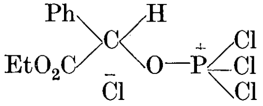
CCCXI.—*The Conversion of Ethyl* l-α-*Chloroformoxyphenylacetate into Lævorotatory and Dextrorotatory Ethyl Phenylchloroacetate.*

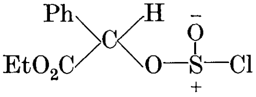
By JOSEPH KENYON, ALFRED GEORGE LIPSCOMB,
and HENRY PHILLIPS.

ALTHOUGH the replacement of a hydroxyl group by a chloro-group, by whatever reagent effected, doubtless proceeds by a variety of mechanisms, it is possible that in the absence of disturbing factors, such as adjacent carboxyl groups, this replacement occurs mainly along one of two distinct routes. With optically active compounds, both these routes lead to the formation of optically active products, but these are of opposite configuration.

The first route can be illustrated by the interaction of ethyl *l*-mandelate and phosphorus pentachloride. The initial stage is probably a complex (I), in which the entering chloro-group exists as an anion. Decomposition of (I) leads to the formation of dextrorotatory ethyl phenylchloroacetate (Walden, *Ber.*, 1895, **28**, 1287).

(I.)





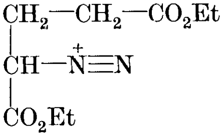
(II.)

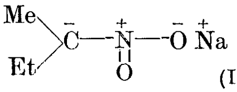
According to Kenyon and Phillips (*Trans. Faraday Soc.*, 1930, **26**, 451), when the chloro-group takes part in all stages of the reaction as an anion, the product results with inversion of configuration: this assumption is based on deductions from a study of the reactions of *p*-toluene-sulphinic and -sulphonic esters (Houssa, Kenyon, and Phillips, J., 1929, 1700).

An example of the second type of replacement reaction is afforded by the interaction of ethyl *l*-mandelate and thionyl chloride. In this case an intermediate complex, a chlorosulphinate (II), is formed in which the chloro-group is still covalently linked. In marked contrast to complex (I), the chloro-sulphinic ester molecule decomposes to give lævorotatory ethyl phenylchloroacetate (McKenzie and Barrow, J., 1911, **99**, 1910), and in order to explain this result, Kenyon, Lipscomb, and Phillips (J., 1930, 415) assumed that the optically active mandelyl radical separates as an anion and subsequently unites with a chlorine kation, and that, in addition, neither of these two changes is accompanied by a change of configuration or complete racemisation.

These views receive experimental support from two standpoints. First, that an optically active anionic carbon atom can retain its asymmetry in the free state is proved by the isolation of, *e.g.*, ethyl diazoglutarate (III) (Marvel and Noyes, *J. Amer. Chem. Soc.*, 1920, **42**, 2259; Chiles and Noyes, *ibid.*, 1922, **44**, 1798) and also of sodium *aci*-β-nitrobutane (IV) (Kuhn and Albrecht, *Ber.*, 1927, **60**, 1297).

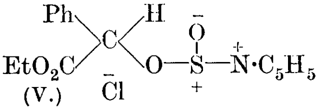
(III.)



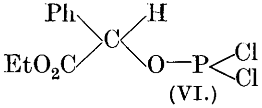


(IV.)

Secondly, evidence is required to show that if the decomposition of complex (II) is effected under conditions which compel the chlorine atom to separate as an anion, then subsequent changes occur along the route which is followed by the decomposition of complex (I), *i.e.*, the reaction occurs with inversion of configuration. This evidence was supplied by the discovery (Kenyon, Lipscomb, and Phillips, *loc. cit.*) that dextrorotatory ethyl phenylchloroacetate results if the chlorosulphinate decomposes in the presence of pyridine, in which case it can be assumed that complex (II) is converted into complex (V) which contains the entering chloro-group as an anion (see also Kenyon, Phillips, and Taylor, this vol., p. 382).



