

CLXXII.—*Racemisation by Alkali as Applied to the Resolution of *r*-Mandelic Acid into its Optically Active Isomerides.*

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SOME three years ago, one of us (Trans., 1904, 85, 1249) attempted to effect the asymmetric synthesis of mandelic acid from benzoylformic acid by the aid of *l*-menthol, the method adopted being to reduce *l*-menthyl benzoylformate by aluminium amalgam, saponify the product, and then completely remove the menthol from the resulting mixture. It was anticipated at the time that an asymmetric synthesis would be brought about in accordance with the scheme: $\text{C}_6\text{H}_5 \cdot \text{CO} \cdot \text{CO}_2\text{H} \rightarrow \text{C}_6\text{H}_5 \cdot \text{CO} \cdot \text{CO}_2 \cdot \text{C}_{10}\text{H}_{19} \rightarrow \text{C}_6\text{H}_5 \cdot \text{CH}(\text{OH}) \cdot \text{CO}_2 \cdot \text{C}_{10}\text{H}_{19} \rightarrow \text{C}_6\text{H}_5 \cdot \text{CH}(\text{OH}) \cdot \text{CO}_2\text{H}$. The mandelic acid, obtained by this method, was, however, invariably optically inactive, although there was distinct evidence that the reduction of the benzoylformate had actually proceeded asymmetrically. That the reduction product in such a case is a mixture of unequal amounts of *l*-menthyl *d*-mandelate and *l*-menthyl *l*-mandelate, containing a slight preponderance of the latter, was indicated by a determination of its specific rotation, which gave a value numerically higher than that of the partially racemic *l*-menthyl *r*-mandelate; the latter ester, which is readily formed from the *r*-acid, would have been produced if the reduction had proceeded symmetrically. The failure to realise the asymmetric synthesis of mandelic acid was found to be due to the racemising effect exercised by the alkali during the saponification of the ester mixture. It was noted in this connexion that partial racemisation takes place with remarkable ease when *l*-menthyl *l*-mandelate is saponified by alcoholic potassium hydroxide; *l*-mandelic acid is easily converted into this ester, but the *l*-acid cannot be regenerated from it free from the *r*-isomeride, no matter under what conditions the saponification is conducted. The behaviour of *l*-menthyl *d*-mandelate on saponification is similar.

Marckwald and McKenzie showed that, when *r*-mandelic acid is heated at 155° for one hour with *l*-menthol, the unesterified acid is lævorotatory, and on this observation a method was based for resolving optically inactive compounds into their active components differing in principle from any of Pasteur's classical methods (*Ber.*, 1899, 32, 2130; 1900, 33, 208; 1901, 34, 469; Marckwald and Meth, *Ber.*, 1905, 38, 801). The conclusion was drawn that the velocity of formation of *l*-menthyl *d*-mandelate is greater than that of *l*-menthyl *l*-mandelate during the heating of the *r*-acid with *l*-menthol, and it

was found subsequently by direct measurements of the velocity of saponification of these esters that the *d*-mandelate is the more readily saponifiable of the two (McKenzie and Thompson, Trans., 1907, 91, 789). The fractional saponification of *l*-menthyl *r*-mandelate was also studied (*Ber.*, 1899, 32, 2130; Trans., 1904, 85, 378). This ester is obtained by esterifying *r*-mandelic acid by *l*-menthol as completely as possible according to the Fischer-Speier method; it is a partially racemic ester, which is easily prepared in a state of uniformity, since under ordinary conditions it may be crystallised unchanged and is, accordingly, not resolved on crystallisation. When saponified by an excess of alkali, it yields the *r*-acid. When an insufficiency of alkali was used, the fractional saponification method of Marckwald and McKenzie gave, on almost every occasion, a dextrorotatory acid.

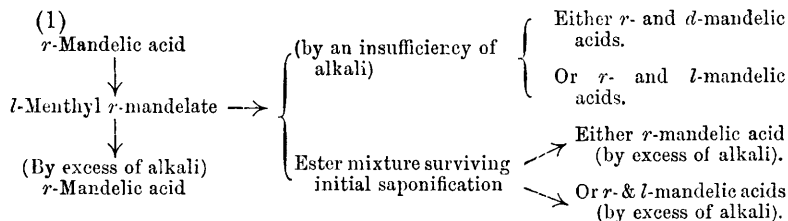
This result is normal. An alcoholic solution of the partially racemic ester contains equal amounts of *l*-menthyl *d*-mandelate and *l*-menthyl *l*-mandelate. Since the former is the more readily saponifiable of the two, the fractional saponification of the partially racemic ester by alcoholic potassium hydroxide might be expected to give a *dextrorotatory* potassium salt. On two separate occasions, however, a *laevorotatory* salt was obtained, and, at the time, the reason of this was not clear. The racemisation phenomena, however, subsequently observed during the saponification of menthyl and bornyl esters by alkali (McKenzie and Thompson, Trans., 1905, 87, 1004) threw light on this problem, and many unsuccessful attempts were accordingly made to obtain the conditions under which a *laevorotatory* potassium salt would result on the fractional saponification of the partially racemic ester in question. These attempts have been continued with success, and the results are embodied in the present paper.

