252. *Reaction Kinetics and the Walden Inversion. Part I. Homogeneous Hydrolysis and Alcoholysis of β-*n*-Octyl Halides.*

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The mechanism of many substitutions having in past papers been related to structure through the examination of kinetics, it was decided to study the spatial orientation of substitution under kinetically defined conditions, thus to elucidate the rules of the Walden inversion in a more rational manner than has hitherto been attempted. The replacement of Hal by OR being taken as the starting point, data are here given for this substitution in the case in which the only substituents at the asymmetric centre, apart from the replaceable group, are hydrogen and alkyl groups: the example studied is the hydroxylation or ethoxylation of β-*n*-octyl chloride or bromide.

In order to interpret the results it is necessary to know the maximal rotatory powers of the factors and products, and the relation of configuration to sign of rotation; also the kinetics of substitution, and the specific rates of the constituent reactions. Evidence on these points is summarised. With this aid, we isolate the bi- and uni-molecular mechanisms, and, from observations of the optical effect of substitution under kinetically definite conditions, determine the stereochemical effect associated with each mechanism. We find that bimolecular substitution leads to inversion of configuration without associated racemisation, whilst unimolecular substitution causes inversion with considerable accompanying racemisation. Quantitative particulars are given.

In a series of papers entitled " Mechanism of Substitution at a Saturated Carbon Atom " we have attempted to bring mechanism as disclosed by reaction kinetics into intelligible relation with the structures of reactants and the physical conditions of reaction. For a general statement of the nature of the connexion revealed, it will be sufficient to refer to a summarising paper published early in 1935, although the principles there laid down have received more extensive illustration since. In this paper (Hughes and Ingold, J., 1935, 244) the steric orientation of substitution was briefly discussed; but this aspect of substitution—the question of what determines the occurrence or non-occurrence of the Walden inversion—seemed so especially important, and to involve so many obscure points, that it was decided to make it the subject of a special experimental campaign, some of the first results of which are now presented. In Parts I—V we report observations and the immediate conclusions to be derived from them, and in Part VI we outline in a more general manner the position of the subject as it appears to us at present.

This paper deals with the steric orientation of the hydrolysis and alcoholysis of β-*n*-octyl halides. The first point to be considered is the connexion between the configuration and sign of optical rotation of β-*n*-octyl alcohol in relation to the halides. As to this matter, Houssa, Kenyon, and Phillips (J., 1929, 1700) have adduced the following argument. Of the four reactions one (if not three) must involve inversion; the only one which could do so is the extrusion of the sulphonate group by the attack of acetate ions in ethyl alcohol (I), since this is the only reaction of the four which exchanges a bond attached to the asymmetric carbon atom. It is now assumed that an attack by chloride ions in ethyl alcohol on the organic sulphonate would proceed by a similar mechanism, and, like the attack by acetate ions, would be accompanied by an inversion of configuration. The

$$\begin{tikzcd}
d\text{-}C_8H_{17}\cdot OH \arrow[r, "R\cdot SOCl"] & d\text{-}C_8H_{17}\cdot O\cdot SOR \arrow[d, "O"'] & l\text{-}C_8H_{17}\cdot OH \arrow[d, "Ac_2O"] \\
& d\text{-}C_8H_{17}\cdot O\cdot SO_2R \arrow[r, "{[OAc]^-}"'] & l\text{-}C_8H_{17}\cdot OAc
\end{tikzcd} \qquad . \quad . \quad . \quad . \quad . \quad . \quad (I)$$

product of the reaction has a rotation of sign opposite to that of the alcohol from which the sulphonate was prepared, and, from the assumption that configuration is inverted in

$$d\text{-}C_8H_{17}\cdot O\cdot SO_2R \xrightarrow[Cl^-]{} l\text{-}C_8H_{17}Cl \quad . \quad . \quad . \quad . \quad . \quad . \quad \mathbf{(II)}$$

