CCXXXV.—*The Influence of Solvents on the Rotation of Optically Active Compounds. Part XIX. The Rotation of Certain Derivatives of Lactic Acid.*

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FROM the stereochemical point of view, lactic acid and its derivatives are of very considerable interest on account of the simple constitution of the molecule, especially, of course, the fact that it contains only one asymmetric carbon atom. We have thought it desirable, therefore, to prepare three of these derivatives of active lactic acid in order to examine their rotations through a fairly wide range of temperature, and also dissolved in two liquids, which, as experience has shown, differ greatly, as a rule, in their action.

Our optically active material was made by three different methods, which may be briefly indicated. The first consisted in resolving ordinary lactic acid by means of morphine (Irvine, T., 1906, **89**, 935). The syrupy lactic acid with which we commenced had a specific gravity of 1.21, and showed a slight positive rotation. By boiling this syrup with ten times its weight of water for six hours and then titrating with sodium hydroxide solution it was found that a quantity of lactic acid was formed, equal to 91.3 per cent. of the weight of the syrup. One hundred and ninety c.c. of this lactic acid were boiled under reflux with 2280 c.c. of water. To half of this solution 350 grams of morphine were added, whilst the other half—adopting a principle suggested by Pope and Peachey in the resolution of tetrahydroquinidine (T., 1899, **75**, 1066)—was neutralised with the equivalent quantity, 46.3 grams, of sodium hydroxide. The solutions were mixed, and on cooling and then further evaporation three crops of crystals of morphine *l*-lactate were obtained, weighing in all 400 grams. The product was dissolved in 1400 c.c. of boiling water, and then an equal volume of alcohol added to the filtered solution. The substance which separated when the solution cooled was again crystallised in the same way, and ultimately a yield of about 83 per cent. of the theoretical was obtained. This is not quite so high as is recorded by Irvine, but it was obtained by the use of only half the proportional quantity of morphine. The pure morphine *l*-lactate was dissolved in hot water, the morphine precipitated by ammonia, and removed by filtration. Two-thirds of the filtrate were boiled with zinc oxide until the ammonia had all

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disappeared, and, after filtration, the solution was added to the other third, the mixture being then concentrated by evaporation and set aside to crystallise, when zinc ammonium *l*-lactate was obtained. This had a rotation of $\alpha_D^{19.5}$ (100 mm.) 0.487° , $c=8.07$, which gives for the specific rotation $+6.03^\circ$, whereas Purdie quotes $+6.06^\circ$ at 20° .

We also prepared active zinc ammonium lactate by the resolution of the zinc ammonium salt exactly according to Purdie and J. Wallace Walker (T., 1895, **67**, 618, 619; see also Purdie, T., 1893, **63**, 1143), and from 500 c.c. of lactic acid syrup 160 grams of zinc ammonium lactate were obtained. The specific rotation of this first crop of crystals was $[\alpha]_D^{20} +5.94^\circ$, $c=8$; α_D^{20} (200 mm.) 0.95° , so that the substance was practically pure, and on recrystallisation it gave $[\alpha]_D^{20} +6.05^\circ$. The yield thus obtained was rather more than three times that recorded by Purdie, and the mother liquor was found to have a rotation of $+0.78^\circ$ (100 mm.) at 20° , so that it still contained *l*-lactate in excess. The lactic acid with which this last experiment had been carried out was a different sample from that first used; it was obtained, through a local dealer, from Merck, and its rotation in a 100 mm. tube was found to be $+4.36^\circ$ at 20° , which is very much higher than the rotation usually found for ordinary lactic acid, and is considerably higher than the rotation of pure active lactic acid, this, of course, being due to the fact that *l*-lactide is present, and has a high positive rotation. Commercial lactic acid often contains a slight preponderance of one or other of the active forms; but it is said to be only seldom that the *d*- or *l*-variety occurs in large excess (Meyer and Jacobson, "Lehrbuch der organischen Chemie," 2nd Ed., Vol. I., Part II, 560), and as this sample had so high an activity we thought it worth while to ascertain in what proportions the two constituents were present. Some of the acid was therefore converted into the ethyl ester by the method described by Purdie and Williamson (T., 1896, **69**, 828). This, after careful purification by distillation with a Sydney Young fractionating column under a pressure of 13 mm., boiled at $47-49^\circ$, and gave α_D^{18} (100 mm.) $+4.5^\circ$, whilst Purdie and Williamson found the observed rotation of the pure ester at 14° to be 11.5° , and Purdie and Irvine (T., 1899, **75**, 485) found the observed rotation of their specimen at 8° to be 11.2° . The rotation of our preparation was therefore almost half that of the pure ester, so that the original lactic acid must have contained about 75 per cent. of *l*-acid and only 25 per cent. of *d*-acid (see Frankland and MacGregor, T., 1893, **63**, 1028; Harden, T., 1901, **79**, 610). We then obtained a number of samples of lactic acid from different sources

