XCIX.—*Resolution of Lactic Acid by Morphine.*

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THE optically active lactic acids have been frequently obtained in quantity in this laboratory by resolving the inactive acid by crystallisation of the zinc ammonium salts, but so far the commoner method of resolution by means of alkaloidal salts has not proved applicable as a working process for preparing the active acids in question. The method of resolution by strychnine (Trans., 1895, 67, 616) is tedious and imperfect, and the use of quinine, as described by E. Jungfleisch in a recent paper (*Compt. rend.*, 1904, 139, 56), judging from the absence of exact data as to the yields and activities of the products obtained, does not appear to be more advantageous.

Experiments on the solubilities of the alkaloidal salts of *d*- and *l*-lactic acids showed that whereas morphine *l*-lactate crystallised readily from dilute aqueous solutions, the salt of the *d*-acid was exceedingly soluble, and only crystallised after standing for several weeks in a vacuum desiccator. Advantage was taken of this marked difference in solubility to resolve the inactive acid, and the process was found to give an almost quantitative yield of pure *l*-lactic acid and about 50 per cent. of the theoretical amount of the *d*-acid. The method, in addition, was found to possess the advantage of being very expeditious, as the morphine *l*-lactate separates quickly and can be readily purified, so that, in spite of the initial expense of the alkaloid, the method of resolution can be recommended when small quantities of active lactic acid displaying the maximum optical activity are required.

On neutralising an aqueous solution of fermentation lactic acid with morphine, the filtered liquid deposited the salt of the *l*-acid on cooling, whilst morphine *d*-lactate remained in solution. The recrystallised salt was converted into zinc lactate, the purity of which was determined by observation of the specific rotation and estimation of the water of crystallisation. The analytical method in this case cannot, however, be regarded as a crucial test of the purity of the product, and as the metallic lactates display comparatively small rotations in solution, it is evident that the presence of traces of inactive material might readily escape detection. Thus, a saturated solution of crystallised zinc lactate gives a polarimetric reading of only 1.02° in a 2-dcm. tube (Trans., 1893, 63, 1154), and the presence of 4 per cent. of the inactive salt would scarcely affect the rotation.

In the present instance, a more accurate index of the purity of the active lactic acid was obtained by converting it into methyl lactate and afterwards into methylic methoxypropionate (Trans., 1899, 75, 485). The latter compound is highly active, and gives in a 1-dcm. tube a polarimetric reading of 95.21° . In determining a rotation of this magnitude, the experimental error is almost eliminated, and even traces of inactive material are readily detected. In this way, it was shown that the *l*-lactic acid obtained in the resolution displayed more than 99 per cent. of the maximum activity recorded for the substance.

EXPERIMENTAL.

Preparation of Morphine d- and l-Lactates.

The *d*- and *l*-lactic acids were obtained by the zinc ammonium salt method of resolution and the morphine salts prepared by neutralising hot aqueous solutions of the acids with the alkaloid. The salt of the *l*-acid crystallised readily in long prisms, which were recrystallised from dilute alcohol. The compound underwent no loss in weight when heated at 120° and was apparently anhydrous. The specific rotation in 5 per cent. aqueous solution was $[\alpha]_D^{20} - 91.8^\circ$.

The salt of the *d*-acid readily formed supersaturated solutions, and only crystallised very slowly in clusters of radiating prisms. Analysis showed the compound to contain one molecule of water of crystallisation (found, $H_2O = 4.40$; calculated = 4.58 per cent.). In 5 per cent. aqueous solution, the salt showed a specific rotation of $[\alpha]_D^{20} - 92.7^\circ$.

Resolution of Inactive Lactic Acid by Morphine.

The lactic acid used (Kahlbaum's syrup) was, as already noted by McKenzie (Trans., 1905, 87, 1375), slightly dextrorotatory, and gave in a 2-dcm. tube a rotation of $+1.85^\circ$. As the activity of a 20 per

cent. aqueous solution altered from dextro- to lævo-rotatory when maintained at 100° , this rotation was evidently due to the presence of a slight excess of the *l*-acid in the mixture. Titration of the syrup before and after hydrolysis showed it to contain 65.5 per cent. of free lactic acid and 23.2 per cent. of the monobasic anhydride.

Forty grams of the syrup were diluted to 400 c.c. with water and boiled under a condenser for six hours in order to hydrolyse the anhydro acid. The hot solution was then neutralised with morphine and filtered. On cooling, an abundant crop of morphine *l*-lactate separated, which was filtered and washed successively with water, alcohol, and ether. A second crop was obtained after evaporating the mother liquor to 250 c.c., but after further concentration no more crystals could be obtained even when the liquid was cooled in a mixture of calcium chloride and ice and nucleated with morphine *d*-lactate. The preparation thus yielded the morphine salts of both the *l*- and *d*-acids, the former being obtained in the crystalline state and the latter as a syrupy solution. The two crops of crystals were united and recrystallised twice from 50 per cent. alcohol. The product (80 grams) was now quite white, and amounted to 95 per cent. of the theoretical yield.

The salt was dissolved in water and decomposed by the addition of ammonium hydrate, and the filtrate, after treatment with animal charcoal, was converted into the calcium salt. The free acid was then liberated by the exact addition of oxalic acid to an aqueous solution of the calcium salt and the filtrate evaporated to a syrup on a water-bath. The residue was extracted with a mixture of alcohol and ether, and, after separation from traces of calcium oxalate and removal of the solvents, pure *l*-lactic acid was obtained as a colourless syrup. A specimen of the crystallised zinc salt was prepared and the rotation determined.