reaction (II), it follows that a β-*n*-octyl alcohol and chloride of like sign of rotation have corresponding configurations. The crux of this argument is the unproved assumption of an analogy of behaviour between acetate ions and halide ions; but, if we take a second step of the same kind and assume similarity of behaviour between the octyl sulphonate and the corresponding halides, we arrive at a conclusion which is undeniably correct: the

$$d\text{-}C_8H_{17}\cdot I \xrightarrow[I^-]{} l\text{-}C_8H_{17}\cdot I \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (III)$$

substitution has been proved by the radioactive indicator method essentially to involve inversion (Hughes, Juliusburger, Masterman, Topley, and Weiss, J., 1935, 1525). Furthermore, although the generalisations which have been proposed by Olson, by Polanyi, and by Hughes and Ingold concerning the occurrence of inversion are not quite identical, they all agree in placing reactions (I), (II), and (III) in the same case and predicting inversion for them all; and, as this is the result to which Houssa, Kenyon, and Phillips's argument leads, our confidence in the correctness of their inference is strengthened.

The same authors extended their conclusion to embrace β-*n*-octyl bromide and iodide on the basis of the following argument, also of a kind which we regard as convincing. On treatment with hydrogen chloride the alcohol gives a chloride with a rotation opposite in sign to that of the alcohol; therefore, by the previous demonstration, this reaction is accompanied by inversion. It is accordingly assumed that the reactions of the alcohol with hydrogen bromide and hydrogen iodide must involve inversion; and since the β-*n*-octyl bromide and iodide thus produced each have a rotation opposite in sign to that of the alcohol, it follows that the relation of rotation to configuration is the same for the three halides. Our results provide a second argument. When the chloride is alcoholised with sodium ethoxide in anhydrous ethyl alcohol, a β-*n*-octyl ethyl ether is formed, the sign of the rotation of which is opposite to that of the chloride:

$$d\text{-}C_8H_{17}\cdot Cl \xrightarrow[OEt^-]{} l\text{-}C_8H_{17}\cdot OEt \quad . \quad . \quad . \quad . \quad . \quad . \quad (IV)$$

It is known that a β-*n*-octyl alcohol and a β-*n*-octyl ethyl ether which have rotations of the same sign have the same configuration, because there is no change in the sign of rotation when the alcohol is etherified through its potassium derivative (Kenyon and McNicol, J., 1923, **123**, 14), a process which must necessarily retain the original configuration. It follows that the alcoholysis of the chloride involves inversion, and this is just what we should expect since reaction (IV) belongs to the same class of substitution as do (I), (II), and (III). It may safely be assumed that a corresponding alcoholysis of the bromide would involve inversion, and since the experiment leads to an ether having a rotation opposite in sign to that of the bromide, it follows that the relation of rotation to configuration is similar for the chloride and bromide. The general conclusion is that when β-*n*-octyl alcohol, its ethyl ether and any of the three halides have rotations of the same sign their configurations correspond.

With this basis for the translation of observations on rotatory power into terms of molecular configuration, we have set out to discover the changes of optical rotation which accompany the hydrolysis of β-*n*-octyl halides under various conditions; we have worked mainly with the bromide. In an accompanying paper (Hughes and Shapiro, this vol., p. 1192) it is shown that β-*n*-octyl bromide undergoes hydrolysis by both the bimolecular and the unimolecular mechanism :

$$\bar{O}H + C_8H_{17}{\cdot}Br \longrightarrow C_8H_{17}{\cdot}OH + \bar{B}r \quad . \; . \; . \; . \; . \quad (S_N2)$$

$$\left.\begin{array}{l} \qquad\quad C_8H_{17}{\cdot}Br \longrightarrow C_8H_{17}^{+} \quad + \bar{B}r \text{ (slow)} \\ \bar{O}H + C_8H_{17}^{+} \quad \longrightarrow C_8H_{17}{\cdot}OH \text{ (fast)} \end{array}\right\} \quad . \; . \quad (S_N1)$$