(V.)

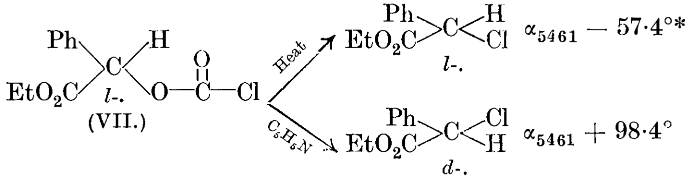


(VI.)

To complete the experimental evidence in favour of this interpretation of the influence of the pyridine, it has now been shown that when the halogenation of ethyl *l*-mandelate proceeds with inversion, as is the case when phosphorus penta- and tri-chlorides are used, the presence of pyridine during the reaction is without influence on the sign of rotatory power of the product.

Although the production of dextro- and of lævo-rotatory ethyl phenylchloroacetates from ethyl *l*-mandelate *via* the complexes (I) and (II) can be said to follow different routes, this is only true in a restricted sense. Both changes consist essentially in the union of positive and negative ions, but whilst the negative ion produced during the decomposition of complex (I) is provided by the entering chloro-group, during the decomposition of the chlorosulphinate (II) the optically active radical becomes the negative ion. Further, this difference in the mode of decomposition is revealed because the chlorine anion cannot unite with an optically active radical to produce an optically active product without the simultaneous occurrence of an inversion.

It follows from these observations that methods by which ethyl *l*-mandelate can be converted into lævorotatory ethyl phenylchloroacetate, *i.e.*, without inversion, should be sought amongst those halogenating agents which give rise to intermediate complexes, such as the chlorosulphinate, in which the entering chloro-group is still covalently linked. Under these conditions it is possible, but not certain, that further reaction may lead to the formation of an anionic mandelyl radical. An example in which, even although the entering chloro-group remains covalently linked, further reaction is not accompanied by inversion, is provided by the preliminary phase in the interaction of phosphorus trichloride and ethyl *l*-mandelate (VI). This phase on decomposition produces dextrorotatory ethyl phenylchloroacetate, and hence, according to the views expressed, the decomposition is initiated by the liberation of a chlorine anion. It has been found, however, that *ethyl* l-α-*chloroformoxyphenylacetate* (VII), the intermediate phase in the interaction of ethyl *l*-mandelate and carbonyl chloride, behaves in a similar manner to the corresponding chloro-sulphinate. Unlike the latter compound, the formation of which has been assumed since it is too unstable to be isolated, ethyl *l*-α-chloroformoxyphenylacetate can be readily distilled at very low pressures. When heated at about 150°/14 mm., it readily decomposes to give carbon dioxide and lævorotatory ethyl phenylchloroacetate, but at lower temperatures, in the presence of pyridine, it decomposes and yields the dextrorotatory ester.



(VII.)

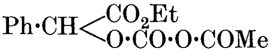
As in the case of the chlorosulphinate, the influence of pyridine on the sign of rotatory power of the product can be attributed to the ability of this base to liberate the chloro-group as an anion and thus to ensure that the decomposition will follow the route which leads to inversion.

It is possible to substitute other groups for the chloro-group in the chloroformoxy-radical. For example, by the interaction of this ester with potassium acetate, potassium benzoate, and sodium *p*-toluenesulphinate the mixed anhydrides (VIII, IX, and X) are produced, which are too unstable to be isolated in a condition of

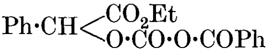
[*] All observed rotatory powers recorded in the theoretical portion of this paper are given for 1-dcm. tubes.

purity but, when heated, decompose with the loss of carbon dioxide and give rise respectively to *ethyl α-acetoxy-*, *α-benzoyloxy-*, and

(VIII.)