$c = 5.6266$, $l = 2$, $\alpha_D^{15} + 0.78^{\circ}$, $[\alpha]_D^{15} + 6.84^{\circ}$. $Zn = 23.39$; $H_2O = 12.98$.

$C_6H_{10}O_6Zn \cdot 2H_2O$ requires $Zn = 23.30$; $H_2O = 12.90$ per cent.

The remainder of the acid syrup was converted into the silver salt, and, by decomposing the latter with methyl iodide, a specimen of methylic *l*-lactate containing a small proportion of methylic *l*-methoxypropionate (Trans., 1898, 73, 296) was prepared. This was then methylated, as described in a previous paper, by means of the silver oxide reaction, with the production of pure methylic *l*-methoxypropionate. The product was entirely distilled without fractionation under diminished pressure [b. p. $61-62^{\circ}$ (78 mm.)], and the rotation of the distillate determined.

$l = 1$, $\alpha_D^{20} + 94.34^{\circ}$, $d_{20}^{20}/4^{\circ} = 0.9967$, $[\alpha]_D^{20} + 94.7^{\circ}$.

The value already published for the pure compound is $[\alpha]_D^{20} + 95.5^\circ$, so that the specimen described above displays 99.2 per cent. of the maximum specific rotation recorded for this substance. As an obvious precaution in determining a rotation of this magnitude, the length of the tube was checked and found to be correct, whilst the temperature of the liquid was taken by a thermometer reading to $\frac{1}{10}^\circ$. An accurate estimation of the activity of the lactic acid produced in the resolution was thus obtained, and, moreover, all possibility of the optical rotations being affected by the presence of traces of morphine is precluded by the preparation of a volatile derivative.

Reduction of Methylic 1-Methoxypropionate by Hydriodic Acid.

The specimen of active methylic methoxypropionate described above was converted into lactic acid in order to ascertain if the configuration of methyl lactate remains unaltered during methylation by the silver oxide reaction. A similar experiment in which methylic dimethoxysuccinate was converted into tartaric acid is quoted by Purdie and Barbour (*Trans.*, 1901, **79**, 972), but no such evidence has hitherto been obtained in the case of the lactates.

Ten grams of the methoxypropionate were introduced into the decomposition flask of a Zeisel apparatus, and heated with 100 c.c. of hydriodic acid (sp. gr. 1.70). The apparatus was connected in the usual way with flasks containing alcoholic silver nitrate solution, and the reduction was carried out at the minimum temperature (85°) at which silver iodide was formed. After four hours' treatment, the formation of methyl iodide ceased and the action was therefore complete. The bulk of the hydriodic acid was removed from the product by heating at 80° under diminished pressure, and the syrupy residue was diluted with water. The dark brown solution was then shaken with excess of silver oxide in order to remove iodine and hydriodic acid. The colourless filtrate, which contained silver lactate in solution, was saturated with sulphuretted hydrogen and the lactic acid thus liberated was converted into the zinc salt. The recrystallised salt (6 grams) was washed with alcohol to remove traces of zinc methoxypropionate and analysed:

Found Zn = 23.18; H_2O = 13.14.

$C_6H_{10}O_6Zn, 2H_2O$ requires Zn = 23.30; H_2O = 12.90 per cent.
 $c = 5.0030$, $l = 2$, $\alpha_D^{20} + 0.67^\circ$, $[\alpha]_D^{20} + 6.69^\circ$.

The results show the product to be nearly pure zinc *l*-lactate, and the silver oxide method of alkylation is therefore without any disturbing effect on the configuration of an active lactate. The above method of carrying out such reactions obviates excessive heating with the

hydriodic acid, and possible racemisation, or the reduction to propionic acid, is thus largely excluded.

Preparation of d-Lactic Acid from Morphine d-Lactate.

The syrupy mother liquor which had deposited the crops of morphine *l*-lactate, and in which the salt of the *d*-acid remained in solution, was utilised for the preparation of zinc *d*-lactate. The removal of the alkaloid and the liberation of the free acid was carried out as already described, and the whole of the product was converted into the zinc salt. After a series of recrystallisations, in which the purity of each crop was determined by means of the polarimeter, over 50 per cent. of the theoretical amount of pure zinc *d*-lactate was obtained.

$$c = 7.1032, l = 2, \alpha_D^{20} - 0.97^\circ, [\alpha]_D^{20} - 6.83^\circ.$$

$$\text{Found Zn} = 23.32; \text{H}_2\text{O} = 12.96.$$

$$\text{C}_6\text{H}_{10}\text{O}_6\text{Zn}, 2\text{H}_2\text{O} \text{ requires } \text{Zn} = 23.30; \text{H}_2\text{O} = 12.90 \text{ per cent.}$$

Reference may be made here to experiments which are in progress in this laboratory on the solubilities of the zinc lactates. It has been found that although active zinc lactate when crystallised in the usual manner readily loses its water of crystallisation at 110° , the residue left on evaporating an aqueous solution of the salt on a water-bath does not become completely anhydrous even at 150° . It is evident, therefore, that in estimating the specific rotation of active zinc lactate the concentration of the solution cannot be determined by the evaporation of a measured volume of the solution.

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