in order, if possible, to find another quantity with a high activity. As is well known, the rotation of lactic acid syrup itself is due chiefly to the presence of lactide, and in order to ascertain whether the rotation of the syrup is a good guide as to the quantity of active acid it contains we took 4 c.c. of each sample, placed it in a 50 c.c. flask, added to this 15 c.c. of a solution of 7 grams of sodium hydroxide in 45 c.c. of water, and then filled up to the mark with water. The rotation of the resulting solution of sodium lactate was then examined. The results were as follows:

Number of sample.	<i>t</i> .	Observed rotation of syrup (100 mm.).	Observed rotation of sodium salt solution (400 mm.).
1.	17.5°	+4.36°	+1.746°
2.	17.5	-0.65	-0.381
3.	17.5	+0.30	+0.164
4.	13.0	+5.30	+2.126

It will be noticed that the numbers for the rotation of the sodium salt solution are roughly proportional to those showing the rotation of the syrup, the rotations in both cases being of the same sign. It will be observed, further, that the last specimen showed an even higher rotation than that already referred to. We therefore obtained a quantity of this acid, which must have contained over 80 per cent. of *L*-lactic acid, and from it we prepared the zinc salt as follows: Three hundred grams, or 250 c.c., of the syrup were added to a mixture of 142 grams of zinc oxide and 3000 c.c. of hot water, and the whole boiled for some time until a neutral reaction was obtained. The liquid was decanted from a slight excess of zinc oxide, and allowed to crystallise. Inactive zinc lactate separated from the hot solution, and was collected. This preparation was repeated six times. The filtrate, on concentration, gave a deposit of active zinc lactate, which was crystallised several times, on each occasion from about six times its weight of boiling water, and in this way some 300 grams of pure zinc *L*-lactate were obtained with ease. If a fairly active specimen of lactic acid can be obtained, this is probably the simplest method of preparing an active salt. In the course of the crystallisation a considerable amount of partly active zinc lactate was obtained, from which zinc ammonium *L*-lactate was prepared. From 450 c.c. of the partly active lactic acid syrup and 250 grams of the partly active zinc lactate—which had a rotation of about 0.9° (400 mm.), *t*=13°, *c*=4; the pure salt would have α_D 1.4° in these circumstances—212 grams of pure active zinc ammonium *L*-lactate were obtained.

One difficulty which occurs in work on lactic acid is the fact that the rotation of its salts, such as the zinc and the zinc ammonium salts, is only low, and it is difficult, by using this criterion, to determine the purity of any sample with much accuracy. We

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therefore adopted the plan of dissolving the salt in ammonia solution instead of in water. This had two advantages: in the first place, the zinc ammonium salt decomposes in water, separating out some less soluble zinc lactate, and this is prevented by the use of ammonia solution; in the second place, the presence of the ammonia considerably raises the rotation of the salt. Our ammonia solution was prepared by making up 300 c.c. of concentrated ammonia solution (D 0.880) to a litre with distilled water. The specific gravity of this solution by the Westphal balance was found to be 0.971, and the strength of the solution by titration with oxalic acid, using phenolphthalein as indicator, was 3.99*N*. Four grams of pure zinc ammonium lactate, made up to 50 c.c. with this solution, gave $\alpha_D^{17.2}$ (400 mm.) + 3.232°, whereas the rotation in water was only 1.948°; thus by using ammonia solution the rotation is almost doubled.