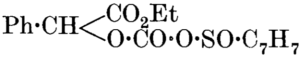
$$\mathrm{Ph{\cdot}CH}<\begin{matrix}\mathrm{CO_2Et}\\ \mathrm{O{\cdot}CO{\cdot}O{\cdot}COMe}\end{matrix}$$



$$\mathrm{Ph{\cdot}CH}<\begin{matrix}\mathrm{CO_2Et}\\ \mathrm{O{\cdot}CO{\cdot}O{\cdot}COPh}\end{matrix}$$

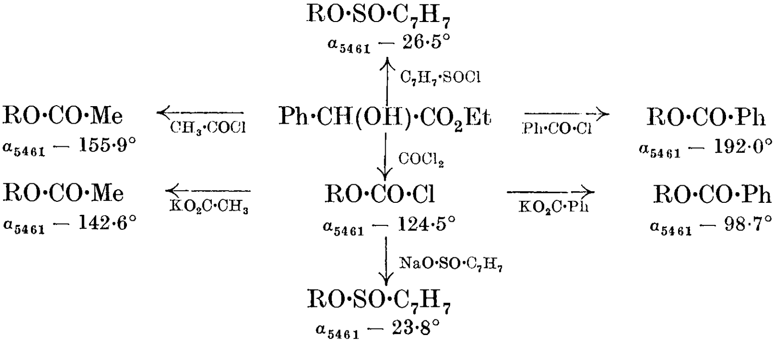
(IX.)

(X.)



$$\mathrm{Ph{\cdot}CH}<\begin{matrix}\mathrm{CO_2Et}\\ \mathrm{O{\cdot}CO{\cdot}O{\cdot}SO{\cdot}C_7H_7}\end{matrix}$$

p-*toluenesulphinoxy-phenylacetates.* These esters prepared in this manner have the same sign of rotation as when prepared directly from ethyl *l*-mandelate by the use of the appropriate acid chloride : they possess, therefore, the same configuration as ethyl *l*-mandelate and ethyl *l*-α-chloroformoxyphenylacetate.



[R = $\mathrm{Ph{\cdot}CH(CO_2Et){\cdot}}$]

It will be seen from the above scheme that the formation of these esters from the chloroformoxy-ester is attended by some racemisation, notably in the case of the benzoate. Although a more detailed investigation is necessary before its source can be traced with certainty, the occurrence of this racemisation is of interest because it suggests, but in no way proves, that the decomposition of the mixed anhydrides may be accompanied by the formation of some ethyl *l*-mandelyl anions.

EXPERIMENTAL.

The *l*-mandelic acid required was prepared by a modification of the method of Freudenberg and Markert (*Ber.*, 1925, **58**, 1753). Amygdalin (100 g.) was heated on a steam-bath for 1 hour with a mixture of concentrated hydrochloric acid (400 c.c.) and water (300 c.c.). The resulting solution was decolorised with norit, filtered, and evaporated in a vacuum to about two-thirds of its bulk. After standing over-night in the ice-chest, the main portion (33 g.) of the *l*-mandelic acid crystallised from the solution, the remainder (7 g.) being obtained from the filtrate by continuous extraction with ether.

Ethyl l-*α-Phenylcarbamylphenylacetate.*—Ethyl *l*-mandelate (1·8 g., and phenylcarbimide (1·2 g.) readily combined at ordinary temperatures to give *ethyl* l-*α-phenylcarbamylphenylacetate* (l-*mandelyl phenylurethane*), b. p. 165—166°/<0·1 mm., which could not be induced to crystallise (Found : C, 68·1 ; H, 5·7. $C_{17}H_{17}O_4N$ requires C, 68·3 ; H, 5·7%). It had α_{5461} — 123·2° ($c = 4{\cdot}571$; $l = 2$) in ethyl-alcoholic solution.

The corresponding *dl*-compound, prepared as above or from ethyl *dl*-α-chloroformoxyphenylacetate and aniline, crystallised readily from benzene–light petroleum, and had m. p. 97° (Found : N, 4·5. Calc. : N, 4·7%). Lambling (*Compt. rend.*, 1898, **127**, 66) records m. p. 93°.