When the fractional saponification is conducted in concentrated solution under the conditions recorded in the experimental part, a *laevorotatory* potassium salt is formed, and from this a specimen of the pure *l*-acid may be isolated. It is shown that, as a product of the fractional saponification of *l*-menthyl *r*-mandelate in alcoholic solution, either a dextrorotatory or a *laevorotatory* acid may be obtained from the same weight of ester and using the same weight of alkali.

In each case, in addition to the fractional saponification, racemisation by alkali of the active potassium salt formed occurs. The formation of the dextrorotatory potassium salt is easily accounted for, the racemisation phenomena being in this case of secondary importance. The formation of the *laevorotatory* salt, however, is due to the racemisation being pronounced, and is explained as follows. Shortly after the saponification has started, we have a mixture of (1) *l*-menthyl *d*-mandelate and *l*-menthyl *l*-mandelate, the latter being in excess; (2) potassium *r*-mandelate; (3) alkali; (4) ethyl alcohol, and (5)

menthol. If no racemisation had taken place, (2) would have consisted of a mixture of potassium *d*-mandelate and potassium *l*-mandelate with an excess of the former; the alkali is, however, strong enough at this stage to cause the formation of an inactive potassium salt. As the saponification proceeds, the concentration of the alkali becomes less and less, and its tendency to cause racemisation is also diminishing, until towards the end of the operation it is negligible. On the other hand, the ratio of *l*-menthyl *l*-mandelate to *l*-menthyl *d*-mandelate in the unsaponified portion is gradually increasing, so that the potassium salt formed, instead of being inactive as towards the start of the action, now becomes *l*-rotatory. The explanation is simply that, in the initial stages of the saponification, the racemisation caused by the alkali is marked, and becomes less and less as the saponification proceeds. A similar interpretation had been previously advanced to account for the behaviour of *l*-menthyl *dl*-phenylethoxyacetate on fractional saponification (Trans., 1905, 87, 1004).

The following transformations, in which racemisation by alkali plays a part, have accordingly been realised :



(2) By conducting the fractional saponification of *l*-menthyl *r*-mandelate in such a manner that a dextrorotatory potassium salt is formed as the product of the initial saponification, and then saponifying the surviving ester mixture by an excess of alkali in such a manner that the racemising effect of alkali is brought into action, the change *r*-mandelic acid \rightarrow *r*-mandelic acid and *d*-mandelic acid may be accomplished.

(3) By heating *r*-mandelic acid with *l*-menthol, removing the unesterified acid by shaking the ethereal solution of the reaction product with aqueous sodium carbonate, and then saponifying the residual ester mixture with an excess of alkali, the change *r*-mandelic acid \rightarrow *r*-mandelic acid and *l*-mandelic acid may be brought about (Markwald and McKenzie, *loc. cit.*). This transformation can also be effected by conducting the fractional saponification of *l*-menthyl *r*-mandelate in such a manner that a *l*-rotatory potassium salt is formed as the product of the initial saponification and then saponifying the surviving ester mixture by an excess of alkali. In the latter case, the racemising effect of alkali may or may not be caused to be pronounced.

It should be observed that these changes are not examples of asymmetric synthesis, inasmuch as the starting point is *r*-mandelic acid, a compound which already contains an asymmetric carbon atom.

Similar transformations may also be effected by aid of *l*-borneol. When *l*-bornyl *r*-mandelate is saponified by an insufficiency of potassium hydroxide, it generally gives a *l*ævorotatory potassium salt (Trans., 1904, **85**, 378; 1905, **87**, 1004) differing in this respect from *l*-menthyl *r*-mandelate and behaving abnormally, since *l*-bornyl *d*-mandelate is more quickly saponified than *l*-bornyl *l*-mandelate (Trans., 1907, **91**, 789). It is, however, shown in the present paper that it is possible to choose such conditions that the racemising action of the alkali is minimised and a dextrorotatory potassium salt is formed. Accordingly, when *l*-bornyl *r*-mandelate is submitted to fractional saponification, either a dextrorotatory or a *l*ævorotatory potassium salt can be obtained at will.

EXPERIMENTAL.