Methyl l-lactate was prepared by the sulphuric acid method of Purdie and Williamson (T., 1896, **69**, 828) and Purdie and Irvine (T., 1899, **75**, 484), except that the crude ester was distilled through a Sydney Young fractionating column of 15 disks, under a pressure of about 13 mm., when it boiled at 40° and at 48°/16 mm. This is a considerable advantage, and saves the repeated and very wasteful distillation of the ester otherwise necessary. Methyl lactate, it may be noted, is fairly easily volatile along with methyl alcohol, the alcohol recovered in our first distillation (from an ordinary Wurtz flask) having a rotation of + 0.36° (*l*=400 mm.), and, when distilled with the column, gave a residue of 4 c.c. having a rotation of + 4.2°, this quantity being, therefore, equivalent to 2 c.c. of the pure ester.

Rotation of Methyl l-Lactate.

The rotation of this preparation was then examined at various temperatures, with the following results:

t°	-75.0	-62.0	-51.0	-8.6	+16.7	17.8
d	1.2042	1.1882	1.1752	1.1205	1.0971	1.0960
$\alpha_D^{17.2}$ (100 mm.) ..	+6.596	6.726	6.861	8.396	8.882	8.950
$[\alpha]_D^{17.2}$	+5.479	5.661	5.838	7.45	8.10	8.17
$[M]_D^{17.2}$	+5.696	5.887	6.071	7.75	8.42	8.49
t°	35.4	56.0	78.8	96.7	125.0	
d	1.0751	1.0518	1.0256	1.0048	0.9725	
$\alpha_D^{17.2}$ (100 mm.) ..	9.332	9.808	10.238	10.536	10.824	
$[\alpha]_D^{17.2}$	8.68	9.32	9.98	10.48	11.13	
$[M]_D^{17.2}$	9.03	9.70	10.38	10.90	11.57	

Methyl l-Lactate in Nitrobenzene.

The nitrobenzene had been distilled under diminished pressure.

$p=9.877$:

t	16.0	18.9	36.2	37.9	56.5	81.9	104.5	141.0
d	1.1920	1.1910	1.1735	1.1717	1.1525	1.1270	1.1021	1.0670
$\alpha_D^{25}(160 \text{ mm.})$	+1.856	1.876	1.836	1.846	1.850	1.856	1.850	1.846
$[\alpha]_D^{25}$	9.854	9.947	9.902	9.98	10.16	10.42	10.63	10.95
$[M]_D^{25}$	10.24	10.35	10.30	10.38	10.56	10.84	11.05	11.39

Methyl l-Lactate in Tetrachloroethane (Acetylene Tetrabromide).

The tetrachloroethane was distilled under 13 mm. pressure, and boiled at 115—117°.

$p=9.937$:

t	-7.8	+17.6	39.7	69.8	94.3	120	
d	2.5825	2.5292	2.4840	2.4220	2.3706	2.3160	
$\alpha_D^{25}(160 \text{ mm.})$	-3.146	-1.903	-0.998	-0.032	+0.738	+1.376	
$[\alpha]_D^{25}$	-7.66	-4.73	-2.53	-0.033	+1.96	+3.74	
$[M]_D^{25}$	-7.97	-4.92	-2.63	-0.086	+2.04	+3.89	

Methyl l- α -acetoxypropionate was prepared by boiling methyl *l*-lactate with excess of acetyl chloride. The product of the reaction was distilled under diminished pressure, using a Sydney Young column. It boiled at 68—70°/13 mm. and 171—172° at atmospheric pressure.

Rotation of Methyl l- α -Acetoxypropionate.

t	-7.4	+19.8	43.0	59.5	83.2	114.0	141.0
d	1.1199	1.0885	1.0620	1.0435	1.0165	0.9808	0.9500
$\alpha_D^{25}(50 \text{ mm.})$	+30.394	29.552	28.78	28.224	27.448	26.514	25.694
$[\alpha]_D^{25}$	54.26	54.28	54.20	54.09	54.03	54.05	54.08
$[M]_D^{25}$	79.23	79.25	79.14	78.98	78.89	78.93	78.96

Methyl l- α -Acetoxypropionate in Nitrobenzene.

$p=10.14$:

t	0.3	19.2	45.4	65.0	83.5	110.0	141.0
d	1.2105	1.1919	1.1650	1.1445	1.1262	1.10	1.0690
$\alpha_D^{25}(100 \text{ mm.})$	+7.336	6.914	6.364	6.126	5.908	5.708	5.514
$[\alpha]_D^{25}$	+59.78	57.20	53.88	52.77	51.76	51.18	50.88
$[M]_D^{25}$	+87.30	83.52	78.66	77.05	75.58	74.73	74.29

Methyl l- α -Acetoxypropionate in Tetrachloroethane.

