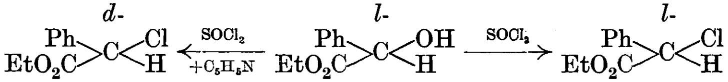
LVII.—*The Interaction of Ethyl* l-*Mandelate and Thionyl Chloride in the Presence of Pyridine. The Mechanism of the Replacement of Hydroxyl by Chlorine by Means of Thionyl Chloride.*

By JOSEPH KENYON, ALFRED GEORGE LIPSCOMB, and HENRY PHILLIPS.

WHEN a lævorotatory hydroxy-acid or its ester is treated with thionyl chloride, the chloro-acid or ester produced is dextrorotatory; *e.g.*, ethyl *l*-malate is converted into ethyl *d*-chlorosuccinate (McKenzie and Barrow, J., 1911, **99**, 1910):

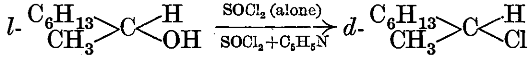
$$l\text{-EtO}_2\text{C}{\cdot}\text{CH}_2{\cdot}\text{CH(OH)}{\cdot}\text{CO}_2\text{Et} \longrightarrow d\text{-EtO}_2\text{C}{\cdot}\text{CH}_2{\cdot}\text{CHCl}{\cdot}\text{CO}_2\text{Et}.$$

McKenzie and Clough (J., 1910, **97**, 2564) discovered, however, that thionyl chloride behaves differently towards hydroxy-acids (and esters) containing a phenyl group directly attached to the asymmetric carbon atom, since from these compounds it produces chloro-acids (and esters) with the same sign of rotation as the parent hydroxy-compound; *e.g.*, ethyl *l*-mandelate is converted into ethyl *l*-phenylchloroacetate (McKenzie and Barrow, *loc. cit.*). It has now been found that if ethyl *l*-mandelate is first dissolved in a tertiary base (pyridine, quinoline, or *iso*quinoline) and then treated with thionyl chloride, ethyl *d*-phenylchloroacetate is obtained instead of ethyl *l*-phenylchloroacetate. The following changes have therefore been realised:



$$\overset{d\text{-}}{\substack{\text{Ph}\\ \text{EtO}_2\text{C}}{>}\text{C}{<}\substack{\text{Cl}\\ \text{H}}} \xleftarrow[+\text{C}_5\text{H}_5\text{N}]{\text{SOCl}_2} \overset{l\text{-}}{\substack{\text{Ph}\\ \text{EtO}_2\text{C}}{>}\text{C}{<}\substack{\text{OH}\\ \text{H}}} \xrightarrow{\text{SOCl}_2} \overset{l\text{-}}{\substack{\text{Ph}\\ \text{EtO}_2\text{C}}{>}\text{C}{<}\substack{\text{Cl}\\ \text{H}}}$$

These results are the more surprising since *l*-β-octanol is converted into *d*-β-chloro-octane by thionyl chloride both in the absence (Levene and Mikeska, *J. Biol. Chem.*, 1924, **59**, 45) and in the presence of pyridine (McKenzie and Tudhope, *ibid.*, 1924, **62**, 551):



$$l\text{-}\substack{\text{C}_6\text{H}_{13}\\ \text{CH}_3}{>}\text{C}{<}\substack{\text{H}\\ \text{OH}} \xrightarrow[\text{SOCl}_2+\text{C}_5\text{H}_5\text{N}]{\text{SOCl}_2\text{ (alone)}} d\text{-}\substack{\text{C}_6\text{H}_{13}\\ \text{CH}_3}{>}\text{C}{<}\substack{\text{H}\\ \text{Cl}}$$

There can be little doubt that the mechanism of the interaction of thionyl chloride with hydroxy-compounds is modified by the presence of a tertiary base. The work now described suggests, however, that such modification only determines the sign of rotation of the resulting chloro-compound when a phenyl group is directly attached to the asymmetric carbon atom.

In the paragraphs below, the results of the experiments are briefly described and then the mechanisms of the chlorination reaction of thionyl chloride in the presence and in the absence of pyridine are discussed. An explanation is also put forward to account for the difference in behaviour of hydroxy-compounds which contain an aromatic radical.