The Change r-Mandelic Acid \longrightarrow r-Mandelic Acid and l-Mandelic Acid.

l-Menthyl *r*-mandelate was prepared as previously described (Trans., 1904, **85**, 378). The ester (145 grams) was heated to melting at the temperature of a boiling-water bath, and 46.3 c.c. of ethyl-alcoholic potassium hydroxide (1 c.c. = 0.45 KOH), which is about three-fourths of the amount necessary for complete saponification, were warmed and quickly added. The mixture was shaken vigorously, and the reaction was accompanied by a considerable development of heat. The product was heated at 100° under a reflux apparatus for five hours, but, since after twenty-four hours more at the ordinary temperature the liquid was still alkaline, the heating was continued for two hours longer, at the end of which time the liquid was neutral. The ethyl alcohol was then distilled off, an excess of water added to the residue, the precipitated ester mixture and menthol drained off, the filtrate extracted with ether, and the ethereal extract added to the ester mixture and menthol. The usual precautions were taken to ensure that the aqueous solution of potassium salt contained neither ester nor menthol, the solution having been evaporated to a small bulk and again extracted with ether, when no residue was obtained on removal of the ether. The aqueous solution of the potassium salt was acidified by mineral acid and extracted with ether (not quantitatively), when 33 grams of a mixture of *r*- and *l*-mandelic acids were obtained. A determination of the specific rotation of this acid mixture in ethyl alcohol gave the result:

$$l = 2, c = 10.57, \alpha_D^{25} - 1.15^\circ, [\alpha]_D^{25} - 5.4^\circ.$$

The mixture was then treated in the manner already described by

Marckwald and McKenzie (*Ber.*, 1899, **32**, 2130) in order to separate a specimen of the pure *l*-acid. The bulk of the *r*-acid was first removed by crystallisation from water in such a manner that all the active acid remained in the mother liquors. The latter were then converted into magnesium salt, which was fractionated so that as much magnesium *r*-mandelate as possible was separated, the mother liquors again retaining the active product. On conversion of the latter into cadmium salt, a small amount of cadmium *r*-mandelate was removed, and the filtrate decomposed by hydrogen sulphide. In this manner, about 1.1 grams of nearly pure acid were obtained, which, on crystallisation from water, gave a specimen of the pure *l*-acid melting at 131.5—132.5°, and having the following rotation in aqueous solution :

$$l = 2, c = 0.9620, \alpha_D^{17} - 3.01^\circ, [\alpha]_D^{17} - 156.4^\circ.$$

The mixture of residual esters and menthol was freed from ether and the complete saponification carried out with a large excess of alkali in such a manner that the racemising action of the alkali was pronounced. The mixture was melted, and a warm solution of 80 grams of potassium hydroxide in 200 c.c. of ethyl alcohol was added quickly. After the vigorous reaction had subsided, the mixture was heated for two hours at the temperature of a boiling-water bath, and the subsequent manipulation conducted as before. The mandelic acid, obtained in this manner, was only slightly laevorotatory, giving, in ethyl-alcoholic solution, $\alpha_D - 0.14^\circ$ for a 10 per cent. solution in a 2-dcm. tube.

Two other experiments may be quoted in order to show how an alteration of conditions affects the activity of the product from the final saponification. To the melted ester (9.7 grams) was added 2.7 c.c. of ethyl-alcoholic potassium hydroxide (1 c.c. = 0.112 KOH) and the mixture heated at 100° for one hour. The aqueous potassium salt, obtained in the usual manner, gave, on evaporation to the bulk, necessary to fill a 2-dcm. tube, the value $\alpha_D - 0.84^\circ$, whilst the resulting mandelic acid mixture (1.5 grams) gave in ethyl-alcoholic solution :

$$l = 2, c = 10.24, \alpha_D^{18} - 0.81^\circ, [\alpha]_D^{18} - 4.0^\circ.$$

The residual ester mixture was then saponified by an excess of alkali, about five times more than was necessary. To the warm ester mixture was added 15 c.c. of ethyl-alcoholic potassium hydroxide (1 c.c. = 0.4536 KOH), but the subsequent heating at 100° was continued in this case for fifteen minutes only, with constant shaking. The mandelic acid mixture (3 grams), obtained in the usual manner, gave the following rotation in ethyl-alcoholic solution :

$$l = 2, c = 7.234, \alpha_D^8 - 2.33^\circ, [\alpha]_D^8 - 16.1^\circ.$$

$$l = 2, c = 10.15, \alpha_D^{10} - 3.25^\circ, [\alpha]_D^{10} - 16.0^\circ.$$

In another experiment, the same amount of ester was used as

before, the same amount of alkali added under the same conditions, and the heating continued for four hours. The aqueous solution of potassium salt, when evaporated to the bulk necessary to fill a 2-dm. tube, gave in this case $\alpha_D - 0.91^\circ$, whilst the acid mixture gave in ethyl-alcoholic solution :

$$l = 2, c = 10.4, \alpha_D^{18.5} - 1.04^\circ, [\alpha]_D^{18.5} - 5.0^\circ.$$

