XLVI.—*The Rotatory Powers of Optically Active Methoxy- and Ethoxy-propionic Acids prepared from Active Lactic Acid.*

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OBSERVATIONS recently communicated to this Journal (Trans., 1899, 75, 157), showing that ethylic malate and ethylic tartrate are readily converted respectively into ethylic mono- and di-ethoxysuccinate by

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treatment with ethylic iodide and silver oxide, have led us to study the application of alkyl iodides and silver oxide as alkylating agents to the ethereal salts of other hydroxy-acids, and in the following research we give the results obtained with optically active methylic and ethylic lactates.

We have prepared active methylic methoxy- and ethylic ethoxy-propionate by this method, and have also made observations on the corresponding acids and their metallic salts, with the view of comparing their activity with that of the same compounds previously obtained (Trans., 1898, 73, 862) by the resolution of the racemic forms.

The *d*-lactic acid used in our preparations was obtained by the resolution of the inactive acid, as described in previous papers (Trans., 1893, 63, 1143; 1895, 67, 616). The zinc ammonium *d*-lactate in the hydrated state had the specific rotation -6.06° ($c=8$, $t=10^\circ$), and the *d*-lactic acid, from which the silver salt used was made, gave a zinc salt containing 12.82 per cent. of water of crystallisation and 23.46 per cent. of zinc, the calculated numbers being 12.88 and 23.41 respectively.

Methylic and Ethylic d-Lactates.

The methylic *d*-lactate, prepared from the silver salt by J. W. Walker (Trans., 1895, 67, 916), owed its abnormally high specific rotation, -11.1° , to the presence of small quantities of methoxypropionate (Trans., 1898, 73, 296); that of Frankland and Henderson (Proc., 1895, 11, 54), on the other hand, had a specific rotation of only -6.80° , and probably contained some of the oppositely active salt. The only other recorded observation is that of Le Bel (*Bull. Soc. Chim.*, 1893, [iii], 9, 674), who gives only the observed rotation, $\alpha = -8.5^\circ$ ($l=1$), of the substance prepared by digesting the alcohol and acid.

We prepared the salt from zinc ammonium *d*-lactate by the method already described (Trans., 1896, 69, 828) for ethylic lactate. From a mixture of 120 grams of dry salt with 462 grams of methylic alcohol and 96 grams of sulphuric acid, we obtained, after repeated fractionation, 37 grams of methylic lactate (b. p. 58° under 19 mm. pressure), showing the specific rotation, $l=1$, $\alpha^{20^\circ} = -9.01^\circ$, $d_{20^\circ/4^\circ} = 1.0925$, $[\alpha]_D^{20^\circ} = -8.25^\circ$, a result somewhat higher than that found by Le Bel. Analysis gave:—

C = 45.92; H = 7.86.

$C_4H_8O_3$ requires C = 46.15; H = 7.69 per cent.

On distilling a small quantity of the substance at the ordinary pressure, before it was completely fractionated, a dark residue was

left in the flask, and the observed rotation of the distillate rose to -32.5° , a result which may have been due to the presence of moisture and the consequent production of a small quantity of the highly active anhydro-acid or lactide.

The yield obtained by this process was so small that the rest of the material required was prepared by the silver salt method (*loc. cit.*). From 91 grams of silver *d*-lactate and 136 grams of methylic iodide, 37 grams of ethereal salt were obtained, boiling at $58-62^\circ$ under 22—33 mm. pressure. The observed rotations of different fractions at about 15° varied from 10.62° to 12.92° ($l=1$), the fractions of lower boiling point being the more active, a result to be expected from the presence of methoxypropionate.

