	3·4	9·58
87	3·35	5·73	87	2·2	9·34
159	2·0	5·69	684	0·2	0·2
3 days	0·0				
	Mean :	5·5		Mean :	9·4

A weighed quantity of alkyl hydrogen phthalate was dissolved in exactly 2 equivalents of aqueous alkali, one being required to form the salt with the free carboxyl group, and the reaction carried out in a thermostat at 25°. Portions (2 c.c.) were removed at intervals, diluted with water (20 c.c.), and titrated against 0·1N-hydrochloric acid (phenolphthalein). (+)-*sec.*-Octyl hydrogen phthalate with 1·026N-sodium hydroxide gave a mean k_2^{25} 6·2 × 10^{-6} sec.$^{-1}$ with maximum deviations of +0·3 and −0·4. With 1·026N-NMeEt$_3$·OH k_2^{25} = 6·95 × 10^{-6} sec.$^{-1}$ with maximum deviations of +0·4 and −0·2. The rate constants, in view of the degree of accuracy, are too similar for a decision whether the difference is significant, especially as a complication arose owing to separation of octyl alcohol during the reaction.

sec.-Butyl hydrogen phthalate and methyl hydrogen phthalate were hydrolysed under similar conditions. Results are given in the Introduction.

The hydrolyses in 90% (v/v) methyl alcohol were carried out as in aqueous solution, a weighed quantity of the ester being dissolved in two equivalents of alkali in aqueous methyl alcohol and kept at 25°. With sodium hydroxide, solid sodium phthalate began to separate after about 8 hours and the values of the rate constants were not very concordant; this did not occur with potassium hydroxide or with methyltriethylammonium hydroxide. The results for *sec.*-butyl hydrogen phthalate are given in Table VIII.

TABLE VIII.

1·047N-NaOH.		0·985N-KOH.		1·077N-NMeEt$_3$·OH.	
Time, hours.	$10^5 k_2^{25}$, sec.$^{-1}$.	Time, hours.	$10^5 k_2^{25}$, sec.$^{-1}$.	Time, hours.	$10^5 k_2^{25}$, sec.$^{-1}$.
2	1·25	2	1·00	2 3	practically no reaction
3	1·16	3	0·91		
12·25	1·66	7	1·09	12·25	(0·041)
26·33	1·77	20·33	1·16	26·33	0·091
31·5	1·93	26·33	1·19	31·5	0·094
61·2	1·39	31·5	1·14	61·2	0·097
81·5	1·30	55·66	1·14	81·5	0·089
108	1·16	92	1·05	108	0·091
146	1·09			146	0·097
193·5	1·03			193·5	0·097
Mean :	1·38	Mean :	1·08	Mean :	0·093

With methyl hydrogen phthalate and sodium hydroxide, over the range 15—315 minutes, whereafter large amounts of sodium phthalate had separated, the mean k_2^{25} was 1·25 × 10^{-4} sec.$^{-1}$ with maximum deviations of ±0·3, and with methyl hydrogen phthalate and methyltriethylammonium hydroxide over the range 35—4440 minutes, the mean k_2^{25} was 0·14 × 10^{-4} sec.$^{-1}$ with a maximum deviation of ±0·01.

Methyl acetate in 90% (v/v) methyl alcohol was hydrolysed at 0° with 1·033N-alkali. Over the range 15—240 minutes with sodium hydroxide k_2^0 was 1·6 × 10^{-4} sec.$^{-1}$ with a deviation of ±0·2, with potassium hydroxide 1·7 × 10^{-4} sec.$^{-1}$ with a deviation of +0·3 and −0·2, and with methyltriethylammonium hydroxide 1·1 × 10^{-4} sec.$^{-1}$ with a deviation of +0·1 and −0·2.

THE SIR WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES,
UNIVERSITY COLLEGE, LONDON.

[*Received, October 7th,* 1949.]