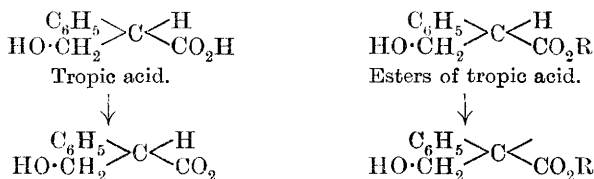


XXIV.—*Studies in the Phenylsuccinic Acid Series.*
Part VI. Racemisation Phenomena Observed
during the Investigation of the Optically Active
Phenyl- and Diphenyl-succinic Acids and their
Derivatives.

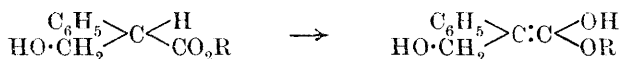
By HENRY WREN.

It has been recently shown (Wren and Still, T., 1917, **111**, 1019) that the esters of *r*- and *meso*-diphenylsuccinic acids are interconvertible under the influence of alkali. To quote a specific example, ethyl *r*-diphenylsuccinate is almost quantitatively transformed into the ester of the *meso*-acid when its alcoholic solution is treated with a solution of sodium ethoxide in ethyl alcohol; also, when the ester is hydrolysed with an insufficient amount of aqueous ethyl-alcoholic potassium hydroxide solution, the non-hydrolysed portion is found to have suffered partial isomerisation, with the production of ethyl *meso*diphenylsuccinate. Since, in solution at any rate, ethyl *r*-diphenylsuccinate may be regarded as a molecular mixture of ethyl *d*-diphenylsuccinate and ethyl *l*-diphenylsuccinate, it was to be expected that the esters of the optically active acids would separately undergo similar transformation, and would therefore become racemised, the possibility of a balanced action being excluded in this case, since any further isomerisation of the *meso*-ester which might be formed would merely lead to the production of the *r*-ester. The theoretical expectations have been fully confirmed by a series of experiments with the methyl and ethyl esters of the optically active acids. A typical example is furnished by the formation of ethyl *meso*-diphenylsuccinate as a product of the action of ethyl-alcoholic sodium ethoxide on ethyl *l*-diphenylsuccinate. Similarly, when ethyl *d*-diphenylsuccinate is hydrolysed with an insufficient amount of aqueous ethyl-alcoholic potassium hydroxide solution, the non-hydrolysed portion is found to be almost inactive towards polarised light and to consist practically entirely of ethyl *meso*diphenylsuccinate. It would thus appear that the racemisation previously observed to occur during the hydrolysis of esters of the optically active diphenylsuccinic acids (Wren and Still, T., 1915, **107**, 1454) takes place in part, at any rate, previous to the actual hydrolysis, and is thus due to rearrangement of the ester, and not of the acid. The greater liability of esters as compared with the corresponding acids to racemisation under the influence of alcoholic alkali has been pointed out by Gadamer (*Chem. Zeit.*, 1910, **34**, 1004; *J. pr.*

Chem., 1913, [ii], **87**, 312), who found that, whilst the esters of tropic acid are readily racemised, the acid itself is not racemised by hydroxyl ions. This difference in behaviour is ascribed to the ionisation of the acid at the carboxyl group, whilst the ester, which behaves as a pseudo-acid, only becomes ionised in the presence of hydroxyl ions, thus:



It has, however, been pointed out by Frankland (*T.*, 1913, **103**, 725) that the racemisation may be due to loss of asymmetry caused by tautomeric change previous to ionisation, thus:



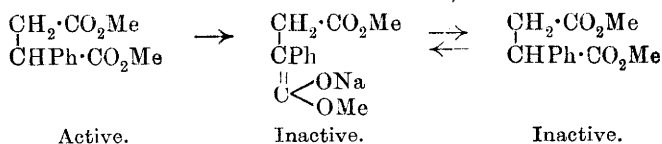
The only instance of racemisation of an ester previous to hydrolysis which appears to have been noted in the literature is the observation of McKenzie and Widdows (*T.*, 1915, **107**, 713) that *l*-menthyl *d*-phenyl-*p*-tolylacetate is, in part, catalytically racemised by alkali prior to its undergoing hydrolysis. In a case which presents some analogies, Wren (*T.*, 1909, **95**, 1596) found that the portion of the ester which escapes conversion into amide is partly inactivated when methyl *l*-mandelate is acted on by cold alcoholic ammonia.