In general these reactions occur simultaneously, but it is possible to choose conditions such that each is more or less completely isolated from the other. There are additional simultaneous reactions leading to the production of octylene, but from our present point of view these processes simply put some of the material out of action, octylene being necessarily optically inactive. We made some observations on the kinetics of the reactions, but we wished to be able to make use of the more comprehensive kinetic data provided by Hughes and Shapiro, and on this account used the same solvent as they did, *viz.*, " 60% " aqueous ethyl alcohol : in this solvent ethyl octyl ether is formed as well as octyl alcohol. Therefore we had to consider the changes of optical activity associated, not only with the hydrolysis formulated above, but also with the corresponding alcoholysis.

Our method was to remove the octylene in the form of its dibromide, then to isolate the octyl alcohol and ethyl octyl ether together, and finally to separate these two substances by converting the former into its hydrogen phthalate. All these isolation processes take place without detectable enantiomeric change. It was unnecessary to hydrolyse the hydrogen phthalate, since the relation of its rotatory power to that of the octyl alcohol obtainable from it is known (" Organic Syntheses," **6**, 68).

Optically pure β-*n*-octyl alcohol has the rotation $[\alpha]_D^{17^\circ} \pm 9{\cdot}9^\circ$. We have used specimens having various rotations above ± 9°, because we needed only easily measurable rotations, not optical purity, and because the halides prepared from the alcohol would in any case be optically impure. As this last statement is contrary to a suggestion made by Pickard and Kenyon (J., 1911, **99**, 45; *Ber.*, 1912, **45**, 1592), we give the evidence. We also calculate the approximate rotation of optically pure bromide, because this datum enables us to express our results in a simple form.

The recorded rotatory powers of the halides prepared by various methods from the optically active alcohols are noted in Table I. In those cases in which the alcohol employed has not been quite fully resolved, the observed rotations of the halides are corrected to correspond to optically pure alcohol. It will be seen that in spite of the practical equality of the dextro- and lævo-rotations recorded for the halides prepared by Pickard and Kenyon using the hydrogen halides as reagents, considerably higher rotations than theirs have been obtained either with the same reagents or with others. It would appear that all the reagents hitherto employed are liable to bring about some degree of racemisation.

TABLE I.

Reagent.	Temp.*	$[\alpha]_D$.		Ref.	Reagent.	Temp.*	$[\alpha]_D$.		Ref.
Chloride.					*Bromide.*				
HCl	17°	+20·40°	−20·44°	1	HBr	17°	+27·53°	−27·47°	1
$SOCl_2$	Room	+33·5	—	2†	HBr	Room	+14·4	—	2†
$SOCl_2$, Pyridine	20	+33·7	—	3	$SOBr_2$, Pyridine	16·5	—	−26·1	3
$SOCl_2$	20	+35·8	—	4	HBr	20	+32·5	−26·9	5†
					Iodide.				
$SOCl_2$, Pyridine	20	+32·2	—	5†	HI	17	+39·83	−40·56	1

* Temperature at which rotations were measured.
† Rotations corrected to correspond to optically pure alcohol.

References.—(1) Pickard and Kenyon (*loc. cit.*). (2) Levene and Mikeska (*J. Biol. Chem.*, 1924, **59**, 473). (3) McKenzie and Tudhope (*ibid.*, 1924, **62**, 551). (4) Houssa, Kenyon, and Phillips (*loc. cit.*). (5) This paper. *Note.*—Other rotations at λ5461 for the chloride produced by various reagents are recorded by Houssa and Phillips (J., 1932, 108).