Ethyl l-*α-Chloroformoxyphenylacetate.*—Carbonyl chloride (12·5 g.) in toluene (12·5 % solution) was added, during 10 minutes, to an ice-cold solution of ethyl *l*-mandelate (20 g.) and quinoline (16 g.) in toluene (30 c.c.), and the mixture gently heated on the steam-bath for 30 mins. Water was added to the cooled reaction mixture, and the toluene layer was washed with dilute hydrochloric acid, followed by water. From the dried toluene extract, *ethyl* l-*α-chloroformoxyphenylacetate* (24 g.) was obtained, b. p. 72—74°/<0·1 mm., which had α_{5461} — 31·12°, α_{4359} — 58·0° ($l = 0{\cdot}25$), $d_{4^\circ}^{20^\circ}$ 1·1742 (Found : Cl, 14·3. $C_{11}H_{11}O_4Cl$ requires Cl, 14·6%).

α-Carbethoxybenzyl Carbonate.—After the removal of the above ester as described, a small quantity of *α-carbethoxybenzyl carbonate*, $CO(\cdot O\cdot CHPh\cdot CO_2Et)_2$, remained as a colourless viscous liquid which distilled at 195—200°/<0·1 mm. (Found : C, 65·2 ; H, 5·7. $C_{21}H_{22}O_7$ requires C, 65·3 ; H, 5·8%). It had α_{5780} — 30·8°, α_{5461} — 35·96° ($l = 0{\cdot}25$). The corresponding *dl*-ester was obtained, b. p. 182—184°/<0·1 mm., by the interaction of ethyl *dl*-mandelate and ethyl *dl*-α-chloroformoxyphenylacetate in boiling ethereal solution in the presence of potassium carbonate.

Ethyl l-*α-Acetoxyphenylacetate.*—(a) *From ethyl* l-*mandelate.* Acetyl chloride (1·8 g.) was added to an ice-cold solution of ethyl *l*-mandelate (3·6 g.) in pyridine (1·8 g.). The l-*ester* had b. p. 147°/13 mm. and α_{5780} — 33·52°, α_{5461} — 38·97°, α_{4359} — 73·2° ($l = 0{\cdot}25$).

(b) *From ethyl* l-*α-chloroformoxyphenylacetate.* Anhydrous potassium acetate (3·0 g.) was triturated with ice-cold ethyl *l*-α-chloroformoxyphenylacetate (4·2 g.), and when effervescence had finished, the mixture was gently warmed for 5 mins. The cooled product was washed with dilute sodium carbonate, dissolved in ether, and dried. On distillation, *ethyl* l-*α-acetoxyphenylacetate* was obtained,

b. p. 146—147°/13 mm., α_{5780} — 30·78°, α_{5461} — 35·66°, α_{4359} — 66·16° ($l = 0{\cdot}25$) (Found : C, 64·3; H, 6·3. $C_{12}H_{14}O_4$ requires C, 64·9; H, 6·3%).

Ethyl l-α-*Benzoyloxyphenylacetate.*—(a) *From ethyl* l-*mandelate.* Benzoyl chloride (3·1 g.) was used instead of acetyl chloride, but otherwise the procedure was as above. The *l*-benzoate (3·5 c.c.) had b. p. 134—135°/<0·1 mm., α_{5461} — 48·0°, α_{4359} — 89·1° ($l = 0{\cdot}25$).

(b) *From ethyl* l-α-*chloroformoxyphenylacetate.* Anhydrous potassium benzoate (5·0 g.) was triturated with the ester (4·8 g.) and after 12 hours the mixture was warmed on the steam-bath for 30 mins. It was then treated as in the case of the acetate. The *ethyl* l-α-*benzoyloxyphenylacetate* obtained had b. p. 122—123°/<0·1 mm., α_{5461} — 24·68°, α_{4359} — 46·30° ($l = 0{\cdot}25$) (Found : C, 72·5; H, 5·2. $C_{17}H_{16}O_4$ requires C, 71·9; H, 5·6%).