The observations have been extended to the optically active phenylsuccinic acids and their esters, since the latter substances are much more readily soluble than the derivatives of the diphenylsuccinic acids, and therefore allow the course of racemisation to be followed directly by polarimetric measurement. It is thus found that ethyl and methyl *d*-phenylsuccinates are rapidly and completely racemised by the action of a solution of the requisite sodium alkoxide in the corresponding alcohol, and also that when the latter ester is treated with potassium hydroxide dissolved in slightly aqueous ethyl alcohol in quantity insufficient for complete hydrolysis, the non-hydrolysed portion is almost completely racemised under the conditions described in the experimental section of the paper.

Some time ago, it was found by Wren and Williams (*T.*, 1916, **109**, 579) that a partly racemised acid was obtained when methyl *d*-phenylsuccinate is hydrolysed by an excess of aqueous ethyl-

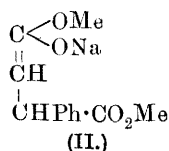
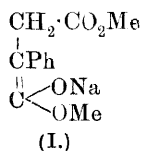
alcoholic potassium hydroxide solution. Thus, in one experiment, the ester was heated with about six times the theoretically necessary quantity of potassium hydroxide dissolved in aqueous ethyl alcohol (water:alcohol::1 vol.:2 vols.), when the recovered acid was found to have $[\alpha]_D +110.2^\circ$ in acetone solution, whilst the parent acid had $[\alpha]_D^{12.5} +175.4^\circ$. The considerable activity of this acid became somewhat remarkable when considered in conjunction with the almost complete racemisation of the non-hydrolysed ester in the experiment just quoted, and pointed to a profound influence of the varying factors, namely, the amount of potassium hydroxide and the water content of the solution. The effect of variation in the latter was therefore studied, and was found to exercise a very marked influence on the optical activity of the recovered acid. In three strictly comparable experiments, in which the only differences consisted in the use of absolute, approximately 80 per cent. and 50 per cent alcohol respectively, the acid formed by hydrolysis was found to have $[\alpha]_D +3.1^\circ$, $+59.1^\circ$, and $+100.3^\circ$ respectively in ethyl-alcoholic solution in which the parent acid had $[\alpha]_D +147.4^\circ$; under closely similar conditions, the latter acid was found to be unaffected by the action of an excess of alcoholic or aqueous-alcoholic sodium hydroxide solution.

During the last few years, a considerable amount of evidence has been accumulated which indicates that racemisation under the influence of alkali may frequently be attributed to keto-enolic desmotropy, with consequent disappearance of the asymmetry of the compound. In the present instance, the inactivation of methyl *d*-phenylsuccinate when acted on by sodium methoxide may be due to the formation of the enolic form, thus:



The evidence which has been brought forward in favour of such an explanation of racemisation in analogous case is, so far, of a purely qualitative nature; in no single instance has the enolic form been isolated or its amount determined. The actual separation of the enolic modification would doubtless be a matter of great difficulty in many cases, since the proportion of enolised molecules need be but infinitesimal to account for the phenomena of racemisation. On the other hand, it was hoped to be able to bring quantitative evidence of the presence of the enolic modification by utilising the method adopted by K. H. Meyer (*Ber.*, 1912, 45, 2864) in his investigations on ethyl malonate and ethyl

methanetricarboxylate. Direct titration of a methyl-alcoholic solution of methyl *d*- or *r*-phenylsuccinate with bromine failed to disclose the presence of any enol, and a similar result was obtained when experiments were performed on the esters dissolved in methyl-alcoholic sodium methoxide solution, although under the latter conditions ethyl malonate was found to be largely enolised. The experimental conditions were not greatly varied in this case, however, since the objection could possibly be raised that, in order to demonstrate the point at issue, it would be necessary to show definitely that enolisation occurs in such a manner as to form compound I, and not II:



It is hoped to apply the method, however, to esters of certain monobasic acids to which this objection cannot be urged.