$p=10.035$:

t	17.6	39.8	54.7	76.4	91.3	119.0	139.3
d	2.5262	2.4817	2.4520	2.4078	2.3772	2.3220	2.2705
$\alpha_D^{25}(160 \text{ mm.})$	+19.294	18.886	18.632	18.234	18.066	17.722	17.428
$[\alpha]_D^{25}$	+47.56	47.37	47.32	47.17	47.34	47.53	47.80
$[M]_D^{25}$	+69.45	69.18	69.08	68.87	69.11	69.40	69.81

Methyl l- α -methoxypropionate was prepared exactly according to the method of Purdie and Irvine (T., 1899, **75**, 485), and was finally distilled with a column, under diminished pressure. It boiled at 40°/18 mm. and 130—131°/760 mm.

Rotation of Methyl l- α -Methoxypropionate.

t°	-16.6	16.4	41.2	51.1	78.4	110.0	130.0
d	1.0361	0.9986	0.9704	0.9590	0.9283	0.8916	0.8685
α_D^{25} (30 mm.) ...	+32.107	29.112	27.28	26.414	24.528	22.826	21.932
$[\alpha]_D^{25}$	+103.3	97.16	93.71	91.81	88.28	85.35	84.16
$[M]_D^{25}$	+121.9	114.7	110.6	108.3	104.2	100.7	99.31

Methyl l- α -Methoxypropionate in Nitrobenzene.

$p=9.802$:

t°	16.6	41.7	70.5	92.8	119.0
d	1.1843	1.1590	1.1290	1.1066	1.0795
α_D^{25} (160 mm.) ...	+16.496	15.55	14.544	13.756	12.928
$[\alpha]_D^{25}$	+88.82	85.27	82.17	79.25	76.40
$[M]_D^{25}$	+104.8	100.7	97.18	93.53	90.36

Methyl l- α -Methoxypropionate in Tetrachloroethane.

$p=10.0616$:

t°	16.7	39.8	52.5	77.0	101.0	119.0
d	2.4860	2.4390	2.4135	2.3630	2.3140	2.2760
α_D^{25} (100 mm.) ...	+18.444	17.798	17.448	16.766	16.156	15.620
$[\alpha]_D^{25}$	+73.69	72.52	71.85	70.52	69.40	68.21
$[M]_D^{25}$	+86.96	85.59	84.78	83.22	81.91	80.48

The diagram represents our experimental data. The relative rotations of methyl *l*-lactate, methyl *l*- α -acetoxypionate, and methyl *l*- α -methoxypropionate at a single temperature were, of course, already known, but the influence of temperature change on them has not previously been studied. The full lines in the diagram represent the behaviour of the homogeneous active substances, and it will be observed that the influence of temperature change in the three cases is comparatively slight; thus the rotation of methyl *l*-lactate only changes some 6° within a temperature range of fully 200°; nevertheless, the curve has two interesting characteristics. First, at the higher temperatures it tends, apparently, towards a maximum value, and second, since there appears to be a point of inflexion somewhere about -10°, it is possible that at lower temperatures than those we have reached, a minimum rotation also may exist for methyl *l*-lactate. The importance of maximum and minimum rotations and points of inflexion has been discussed by one of us in a recent paper (this vol., p. 145), so that the matter need not be further dealt with here.

When methyl *L*-lactate is converted into methyl *L*- α -acetoxypropionate the change is accompanied by a great rise of rotation, but the rotation of the acetyl compound is very little affected by

Temperature-rotation curves for derivatives of l-lactic acid in the homogeneous condition (full lines), in solution in nitrobenzene, $p=10$ (dash-dash-dot curves), and in tetrabromoethane, $p=10$ (dotted curve).

change of temperature within the ordinary limits. A minimum rotation appears to exist, however, at a temperature in the neighbourhood of 40° , and this accounts for the comparative invaria-

bility of the rotation with change of temperature, since it is, of course, in the neighbourhood of a maximum or a minimum that da/dt is a minimum.