Ethyl l-α-p-*Toluenesulphinoxyphenylacetate.*—(a) *From ethyl* l-*mandelate and* p-*toluenesulphinyl chloride.* *p*-Toluenesulphinyl chloride (6·0 g.) was added slowly to a solution of ethyl *l*-mandelate (5·4 g.) in pyridine (2·6 g.). After 48 hrs., the reaction mixture was decomposed with ice and dilute hydrochloric acid, and the product extracted with ether. From the extract ethyl *l*-α-*p*-toluenesulphinoxyphenylacetate (3 c.c.) was isolated by fractional distillation; b. p. 136—139°/<0·1 mm., α_{5461} — 50·4° (in chloroform solution, $c = 4{\cdot}70$; $l = 2{\cdot}0$), $\alpha_{5461}^{20^\circ}$ — 6·63° ($l = 0{\cdot}25$), $n_D^{19^\circ}$ 1·5677.

(b) *From ethyl* l-*mandelate and ethyl* p-*toluenesulphinate.* A mixture of ethyl *l*-mandelate (10 g.) and freshly distilled ethyl *p*-toluenesulphinate (10·2 g.) was heated at 100°/18 mm. for 75 hrs. By fractional distillation of the product, *ethyl* l-α-p-*toluenesulphinoxyphenylacetate* (3 c.c.) was isolated, b. p. 135—140°/<0·1 mm., $\alpha_{5461}^{20^\circ}$ — 5·95° ($l = 0{\cdot}25$), $n_D^{19^\circ}$ 1·5676 (Found : C, 63·6; H, 5·7; S, 10·3. $C_{17}H_{18}O_4S$ requires C, 64·1; H, 5·7; S, 10·0%).

The discrepancy between the rotatory powers of the two specimens of the ester is doubtless due to the partial resolution of the asymmetric *p*-toluenesulphinoxy-radical which occurs during this method of preparation (Phillips, J., 1925, **127**, 2552).

(c) *From ethyl* l-α-*chloroformoxyphenylacetate.* Only a slight evolution of carbon dioxide occurred when anhydrous sodium *p*-toluenesulphinate (8·3 g.) was triturated with the ester (8·0 g.). After an hour, water was added and the oily insoluble products were extracted with ether. The ethereal extract yielded, on distillation, some unchanged ester (2·5 c.c., b. p. 72—76°/<0·1 mm.), and when the temperature was raised a steady effervescence occurred. This was doubtless caused by the decomposition of the anhydride formed by the interaction of the chloroformoxy-ester and the sodium *p*-toluenesulphinate. When this decomposition had ceased ethyl *l*-α-*p*-toluenesulphinoxyphenylacetate distilled, b. p. 136—138°/<0·1 mm., $\alpha_{5770}^{20^\circ}$ − 10·47°; $\alpha_{5461}^{20^\circ}$ − 12·46; $\alpha_{4359}^{20^\circ}$ − 23·6° ($l = 0·25$). After the distillation of this ester a higher-boiling residue remained, which finally distilled at 150—155°/<0·1 mm. and then set to a mass of prismatic needles, m. p. 76—77°, alone or when mixed with di-*p*-tolyldisulphoxide.

The Conversion of Ethyl l-α-*Chloroformoxyphenylacetate into Ethyl* d-*Phenylchloroacetate.*—When pyridine (1·7 c.c.) was added to the ethyl *l*-chloroformoxy-ester (5 g.) cooled in ice, a gelatinous mass was formed which subsequently liquefied with effervescence. The reaction was completed by gently warming the mixture and keeping it for 2 hrs. at the ordinary temperature; dilute hydrochloric acid was then added, and the ethyl *d*-phenylchloroacetate extracted with ether. It (3·5 c.c.) had b. p. 133°/18 mm., $\alpha_{5461}^{20^\circ}$ + 24·60°, $\alpha_{4359}^{20^\circ}$ + 45·60° ($l = 0·25$) (Found : Cl, 18·2. Calc. : Cl, 17·9%).