We can calculate an approximate value for the specific rotation of optically pure β-*n*-octyl bromide, the halide with which we are mainly concerned, in the following way. The highest recorded specific rotation is our value $[\alpha]_D^{20°}$ 32·5°; this is a lower limit. An upper limit follows from our observation that the same specimen of bromide could be hydrolysed back to an alcohol having 85·2% of the activity of the alcohol from which the bromide was originally made. This limit, 32·5°/0·852 = 38·1°, is obtained by supposing that the loss of enantiomeric identity occurs exclusively in the formation of the bromide, the hydrolysis occurring entirely without racemisation. Now this last supposition is untrue, but there are reasons (Part VI) for the belief that it would be very nearly true if the hydrolysis were to proceed exclusively by mechanism S_N2. On the other hand, the results recorded in this paper prove that considerable racemisation accompanies the hydrolysis of β-*n*-octyl bromide by mechanism S_N1. The particular hydrolysis which forms the basis of this computation occurs mainly by mechanism S_N2, but also partly by mechanism S_N1, and we can calculate the ratio $S_N2 : S_N1$ either from the kinetic measurements which we have made, or, more accurately, from data provided by Hughes and Shapiro (*loc. cit.*). The ratio is $S_N2 : S_N1 = 88 : 12$. Furthermore we show that, in the solvent used, the enantiomeric purity of material which is hydrolysed by the S_N1 process drops to 35% of its original value. Hence, if we assume no racemisation in the S_N2 reaction, the retention of enantiomeric purity in the total hydrolysis should amount to 92·2%, and the retention in the formation of the bromide to 85·2/0·922 = 92·4%. On this basis the specific rotation of the optically pure bromide would be $[\alpha]_D$ 35·1°. This figure is a closer upper limit, and we have another experiment which proves that it is still slightly too high. Using anhydrous ethyl alcohol as solvent, we have converted β-*n*-octyl bromide into an ethyl octyl ether the rotatory power of which, if calculated to correspond to a bromide having $[\alpha]_D$ 35·1°, comes out 3·8% greater than the rotatory power, $[\alpha]_D^{20°}$ 17·1°, of ether prepared directly from optically pure β-*n*-octyl alcohol by a method which cannot involve racemisation. The best value we can obtain for the rotatory power of the bromide is thus 35·1°/1·038 = 33·8°. This assumes that our etherification of the bromide proceeded without racemisation, as substantially it must have done. We etherified the chloride by exactly the same method, and, supposing that this reaction likewise went without racemisation, calculated the specific rotation of optically pure chloride to be $[\alpha]_D^{20°}$ 38·3°. The first of these figures is used below in estimating percentages of retention of enantiomeric purity, and any uncertainty attaching to the value cannot be large enough to affect the principal conclusions.

The bromide has been hydrolysed in boiling "60%" aqueous ethyl alcohol, *i.e.*, a mixture made from 60 vols. of anhydrous alcohol and 40 vols. of water, under the following conditions: (1) In the presence of potassium hydroxide in concentration which decreases during the reaction but always remains of the order 1·0*N*; in these circumstances both the hydrolysis and the alcoholysis are mainly bimolecular, but are also partly unimolecular. (2) In the absence of any added substance, the solution being neutral at the commencement of reaction but acid with hydrobromic acid during its progress; both the hydrolysis and alcoholysis are now unimolecular.

The bromide and chloride have also been alcoholysed by means of sodium ethoxide in anhydrous ethyl alcohol at the boiling points of the solutions. In these conditions, there is, of course, no hydrolysis; and the alcoholysis must be practically exclusively bimolecular as the action of the pure solvent on the halides is relatively very slow.

Results and Conclusions.

The upper part of Table II summarises the results relating to hydrolysis. The conditions of the various experiments are noted in the first few cols., the headings of which are self-explanatory. The next two cols. give the percentages in which hydrolysis proceeds by the second- and first-order reactions, the figures being calculated from the kinetic data. The next three cols. record respectively the specific rotation of the bromide used, that of the alcohol obtained, and that which the alcohol would have had if prepared from optically pure bromide. In the penultimate column this rotation is expressed as a percentage of the specific rotation of optically pure alcohol; the figures therefore represent the percentage extent to which enantiomeric purity is retained in the hydrolytic substitution, and their differences from 100 are percentages of racemisation. In the last col. a correction is made for the fact that some of the β-*n*-octyl bromide becomes racemised before substitution owing to attack by the bromide ions liberated in the course of reaction; the figures thus represent the percentages in which optical purity would be retained if the octyl bromide underwent no racemisation prior to substitution. The correction is based on a study of the kinetics by polarimetric as well as analytical methods. The third row of figures, which relate to a purely bimolecular hydrolysis, are calculated from the experimental data in the first two rows. The lower part of the table contains the results for alcoholysis.