The ester mixture was then saponified at the ordinary temperature and in dilute solution with slightly more than the calculated amount of alkali. The mixture of esters and menthol was dissolved in 100 c.c. of ethyl alcohol, and 50 c.c. of ethyl-alcoholic potassium hydroxide, containing 1.4 grams of alkali, was added, with constant stirring, during the space of two hours. After forty-eight hours, the solution was only slightly alkaline. The resulting mandelic acid mixture (3 grams) gave in ethyl-alcoholic solution :

$$l = 2, c = 5.21, \alpha_D^{14} - 1.25^\circ, [\alpha]_D^{14} - 12.0^\circ.$$

The Change r-Mandelic Acid \rightarrow r-Mandelic Acid and d-Mandelic Acid.

l-Menthyl *r*-mandelate (145 grams) was submitted to fractional saponification under conditions differing from those already given in the first experiment quoted in this paper. It is of importance to note that the weight of ester is the same as before, as also is the weight of alkali. The partially racemic ester was dissolved in 1500 c.c. of ethyl alcohol, and 500 c.c. of ethyl-alcoholic potassium hydroxide, containing 20.8 grams of alkali, was added, drop by drop, at the ordinary temperature within an interval of five hours, the solution being continuously stirred. In this manner, the racemising action of the alkali was reduced to a minimum. The solution was then allowed to remain for forty-eight hours at the ordinary temperature and was then neutral. The ethyl alcohol, unsaponified esters, and menthol were then removed as usual, and the aqueous solution of potassium salt, when decomposed by mineral acid, gave a mandelic acid mixture having the following rotation in ethyl-alcoholic solution :

$$l = 2, c = 10, \alpha_D^{14} + 0.76^\circ, [\alpha]_D^{14} + 3.8^\circ.$$

The yield of acid was 55 grams. The *r*-acid was removed in a manner similar to that already described for the isolation of the *l*-acid from the levorotatory acid mixture. Finally, 1.3 grams of nearly pure *d*-acid were obtained which, on crystallisation from water, gave a specimen of pure *d*-mandelic acid, melting at $132-133^\circ$, and showing the following rotation in aqueous solution :

$$l = 2, c = 1.065, \alpha_D^{14} + 3.29^\circ, [\alpha]_D^{14} + 154.4^\circ.$$

After the ether had been expelled from the solution of menthyl esters and menthol, which survived the initial saponification, the

product was completely saponified, using the same weight of alkali as in the first experiment quoted, namely, 80 grams. The resulting acid was slightly lævorotatory, giving $\alpha_D - 0.12^\circ$ for a 10 per cent. ethyl-alcoholic solution in a 2-dcm. tube.

In the case of the final saponification, it is possible, by minimising the racemising effect of the alkali, to obtain an acid mixture with a specific rotation in aqueous solution as high as -15° . In the example just quoted, the racemising action of the alkali was caused to be pronounced in order to make the change *r*-mandelic acid \rightarrow *r*-mandelic acid and *d*-mandelic acid more obvious.

The Normal Fractional Saponification of l-Bornyl r-Mandelate.

As has already been pointed out in the introduction, *l*-bornyl *r*-mandelate generally behaves abnormally on fractional saponification giving a lævorotatory potassium salt, the residual ester mixture under the conditions formerly employed having given an inactive potassium salt. By varying the experimental conditions, a dextrorotatory acid mixture may be obtained from the initial saponification and a lævorotatory acid mixture from the final saponification. Both saponifications were conducted at the ordinary temperature and in dilute solution.

Thirty grams of *l*-bornyl *r*-mandelate (Trans., 1905, 87, 1004) were dissolved in 1000 c.c. of ethyl alcohol and partially saponified by the addition, during the space of one hour, of 200 c.c. of ethyl-alcoholic potassium hydroxide; the amount of alkali in the latter solution was one-half of that necessary for complete saponification. The action was conducted with constant stirring at the ordinary temperature. After four hours at the ordinary temperature, the neutral solution was freed from ethyl alcohol, borneol, and residual esters, and gave a dextrorotatory acid mixture:

$l = 2$, $c = 7.85$, $\alpha_D^{18} + 0.21^\circ$, $[\alpha]_D^{18} + 1.3^\circ$ (in ethyl-alcoholic solution).

The mixture of residual esters and borneol was dissolved in 500 c.c. of ethyl alcohol and completely saponified by the addition, within the space of one hour, of 200 c.c. of ethyl-alcoholic potassium hydroxide containing slightly more than the calculated amount of alkali. After the solution had remained for twenty-four hours at the ordinary temperature, it was manipulated in the usual manner, the resulting mandelic acid being lævorotatory:

$l = 2$, $c = 9.98$, $\alpha_D^{11} - 0.99^\circ$, $[\alpha]_D^{11} - 5.0^\circ$ (in ethyl-alcoholic solution).

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