The Conversion of Ethyl l-α-*Chloroformoxyphenylacetate into Ethyl* l-*Phenylchloroacetate.*—Ethyl *l*-α-chloroformoxyphenylacetate (5·0 g.) was heated for 4 hrs. at 150°/14 mm., during which effervescence occurred. The resulting ethyl *l*-phenylchloroacetate had b. p. 131—133°/14 mm. and, after redistillation, $\alpha_{5461}^{20^\circ}$ − 14·35°; $\alpha_{4359}^{20^\circ}$ − 26·59° ($l = 0·25$) (Found : Cl, 17·9. Calc. : Cl, 17·9%).

Ethyl d-*Phenylchloroacetate.*—Ethyl *l*-mandelate, cooled in an ice–salt mixture, was treated with phosphorus trichloride or pentachloride in either the presence or the absence of pyridine; the proportion of the various reagents taken are set out below. The reaction in each case was completed by gentle warming on a steam-bath for periods up to 2 hrs. The reaction mixtures were washed with water, and the products extracted with ether. The products sometimes contained unreacted hydroxy-ester as well as the chloro-ester. Since these two esters have practically the same b. p., it is not possible to separate them by fractional distillation. Determination of the chlorine content of the product afforded a measure of the proportion of chloro-ester present.

Halogenating agent.	Pyridine, mols.	Rotatory power of product, α_{5461} ($l = 1·0$).	Chloro-ester in product, %.
PCl_5, 1 mol.	2	+ 45·5°	98
PCl_3, 2 mols.	2	+ 13·44	63
PCl_3, 1 mol.	0	+ 79·30	96

dl- *and* d + dl-α-*Carbethoxybenzyl*-p-*tolylsulphone.*—A solution of ethyl *dl*-phenylchloroacetate (5 g.) and sodium *p*-toluenesulphinate (5 g.) in ethyl alcohol (25 c.c.) was heated under reflux for 1·5 hrs. The reaction mixture was then diluted with water to dissolve the sodium chloride which had separated, and on standing, the *sulphone* (4·6 g.) separated as fine needles, m. p. 112—113° before and after recrystallisation from aqueous alcohol or ether (Found: C, 64·2; H, 5·7. $C_{17}H_{18}O_4S$ requires C, 64·2; H, 5·7%). The *d* + *dl*-sulphone, prepared in a similar manner from ethyl *d*-phenylchloroacetate of α_{5461} + 30·5° (l = 0·25), had m. p. 111—112°, α_{5461} + 25·6° (c = 1·25 in chloroform; l = 2·0). It is more soluble in aqueous alcohol than the *dl*-compound, which therefore tends to crystallise from solutions of the partially racemised sulphone.

dl-α-*Carboxybenzyl*-p-*tolylsulphone*.—The above sulphone (1·6 g.; finely powdered), barium hydroxide (0·8 g.), and water (20 c.c.) were mixed and shaken occasionally during several days. A little unchanged sulphone was then removed by filtration, and dl-α-*carboxybenzyl*-p-*tolylsulphone* (1·15 g.) was precipitated by dilute hydrochloric acid. It separated from aqueous alcohol as stellate clusters of prismatic needles, m. p. 169—170° (decomp.) (Found: C, 62·4; H, 4·9. $C_{15}H_{14}O_4S$ requires C, 62·1; H, 4·8%). When heated at 170 for 2 mins., this sulphone is converted into benzyl-*p*-tolylsulphone, m. p. 144—145°, either alone or when mixed with a specimen prepared by the interaction of benzyl chloride and sodium *p*-toluenesulphinate. *dl*-α-Carbethoxybenzyl-*p*-tolylsulphone yields the same compound when gently heated with 0·5*N*-alcoholic sodium hydroxide.

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