Lastly, if racemisation be attributable to the formation of an enolic derivative, it would be expected that the nature of the basic atom or group of the alkali would have an influence on the result. Experiments on the hydrolysis of methyl *d*-phenylsuccinate with aqueous ethyl-alcoholic tetramethylammonium hydroxide solution were therefore performed; racemisation was found to be even more pronounced than with potassium hydroxide solution under nearly similar conditions.

EXPERIMENTAL.

Formation of Ethyl mesoDiphenylsuccinate from Ethyl d- and l-Diphenylsuccinates.

A. By the Action of Ethyl-alcoholic Sodium Ethoxide Solution.—Ethyl *l*-diphenylsuccinate (1 gram) was warmed with a solution of sodium ethoxide in ethyl alcohol (0.666*N*; 20 c.c.) in a closed vessel to about 50°, when it dissolved completely; the solution was allowed to cool to the ordinary temperature, when it became almost solid. After remaining during three days at the temperature of the laboratory, the precipitate was removed and washed successively with alcohol, warm water, and, finally, alcohol. It melted at 139–140°, and was optically inactive in acetone solution. After being crystallised from rectified spirit, ethyl *meso*diphenylsuccinate was obtained in well-defined needles melting at 140–141°.

B. By Partial Hydrolysis.—Ethyl *d*-diphenylsuccinate (1.5

grams) was heated during four hours with aqueous ethyl-alcoholic potassium hydroxide solution ($0.25N$; 15 c.c.), this being about three-fifths of the quantity required for complete hydrolysis. The solution was diluted with water, and the unattacked esters were extracted with chloroform. The residue, obtained after removal of the latter, melted at $138-140^\circ$; it had $[\alpha]_D + 5.4^\circ$ in acetone solution ($l=2$, $c=1.113$, $\alpha_D + 0.12^\circ$), whereas the pure *d*-ester has $[\alpha]_D + 279.4^\circ$ under similar conditions. After being crystallised from rectified spirit, it yielded pure ethyl *mesodiphenylsuccinate*, which was optically inactive in acetone solution and melted at $140-141^\circ$.

*Formation of Methyl mesoDiphenylsuccinate from Methyl
l- and d-Diphenylsuccinates.*

A. By the Action of a Methyl-alcoholic Solution of Sodium Methoxide.—Methyl *l*-diphenylsuccinate (1 gram) was heated in a stoppered flask during four hours at $55-65^\circ$ with a solution of sodium methoxide in absolute methyl alcohol ($0.704N$; 60 c.c.). When the solution was cooled, a quantity of fine, prismatic crystals separated, which were removed, washed with water and methyl alcohol, and dried. After being crystallised from acetone, the product was obtained in well-defined needles, which were optically inactive when dissolved in chloroform ($l=2$, $c=0.5115$), and were identified as methyl *mesodiphenylsuccinate* by their crystalline form, melting point ($218.5-219.5^\circ$) alone, and when mixed with an approximately equal quantity of the synthetic *meso*-ester.

B. By Partial Hydrolysis.—A solution of methyl *l*-diphenylsuccinate (1.5 grams) in boiling methyl alcohol (100 c.c.) was heated during four hours with aqueous methyl-alcoholic potassium hydroxide solution ($0.593N$; 8 c.c.), this being approximately half the quantity of alkali required for the complete hydrolysis of this amount of the ester. The alcohol was removed on the water-bath and the residue warmed with water. The undissolved portion was removed and dried. It was optically inactive when dissolved in chloroform ($l=2$, $c=0.8365$), and, after being crystallised from acetone, yielded methyl *mesodiphenylsuccinate*, which melted at $218.5-219.5^\circ$; the melting point was unaltered by admixture with the synthetic *meso*-ester.

Racemisation of Methyl and Ethyl d-Phenylsuccinates under the Influence of Alkali.