Results of the Experiments.—Thionyl chloride (1 or 2 mols.) was added slowly to an ice-cold solution of ethyl *l*-mandelate and the tertiary base (1 or 2 mols.) in about five volumes of dry ether. After the initial vigorous reaction had ceased, the reaction mixture was warmed on a steam-bath for 30 minutes. Water was then added, and the product extracted with ether. The ethereal extract was washed with dilute hydrochloric acid and dried, and the product isolated and distilled. The ethyl *d*-phenylchloroacetate obtained was sometimes contaminated with ethyl *l*-mandelate, particularly in those experiments in which the *l*-ester was dissolved in only one molecular proportion of the tertiary base. This was most probably due to incomplete reaction under the mild experimental conditions employed, which were chosen to minimise the interaction between the chloro-ester produced and the tertiary base.

In Table I are recorded the rotatory powers of the ethyl *d*-phenylchloroacetate and of the mixtures of ethyl *d*-phenylchloroacetate and ethyl *l*-mandelate which were isolated. The percentages of *d*-chloro-ester in the mixtures were calculated from the percentages of chlorine which they were found to contain. For purposes of comparison, the rotatory power of the ethyl *l*-phenylchloroacetate prepared by McKenzie and Barrow (*loc. cit.*) is also included in the Table. The observed rotatory power of this *l*-ester ($[\alpha]_{5461}$, $l = 1{\cdot}0$) was calculated from the recorded value ($[\alpha]_{5893}$, $l = 1{\cdot}0$) by aid of the dispersion ratio $\alpha_{5893}/\alpha_{5461}$ 0·816, which was determined for this purpose.

TABLE I.

The Observed Rotatory Powers of Ethyl Phenylchloroacetate prepared from Ethyl l-*Mandelate by Means of Thionyl Chloride in the Presence of Tertiary Bases.*

Tertiary base used.	Observed rotatory power, $[\alpha]_{5461}$ ($l = 1{\cdot}0$).	% Ethyl phenylchloroacetate in the product.	% Cl in the product.*
None (McKenzie and Barrow)	$-$ 91·3°	100·0	—
Pyridine.			
1 mol.; $SOCl_2$, 1 mol.	$+$ 41·2	63·3	11·3
2 mols.; $SOCl_2$, 2 mols.	$+$122·0	100·0	18·0
Quinoline.			
1 mol.; $SOCl_2$, 1 mol.	$+$107·2	83·3	14·9
2 mols.; $SOCl_2$, 2 mols.	$+$116·2	100·0	17·7
*iso*Quinoline.			
1 mol.; $SOCl_2$, 1 mol.	$+$114·4	100·0	18·2
2 mols.; $SOCl_2$, 2 mols.	$+$ 73·0	88·4	15·8

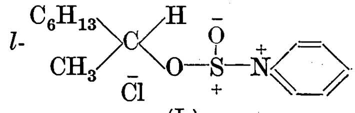
* Ethyl phenylchloroacetate contains 17·9% Cl.

It will be seen that the magnitudes of the rotatory powers of the ethyl *d*-phenylchloroacetate obtained in these experiments were higher than that of the *l*-ester obtained by means of thionyl chloride alone. They are also greater than the rotatory power of the *d*-ester obtained by Walden (*Ber.*, 1895, **28**, 1287) by the action of phosphorus pentachloride on a solution of ethyl *l*-mandelate in chloroform. The rotatory power of this ester was $[\alpha]_{5893} + 25{\cdot}19^\circ$, from which it can be calculated that it had $\alpha_{5461} + 37{\cdot}0^\circ$ ($l = 1{\cdot}0$).

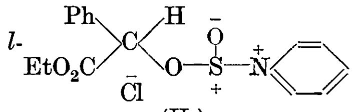
The Interaction of Thionyl Chloride with l-β-*Octanol and Ethyl* l-*Mandelate in the Presence of Pyridine.*—The reaction between thionyl chloride and an alcohol takes place in two stages. The alcohol is first converted into a chlorosulphinic ester, and this ester then loses sulphur dioxide and forms the chloride. In the case of *d*-amyl alcohol, McKenzie and Clough (J., 1913, **103**, 698) were able to isolate the *d*-amyl chlorosulphinate and showed that by heating to 120° it was converted into *d*-amyl chloride. Similarly, Frankland and Garner (J., 1914, **105**, 1101) have isolated ethyl *d*-α-chlorosulphinoxypropionate. Attempts made in these laboratories to isolate *l*-β-octyl chlorosulphinate from the product of the interaction of *l*-β-octanol and thionyl chloride have been unsuccessful, the sole product obtained in every experiment being *d*-β-chloro-octane. Nevertheless, it is probable that this reaction, as with *d*-amyl alcohol, also occurs in two stages, and that the chlorosulphinic ester, which is the product of the first stage of the reaction, is difficult to isolate owing to its instability.