TABLE II.

Hydrolysis of β-n-Octyl Bromide.

Solvent.	Concn. of KOH, HBr, etc. (*N*). Initial. Final.	Proportions of simultaneous reactions. S_N2 (%).	S_N1 (%).	Bromide, $[\alpha]_{\mathrm{D}}^{20^\circ}$.	Alcohol, $[\alpha]_{\mathrm{D}}^{20^\circ}$. Obs.	Corr. to pure halide.	Retention of optical purity (%).* Uncorr.	Corr.
60% Aqueous EtOH	1·23—0·91 KOH	88	12	+29·78°	− 7·73°	− 8·78°	− 89	− 93
	0·00—0·31 HBr	0	100	−24·54	+ 2·54	+ 3·46	− 35	− 66
	(Calculated)	100	0	+33·80	− 9·50	− 9·50	− 96	− 96

Ethyl Alcoholysis of β-n-Octyl Halides.

				Halide, $[\alpha]_{\mathrm{D}}^{20^\circ}$.	Ether, $[\alpha]_{\mathrm{D}}^{20^\circ}$. Obs.	Corr.		
β-n-Octyl bromide.								
60% Aqueous EtOH	1·23—0·91 KOH	95	5	−30·28	+13·93	+15·53	− 91	− 95
	0·00—0·31 HBr	0	100	−24·54	+ 4·90	+ 6·74	− 39	− 74
	(Calculated)	100	0	+33·80	−15·98	−15·98	− 94	− 96
EtOH	2·18—1·67 NaOEt	100	0	−24·54	+12·41	+17·10	−100	−100
β-n-Octyl chloride.								
EtOH	2·18—1·67 NaOEt	100	0	+29·79	−13·30	−17·10	−100	−100

* The negative sign signifies that configuration is inverted.

It will be observed that the common result of all these reactions—bimolecular and unimolecular, the alcoholyses as well as the hydrolyses—is to give a product having an inverted sign of rotation, and this, as we have seen, means an inverted configuration. On the other hand, the bimolecular and unimolecular reactions are distinguished in that the latter involve much larger amounts of racemisation than the former. These results will be considered along with other data in Part VI.

EXPERIMENTAL.

Optically Active β-n-*Octyl Halides.*—β-*n*-Octyl alcohol was treated at 60—70° with dry hydrogen bromide until two layers were formed and the lower ceased to increase. The product was extracted with ether, washed successively with sodium hydrogen sulphite, sodium carbonate and water, dried with sodium sulphate, and distilled. The distilled material was shaken with concentrated sulphuric acid, left in ethereal solution in contact with anhydrous sodium carbonate, and again distilled. Octyl alcohol with $[\alpha]_{\mathrm{D}}^{20^\circ}$ − 9·07° and + 9·17° gave in separate experiments bromide with $[\alpha]_{\mathrm{D}}^{20^\circ}$ + 29·78° and − 24·54° respectively (Found: C, 49·6; H, 8·5; Br, 42·2. Calc.: C, 49·7; H, 8·8; Br, 41·5%). β-*n*-Octyl chloride was prepared as described by McKenzie and Tudhope (*loc. cit.*); alcohol with $[\alpha]_{\mathrm{D}}^{20^\circ}$ − 9·15° gave chloride with $[\alpha]_{\mathrm{D}}^{20^\circ}$ + 29·79°.