When the acetoxy-group is replaced by a methoxy-group a compound is obtained which has a still higher rotation, a rotation which diminishes fairly rapidly with rise of temperature. Now it has been suggested in the paper already referred to (*loc. cit.*) that the temperature-rotation curves for a set of closely-related compounds such as these may all be of the same type, the exchange of certain groups for others merely producing a shift of the fundamental type of curve to the right or the left, to the top or bottom of the diagram, accompanied, however, by individual but minor differences and characteristics. It is thus possible that the minimum which occurs in the rotation of methyl *l*-lactate at a low temperature of about -80° or -100° represents a condition of the molecule corresponding with that which is assumed by methyl *l*- α -acetoxypropionate at a temperature of $+40^{\circ}$ and in methyl *l*- α -methoxypropionate at a temperature in the neighbourhood of 200° , and this affords some explanation of the fact that whilst the rotation of methyl lactate increases on heating, that of methyl *l*- α -acetoxypropionate is but little altered, and that of methyl *l*- α -methoxypropionate diminishes.

The rotation of each of these active compounds was also examined in nitrobenzene and in tetrabromoethane solution. Previous work with ethyl tartrate had shown that whereas nitrobenzene has a very pronounced effect in raising the rotation of ethyl tartrate, tetrabromoethane is almost equally powerful in diminishing it. Therefore, it appeared to be of interest to ascertain in what way the rotation of these other active compounds would be influenced by the same two solvents. In the case of methyl *l*-lactate it seems tolerably clear that in nitrobenzene solution the minimum rotation would occur at a higher temperature than in the homogeneous ester. It is probable also that a maximum rotation would exist in this same solution, but the curves are not sufficiently extensive to decide whether at a higher or a lower temperature than in the homogeneous ester. A point of inflexion is indicated at about 60° .

Nitrobenzene as a solvent does not produce so great an elevation of the rotation of methyl *l*-lactate as of that of ethyl tartrate, and similarly tetrabromoethane, although it considerably diminishes the rotation of the lactate, does so to a less extent than in the case of ethyl tartrate. No point of inflexion is apparent in this curve, so that a minimum rotation would be expected to occur at a still lower temperature than in the homogeneous ester. From the curves it is hardly possible to say whether the maximum rotation

of this solution will lie at a lower temperature than that of the homogeneous ester or of the ester dissolved in nitrobenzene.

The influences of nitrobenzene and of tetrabromoethane on the rotation of methyl *l*- α -methoxypropionate are, on the whole, somewhat similar to their effects on the rotations of the other two esters examined. Tetrabromoethane brings about the greater lowering of rotation, but the nitrobenzene curve does not cut that for the homogeneous ester. We may point out, however, although it may seem to be arguing on somewhat slender premisses, that whereas the curve for the homogeneous ester and that in nitrobenzene solution for methyl *l*-lactate occurs at a fairly high temperature of about 100°, a similar intersection takes place for methyl *l*- α -acetoxypropionate at about 40°, and therefore it may possibly be that a corresponding intersection in the case of methyl α -methoxypropionate should occur at a still lower temperature. For this ester also it may be noticed that the three curves are more widely separated from each other, thus suggesting that as the rotation of the compound becomes greater the sensitiveness of the molecular asymmetry to the influences of different solvents becomes greater also; in other words, the change produced in passing from one solvent to another is greater for the methyl *l*- α -methoxypropionate with its high rotation than for the methyl *l*-lactate with its low rotation. The three curves in this case appear to be tending towards a minimum value, but it is obviously difficult or impossible to say what the relative position of these minima would be.

The effect of the two solvents is much the same on the three different esters, thus supporting the view, which is steadily gaining ground, that the relative influence of a set of solvents on several active compounds is closely similar.

On the whole, it may be said that these curves, although perhaps they do not present any very striking confirmation or support of the ideas suggested in the paper referred to, are quite in harmony with these suggestions. It is a little unfortunate that the comparatively easy volatility of the substances examined has somewhat limited their investigation.

In conclusion, we have to thank Messrs. T. and H. Smith, of Edinburgh, for the loan of a considerable quantity of morphine and for presenting us with another quantity of it for use in the experiments recorded, whilst we desire also to acknowledge that some of the rotation data quoted in the paper were obtained with a polarimeter placed at the disposal of one of us by the Carnegie Trustees for the Universities of Scotland.

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