$$\begin{aligned} l\text{-}C_8H_{17}{\cdot}OH + SOCl_2 &= l\text{-}C_8H_{17}{\cdot}O{\cdot}SOCl + HCl. \\ l\text{-}C_8H_{17}{\cdot}O{\cdot}SOCl &= d\text{-}C_8H_{17}Cl + SO_2. \end{aligned}$$

If pyridine were present, it could take part in both stages of the reaction. It could facilitate the formation of the chlorosulphinate, and also aid its decomposition by combining with it to form the unstable intermediate complex (I), a pyridinium chloride.

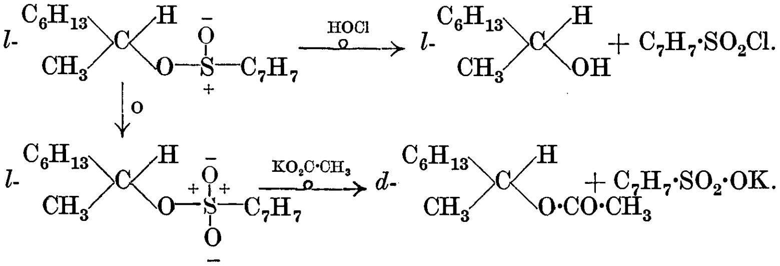


(I.)

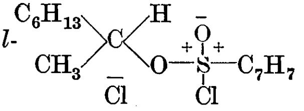


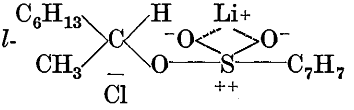
(II.)

A similar unstable pyridinium chloride (II) might also arise during the reaction between ethyl *l*-mandelate and thionyl chloride in the presence of pyridine. The constitutions assigned to (I) and (II) involve few, if any, assumptions. It is also considered that they emphasise certain important characteristics of the unstable intermediate complexes the formation of which can be postulated in many reactions which lead to a Walden inversion. In previous papers two reactions have been described which are known, with some degree of certainty, to take place with a Walden inversion. One is the conversion of *p*-toluenesulphonic esters into carboxylic esters (Phillips, J., 1923, **123**, 44; 1925, **127**, 2566; Kenyon, Phillips, and Turley, *ibid.*, p. 399; Gough, Hunter, and Kenyon, J., 1926, 2052), and the other the conversion of *l*-β-octyl *p*-toluenesulphinate into *d*-β-octanol (Houssa, Kenyon, and Phillips, J., 1929, 1700). The results obtained with the *p*-toluenesulphinate and the *p*-toluenesulphonate of *l*-β-octanol were as follows :



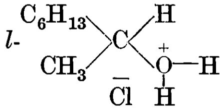
It was also found (Houssa, Kenyon, and Phillips, *loc. cit.*) that *d*-β-chloro-octane could be obtained either by the action of chlorine on the *l*-sulphinic ester or by the action of lithium chloride on the *l*-sulphonic ester. It was considered highly probable that these reactions were also accompanied by an inversion, since they were similar to the corresponding reactions with hypochlorous acid and potassium acetate. On this assumption, *d*-β-chloro-octane has the same configuration as *d*-β-octanol. Houssa, Kenyon, and Phillips (*loc. cit.*), abandoning the α-hydrogen hypothesis of Phillips (*loc. cit.*), made use of the revised structural formulæ for *p*-toluenesulphinic esters (Phillips, *loc. cit.*, p. 2552) and sulphonic esters (Sugden, Reed, and Wilkins, J., 1925, **127**, 1525), and suggested that during the reactions, mentioned above, which lead to the formation of *d*-β-chloro-octane, the intermediate complexes (III) and (IV) were formed.

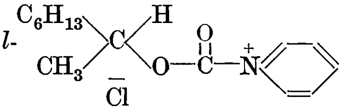

(III.)


(IV.)