Alkaline Hydrolysis of Bromide.—The bromide (30 g.) was hydrolysed for 5 hours under the conditions specified in Table II. The product was diluted with water (5 l.), acidified with sulphuric acid, and extracted with light petroleum. After removal of most of the solvent, bromine was added at 0° until the liquid remained faintly coloured, and the octyl alcohol and ethyl octyl ether were separated by distillation from the bulk of the dibromo-octane (17·5 g., b. p. 110°/14 mm.). The mixture of alcohol and ether (6 g.) was heated with phthalic anhydride (6 g.) for 12 hours at 110—115°, and the product digested with 2*N*-aqueous sodium carbonate (400 c.c.) and extracted with ether. The extract yielded ethyl β-*n*-octyl ether, b. p. 68°/18 mm. (yield 1·6 g. after a further non-ebullient distillation) (Found: C, 76·0; H, 13·9. Calc.: 75·9; H, 13·9%), and dibromo-octane (2·2 g., b. p. 114°/16 mm.). The alkaline solution was freed from ether by means of a current of air, acidified, and extracted with chloroform; the residue from the chloroform extract was evaporated with additions of light petroleum, and the β-*n*-octyl hydrogen phthalate was crystallised (1·35 g., $[\alpha]_D^{20^\circ}$ − 42·8°) in the presence of this solvent. A further small quantity (0·04 g., $[\alpha]_D^{20^\circ}$ − 19·5°) of the hydrogen phthalate (Found : C, 69·5; H, 8·0. Calc. : C, 69·1; H, 7·9%) was obtained by cooling the petroleum filtrate in solid carbon dioxide. The rotations were taken in dry ethyl alcohol. The two specimens of hydrogen phthalate differed in rotation because the crystallisation effects a partial resolution; the rotation of the total phthalate is, of course, used in calculating the rotation of the equivalent β-*n*-octyl alcohol. The losses in the crystallisation of the hydrogen phthalate are insignificant, and in these isolation processes generally the losses of material occur practically exclusively in the extraction and distillations of liquids; hence they are not optically selective.

Acid Hydrolysis of Bromide.—The bromide (15 g.) was hydrolysed for 3 days under the conditions defined for acid hydrolysis in Table II. The product was worked up as described in the previous paragraph, except that it was unnecessary to add acid after pouring into water, and that the hydrogen phthalate of the alcohol was not collected in two parts, but altogether (8·87 g., $[\alpha]_D^{20^\circ}$ + 12·23°) at the temperature of a carbon dioxide freezing mixture. The other products were octyl ether (0·65 g.) (Found : C, 74·2; H, 13·6%) and dibromo-octane (0·1 g.).

Alcoholysis of Bromide and Chloride.—The bromide (20 g.) was alcoholysed with a solution of sodium ethoxide in anhydrous ethyl alcohol for 2 hours, the other conditions being as specified in Table II. The products, worked up as already described except that the treatment with phthalic anhydride was omitted, were dibromo-octane (17 g.) and ethyl octyl ether (1·2 g.). The chloride (15 g.), similarly treated, also gave dibromo-octane (11·65 g.) and the ether (1·45 g.) (Found : C, 75·9; H, 14·0%). The yields of liquid products quoted here and throughout are those of analysis samples or of fully rectified material, usually thrice distilled.

Note.—The preceding measurements with optically active material were carried out before the kinetic data by Hughes and Shapiro had been completed, and it was therefore necessary to conduct approximate kinetic measurements in order to establish appropriate conditions in which to investigate the optical effects. These measurements were made at the b. p.'s of the solutions, the temperatures used in the optical investigations; but as these temperatures are very close to the temperature 80·0° used by Hughes and Shapiro it is unnecessary to publish the results, which only serve to confirm the more accurate data obtained by these authors. We omit also all description of the methods of calculation, since these were quite similar to those illustrated in Part III.

We wish to thank the Chemical Society for a grant for materials.

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[*Received, April 24th*, 1937.]