A. *By Sodium Alkylxide.*—Methyl *d*-phenylsuccinate (0.8157 gram) was dissolved in methyl-alcoholic sodium methoxide solution (20.5 c.c.), and transferred as rapidly as possible to a 2-dcm. tube. Approximately three minutes after being prepared, the solution had $\alpha_D + 8^\circ$, but the field was somewhat cloudy, and the activity altered too rapidly to allow of accurate measurement. After about fifteen minutes, the value had decreased to $+3.5^\circ$, after forty minutes to $+0.5^\circ$, after seventy minutes to $+0.17^\circ$, after one hundred minutes to $+0.05^\circ$. After two hours, the solution was poured into a slight excess of dilute hydrochloric acid. The ester was extracted with ether, the ethereal solution washed with sodium carbonate, and dried over calcium chloride. The residue, obtained after removal of the solvent, solidified readily, and was optically inactive in acetone solution ($l=2$, $c=1.555$). After being crystallised from light petroleum, it yielded characteristic clusters of prisms of methyl *r*-phenylsuccinate, which melted at $57.5\text{--}58.5^\circ$. The melting point remained unchanged when the substance was mixed with the synthetic *r*-ester.

In a similar manner, ethyl *d*-phenylsuccinate (0.9964 gram) was dissolved in ethyl-alcoholic sodium ethoxide solution (1.059*N*; 20 c.c.). In this case, racemisation proceeded so rapidly as to be almost complete before polarimetric measurements could be made, and the solution had become quite inactive within ten minutes. Since the liquid nature of the ethyl *r*-ester rendered the identification of a small quantity of it a matter of difficulty, water was added to the solution, and the ester hydrolysed. The resulting *r*-phenylsuccinic acid melted at $167\text{--}168^\circ$, whereas Higson and Thorpe (T., 1906, **89**, 1470) give 168° as the melting point of this acid.

B. *By Partial Hydrolysis.*—Methyl *d*-phenylsuccinate (3 grams) was heated to boiling during two and a-half hours with slightly aqueous methyl-alcoholic potassium hydroxide solution (0.395*N*; 25 c.c.), this being rather more than one-third of the quantity theoretically necessary for complete hydrolysis. The alcohol was removed on the water-bath, and the residue mixed with water and shaken with ether. The residue (about 0.3 gram) obtained after removal of the ether solidified readily, and had $[\alpha]_D + 2.12^\circ$ when dissolved in acetone ($l=2$, $c=1.178$, $\alpha_D + 0.05^\circ$), whereas the pure ester has $[\alpha]_D^{20} + 152.2^\circ$ under similar conditions. After being crystallised from light petroleum (b. p. $40\text{--}60^\circ$), it yielded pure

methyl *r*-phenylsuccinate, which melted at 57—58·5°; this value remained unchanged after admixture with the synthetic ester.

Action of Alkali on l-Phenylsuccinic Acid.

The *l*-phenylsuccinic acid used in these experiments had $[\alpha]_D -148\cdot3^\circ$ in ethyl-alcoholic solution, a value which agrees well with the data of Wren and Williams (*loc. cit.*).

Three comparative experiments were performed, in which the acid (1 gram) was treated in a closed vessel with (a) sodium ethoxide solution (1·059*N*; 50 c.c.) and absolute ethyl alcohol (20 c.c.); (b) sodium ethoxide solution (50 c.c.), alcohol (20 c.c.), and water (0·95 c.c.), and (c) sodium ethoxide solution (50 c.c.), alcohol (10 c.c.), and water (10 c.c.). In each case a certain amount of precipitate separated. The mixtures were heated with frequent agitation during five hours at 70°, then neutralised with hydrochloric acid, and evaporated to remove alcohol; the acids were isolated by extraction of the acidified solutions with ether. The dried acids were polarimetrically examined in ethyl-alcoholic solution, the values for the specific rotations being (a) $-146\cdot6^\circ$ ($l=2$, $c=2\cdot8815$, $\alpha_D -8\cdot45^\circ$), (b) $-145\cdot5^\circ$ ($l=2$, $c=1\cdot691$, $\alpha_D -4\cdot92^\circ$), and (c) $-146\cdot2^\circ$ ($l=2$, $c=1\cdot7035$, $\alpha_D -4\cdot98^\circ$). In no case, therefore, was any evidence of racemisation obtained.

Complete Hydrolysis of Methyl d-Phenylsuccinate by Alcoholic Sodium Hydroxide containing differing Proportions of Water.