On comparing the constitutions assigned to these two complexes, the decomposition of which is accompanied by a Walden inversion, with those assigned to the complexes (I) and (II), certain striking similarities are found. In all four the group about to sever its union with the asymmetric carbon atom has become preponderantly positive in character. Further, the chlorine atom, about to unite with the asymmetric carbon atom, exists in each case as a negative ion. It is also noteworthy that intermediate complexes possessing these two characteristics may also be formed during two other reactions, by the aid of which, and according to the conclusions of Houssa, Kenyon, and Phillips (*loc. cit.*), *l*-β-octanol can be converted into *d*-β-chloro-octane. These are the interaction of *l*-β-octanol and hydrogen chloride (V) (Pickard and Kenyon, J., 1911, **99**, 45) and the interaction of *l*-β-octyl chlorocarbonate and pyridine (Houssa and Phillips, J., 1929, 2510) (VI).

(V.)

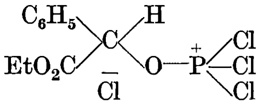




(VI.)

By the interaction of *l*-β-octanol and thionyl chloride, in the presence of pyridine (I), *d*-β-chloro-octane is produced and therefore this reaction can also be assumed to take place with inversion of configuration. It thus appears that in all the reactions by which *l*-β-octanol, *l*-β-octyl *p*-toluenesulphonate or *p*-toluenesulphinate can be converted into β-chloro-octane a Walden inversion occurs. Moreover, each of these reactions and also those by which *l*-β-octyl *p*-toluenesulphonate is converted into carboxylic esters of *d*-β-octanol, and *l*-β-octyl *p*-toluenesulphinate into *d*-β-octanol, all pass through a phase in which unstable intermediate complexes, possessing certain notable characteristics in common, are produced.

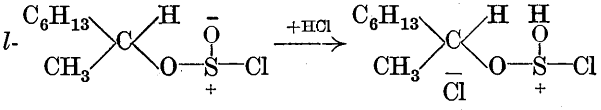
It will be assumed that since, during the reaction between ethyl *l*-mandelate and thionyl chloride in the presence of pyridine, the formation of an intermediate complex of the same type may also be postulated, this reaction is accompanied by a Walden inversion: in other words, that ethyl *l*-phenylchloroacetate has the same configuration as ethyl *l*-mandelate. It follows, therefore, on this assumption, that the interaction of ethyl *l*-mandelate and phosphorus pentachloride is also attended by a configurative change. It is significant that here again the same type of intermediate complex (VII) may arise.



(VII.)

A general idea underlying most of the theories of the Walden inversion (Fischer, *Annalen*, 1911, **381**, 132; Werner, *Ber.*, 1911, **44**, 881; Pfeiffer, *Annalen*, 1911, **383**, 123; Gadamer, *Chem. Ztg.*, 1912, **36**, 1327; Lowry, *Deuxième Conseil de Chimie Solvay*, 1925, 40) is that in such reactions the entering group attaches itself to the opposite side of the asymmetric molecule to that occupied by the group to be displaced. It is essential, therefore, for the occurrence of a Walden inversion that the entering group should be free to take up this position. In the unstable intermediate complexes of the inversion reactions described in this paper, the entering group, the chlorine anion, is always available to assume this favourable position in the molecular complex, before the groups to be displaced leave the asymmetric carbon atoms.

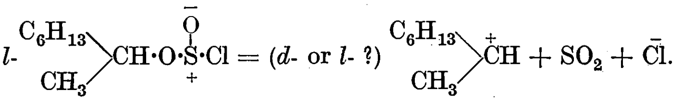
The Interaction of Thionyl Chloride with l-β-*Octanol and Ethyl* l-*Mandelate in the Absence of Pyridine.—With* l-β-*octanol.* Levene and Mikeska (*loc. cit.*) have shown that the action of thionyl chloride on *l*-β-octanol in the absence of pyridine leads to the formation of *d*-β-chloro-octane; hence a Walden inversion occurs, since it has been concluded that *d*-β-chloro-octane has the same configuration as *d*-β-octanol. Furthermore, since the inversion is unlikely to occur during the first stage of the reaction (as the bonds of the asymmetric carbon atom are not disturbed), it follows that it takes place when the *l*-β-octyl chlorosulphinate decomposes.

(VIII.)

(IX.)

$$l\text{-}\begin{matrix}C_6H_{13}\\CH_3\end{matrix}\!>\!C\!<\!\begin{matrix}H\\O\text{—}\overset{\overset{-}{O}}{\underset{+}{S}}\text{—}Cl\end{matrix}\xrightarrow{+HCl}\begin{matrix}C_6H_{13}\\CH_3\end{matrix}\!>\!\underset{\overset{-}{Cl}}{C}\!<\!\begin{matrix}H\quad H\\O\text{—}\overset{O}{\underset{+}{S}}\text{—}Cl\end{matrix}$$

It has been found that the interaction of thionyl chloride and *l*-β-octanol in the presence of potassium carbonate also leads to the formation of *d*-β-chloro-octane. This result indicates that the *d*-β-chloro-octane obtained in the absence of potassium carbonate does not arise from the interaction, as shown in (IX), of the chlorosulphinate with the hydrogen chloride produced in the first stage of the reaction.

It seems reasonable to assume that when the various intermediate complexes, which have been postulated, decompose, the asymmetric carbon atoms necessarily acquire a positive charge, since, ultimately, they each unite with a negative chlorine ion. It is therefore possible that, when *l*-β-octyl chlorosulphinate decomposes, it splits up into a carbonium kation, sulphur dioxide, and a chlorine anion, and that the *d*-β-chloro-octane is formed by the union of the carbonium ion with the chlorine ion :

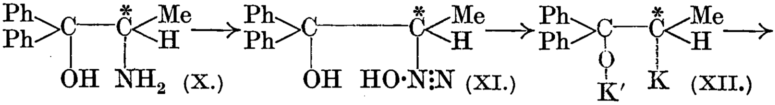


$$l\text{-}\begin{matrix}C_6H_{13}\\CH_3\end{matrix}\!>\!CH\cdot O\cdot\overset{\overset{-}{O}}{\underset{+}{S}}\cdot Cl=(d\text{- or }l\text{- ?})\ \begin{matrix}C_6H_{13}\\CH_3\end{matrix}\!>\!\overset{+}{C}H+SO_2+\overset{-}{Cl}.$$

Experimental evidence, however, is still wanted which will show whether the formation of a carbonium kation is attended with a

Walden inversion and also whether the kation is capable, even momentarily, of a free existence in an optically active state.

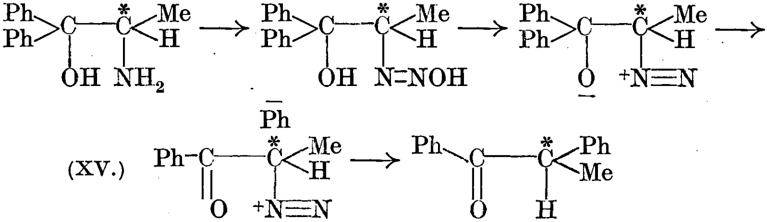
McKenzie, Roger, and Wills (J., 1926, 779) have, however, already described a remarkable molecular rearrangement, from the results of which they conclude that a carbonium ion can retain its asymmetry in the free state. The nature of the charge on this ion is not specified, but it is difficult to conceive it as being other than positive. These authors found that lævorotatory β-amino-αα-diphenyl-*n*-propyl alcohol was converted into a dextrorotatory ketone by the action of nitrous acid. The following mechanism was suggested for the change:



(X.) (XI.) (XII.)

$Ph{\cdot}CO{\cdot}\overset{*}{C}H{<}^{Me}_{Ph}$ (XIII.)

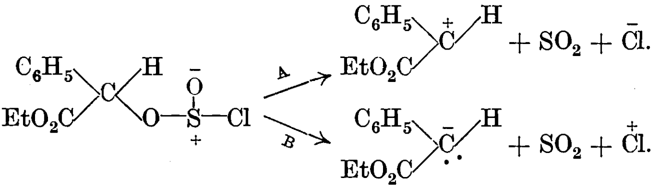
The weak points in this interpretation are, first, that a nitrogen atom in (XI) is linked to other atoms by *five* covalencies and, secondly, that it has to be assumed that the carbon and oxygen atoms in (XII) bear charges of the same sign (K′ and K) to explain the absence of the stable compound, diphenylpropylene oxide, in the products of the rearrangement. In the interpretation of the change given below, the non-formation of this oxide is accounted for without departing from accepted theories of valency.



(XV.)