In these experiments, the weight of ester and alkali, the total volume of the solution, the temperature, and duration were maintained uniform, the only variation consisting in the replacement of differing volumes of alcohol by water. Stock solutions of ester were prepared by dissolving 2 grams of the latter in 30 c.c. of ethyl alcohol, and of alkali by dissolving sodium in absolute ethyl alcohol; the latter solution was 1·1*N*. Ten c.c. of the ester solution were mixed with (a) alkali solution (25 c.c.), alcohol (25 c.c.), and water (0·45 c.c.); (b) alkali solution (25 c.c.), alcohol (15 c.c.), water (10 c.c.), and (c) alkali solution (25 c.c.), water (25 c.c.). The solutions were heated in closed flasks during four hours at 60—65°; precipitates speedily separated in (a) and (b) but (c) remained homogeneous throughout. The resulting mixtures were nearly neutralised with hydrochloric acid and evaporated to remove alcohol; the aqueous solutions were extracted with ether after acidification with mineral acid. The residual phenylsuccinic acids were polarimetrically examined in ethyl-alcoholic solution, when

the following values were observed for the specific rotation: (a) $+3.1^\circ$ ($l=2$, $c=2.2391$, $\alpha_D + 0.14^\circ$); (b) $+59.1^\circ$ ($l=2$, $c=1.913$, $\alpha_D + 2.26^\circ$); (c) $+100.3^\circ$ ($l=2$, $c=2.0731$, $\alpha_D + 4.16^\circ$).

Complete Hydrolysis of Methyl d-Phenylsuccinate by Aqueous-Alcoholic Tetramethylammonium Hydroxide Solution.

The solution of the alkali was prepared by warming an aqueous solution of tetramethylammonium iodide with a slight excess of silver oxide, and removal of silver iodide and unchanged oxide. The filtrate was concentrated to 14 c.c., and then diluted with ethyl alcohol to 55 c.c. An approximately *N*-solution was thus obtained.

The methyl *d*-ester (1 gram) was heated during two and a-half hours with the solution described above, and the corresponding acid isolated in the usual manner; it melted at $164\text{--}168.5^\circ$, and had $[\alpha]_D + 10.1^\circ$ in ethyl-alcoholic solution ($l=2$, $c=3.329$, $\alpha_D + 0.67^\circ$).

Action of Ferric Chloride on Methyl d-Phenylsuccinate.

It has been shown by Meyer (*Ber.*, 1911, **44**, 2725) in the case of ethyl acetoacetate that ferric chloride exerts a direct enolising action. The behaviour of an ethyl-alcoholic solution of methyl *d*-phenylsuccinate towards anhydrous ferric chloride has therefore been polarimetrically investigated in the expectation that enolisation, if induced at the asymmetric carbon atom, would betray itself by racemisation. The solutions, however, were found to be optically stable under these conditions.

Methyl *d*-phenylsuccinate (0.4869 gram) was dissolved in ethyl alcohol and the solution made up to 20 c.c.; a portion of this solution had $\alpha_D + 6.73^\circ$ when examined in a 2-dcm. tube, and this value had not changed at the end of forty hours after the addition of a small quantity of ferric chloride. A further portion of the latter substance was added, and the solution allowed to remain at the temperature of the laboratory during nine days, at the end of which period the ester was isolated and examined in ethyl-alcoholic solution; it had $[\alpha]_D + 129.8^\circ$, whereas the value $+138.2^\circ$ had been determined for the original specimen.

Possible Enolisation of Methyl Phenylsuccinate in Solution.

Methyl *d*-phenylsuccinate (0.5369 gram) and methyl *r*-phenylsuccinate (0.4496 gram) were separately dissolved in methyl alcohol

(20 c.c.) and titrated with an *N*/10-solution of bromine in the same solvent until a faint, permanent, yellow coloration was produced; 0.55 c.c. of bromine was required in each case, whilst in a blank experiment 0.60 c.c. was necessary.

Methyl *d*-phenylsuccinate (0.3292 gram) was dissolved in a well-cooled methyl-alcoholic solution of sodium methoxide, and the product poured into an excess of a solution of bromine in methyl alcohol containing hydrogen chloride. Excess of bromine was removed by the addition of β -naphthol dissolved in methyl alcohol, and the resulting solution warmed after addition of aqueous potassium iodide (10 per cent.). The liberated iodine required 0.3 c.c. of *N*/10-sodium thiosulphate solution, this quantity being the same as that required in a blank experiment.

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