From this interpretation of the rearrangement it is no longer possible to draw the conclusion of McKenzie, Roger, and Wills that "During the transposition of the phenyl group . . . we are dealing with a reaction of substitution, the electric charge K, playing the part of a group and being displaced by a phenyl group. . . ." Unfortunately, therefore, this remarkable transformation cannot be advanced as evidence that a carbonium ion can remain optically active in the free state. It is, however, again significant that to explain this complicated change, which may lead to a Walden inversion, the formation of an unstable complex (XV) must be postulated which contains an entering group (the phenyl group) as a negative ion and a positively charged group (the nitrogen molecule) about to leave the asymmetric carbon atom.

With ethyl l-*mandelate.* McKenzie and Barrow (*loc. cit.*) have shown that thionyl chloride, in the absence of pyridine, converts ethyl *l*-mandelate into ethyl *l*-phenylchloroacetate. It has been suggested that these two compounds have the same configuration and therefore that the reaction is not accompanied by a Walden inversion. As in the study of the interaction of *l*-β-octanol and thionyl chloride, an experiment was made to prove that the ethyl *l*-phenylchloroacetate was not formed by the interaction of the products of the first stage of the reaction, namely, hydrogen chloride and ethyl *l*-mandelylchlorosulphinate. It was found that potassium carbonate (*in marked contrast to pyridine*) had no influence on the sign of rotation of the ethyl phenylchloroacetate obtained. There appear to be two possible mechanisms (A and B) by which the decomposition might take place.



Of these two alternatives, only (B) sharply differentiates the decomposition of ethyl *l*-mandelylchlorosulphinate from that of *l*-β-octyl chlorosulphinate and assigns a definite function to the phenyl group. This function is to confer on the asymmetric carbon atom the power to retain electrons during the decomposition. A phenyl group can function in this way, since it is strongly electron-attracting, whereas purely aliphatic groups, such as methyl and *n*-hexyl, are electron-donating groups, which, therefore, when attached to an asymmetric carbon atom, weaken its power to retain electrons. This mechanism also gives a satisfactory explanation of the power of pyridine to change the sign of rotation of the product of this decomposition. The interaction of pyridine with the chlorosulphinate produces a pyridinium chloride (II) in which the positive character of the chlorosulphinoxy-group has been augmented and its electron-retaining power therefore increased. Hence, when the chlorosulphinate decomposes in the presence of pyridine, the increased electron-retaining power of the chlorosulphinoxy-group enables it to overcome the electron-retaining power conferred on the asymmetric atom by the phenyl group, with the result that the asymmetric carbon atom loses two electrons during the further stages of the decomposition, which now leads to a Walden inversion.

EXPERIMENTAL.

l-Mandelic acid, isolated from amygdalin (Freudenberg and Markert, *Ber.*, 1925, **58**, 1753), was converted into ethyl *l*-mandelate by the method of Fischer and Speier.

The Interaction of Thionyl Chloride with Ethyl l-*Mandelate and* d-β-*Octanol in the Presence of Potassium Carbonate.*—*With ethyl* l-*mandelate.* Thionyl chloride (2·97 g.) in ether (10 c.c.) was added to a solution of ethyl *l*-mandelate (4·5 g.) in ether (50 c.c.) containing recently ignited potassium carbonate (10·4 g.). The mixture was heated under reflux for ½ hour, the potassium carbonate and chloride were removed by filtration, and the ether was distilled from the filtrate. The residue on distillation gave a mixture of ethyl *l*-mandelate and ethyl *l*-phenylchloroacetate, b. p. 136—138°/18 mm., with α_{5461} −30·94° ($l = 0{\cdot}25$) (Found : Cl, 7·7%). The mixture therefore contained 43% of the chloro-ester. 1·14 G. of ethyl *l*-mandelate were dissolved in 0·86 g. of ethyl *dl*-phenylchloroacetate. This solution had α_{5461} −20·98° ($l = 0{\cdot}25$) and hence the ethyl phenylchloroacetate in the mixture isolated in the above experiment was lævorotatory.

With d-β-*octanol.* *d*-β-Octanol (2·9 g.) in ether (30 c.c.) was added slowly to an agitated solution of thionyl chloride (10 g.) in ether (30 c.c.) containing potassium carbonate (12 g.). After 12 hours, the ether was removed by distillation, and the residue extracted with ether. In this manner the reaction was completed in the presence of potassium carbonate. The ethereal extract, on evaporation, gave *l*-β-chloro-octane (2·5 g.), b. p. 60—61°/14 mm. and α_{5461} −5·05° ($l = 0{\cdot}25$).

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