Ethylic *d*-lactate was prepared directly from zinc ammonium lactate in the same manner as the methylic salt, the yield and the activity, $\alpha = -11.20^\circ$ at 8° ($l=1$), being nearly the same as in a previous preparation (*loc. cit.*). The boiling point of the liquid was not very constant, and in the course of repeated distillation under reduced pressure small fractions of slightly higher boiling point were collected, giving a rotation in one instance as high as -12.1° . As, however, the rotation did not alter after distilling a portion of the main liquid at the ordinary pressure (b. p. $151-152^\circ$), and as the mixed more active fractions referred to yielded, on redistillation, a liquid of the lower activity, $\alpha = -10.8^\circ$, and a gummy residue, we conclude that the higher activity observed was probably due to the presence of anhydride, and that the specific rotation formerly given for ethylic lactate (*loc. cit.*) is nearly correct.

Methoxy- and Ethoxy-propionic Acids.

Methylic Lævo-methoxypropionate.—When silver oxide is added slowly to methylic iodide at the ordinary temperature, only a slight reaction occurs, the temperature rising a few degrees on each addition. When methylic lactate, however, is added to the mixture, it rapidly becomes warm and boils violently. In our experiments, the oxide was added gradually to the mixture of lactate with iodide, the proportions used being oxide ($1\frac{1}{2}$ mols.), iodide (3 mols.), and lactate (1 mol.). The reaction was moderated by occasional cooling, and completed by heating for some time on a water-bath. The product, having been diluted with dry ether and filtered, was distilled under reduced pressure and fractionated until the rotation was constant. The crude distillate, obtained after boiling off the ether, amounted to 65 per cent. of the yield calculated for methylic methoxypropionate, and gave in different preparations the observed rotations -90.25° , -95.18° , and -93.73° ($l=1$). Practically no lactate was left unacted on, as the liquid, after

being shaken with a dilute solution of potassium hydroxide, dried with anhydrous sodium sulphate and redistilled, showed no increase of activity. The product, after fractional distillation, boiled at 45° under 22 mm. pressure, and on analysis gave:—

I. C = 50.79 ; H = 8.63. II. C = 50.67 ; H = 8.61.
 $C_5H_{10}O_3$ requires C = 50.84 ; H = 8.47 per cent.

The optical observations made on this and the other substances described are given below.

Levo-methoxypropionic acid.—The acid was prepared from the methylic salt by the method previously indicated in the case of the inactive form (Trans., 1898, 73, 869). In order to observe its activity in the anhydrous state, the liquid, after being dried in a vacuum, was distilled. It boiled without decomposition at $108-110^{\circ}$ under 30 mm. pressure. The substance was a thick, colourless, pleasant-smelling liquid, which, on analysis, gave

C = 46.03 ; H = 7.70.
 $C_4H_8O_3$ requires C = 46.15 ; H = 7.69 per cent.

The activity of the acid was unaltered after distilling a second time, and moreover, was proved to be unaffected on distillation by the fact that the rotations of the aqueous solutions of the distilled and undistilled acid, which are quoted later, were nearly the same.

Ethylic Levo-methoxypropionate.—The substance was obtained by the action of ethylic iodide on the silver salt. An analysis of the liquid (b. p. 46° under 12 mm. pressure) gave:—

C = 54.49 ; H = 9.22.
 $C_6H_{12}O_3$ requires C = 54.55 ; H = 9.09 per cent.

The substance, however, was probably not quite pure, as owing to its small quantity it could be only once distilled. The specific gravity of the inactive compound (*Annalen*, 1879, 197, 21) is considerably higher than that given below. The rotation found must, therefore, probably be regarded only as approximate.

Ethylic Levo-ethoxypropionate.—This substance was prepared from ethylic *d*-lactate in the same manner as methylic methoxypropionate from methylic lactate but the iodide used amounted to only a little in excess of 1 mol., and the product on combustion gave results which indicated the presence of unaltered lactate. As this was not removed by fractional distillation or by treatment with water, the oily liquid was shaken with a cold 5 per cent. aqueous solution of potassium hydroxide, dried with anhydrous sodium sulphate, and redistilled. This treatment raised the rotation about 6° , and the liquid (b. p. $58.5-60^{\circ}$

under 16—19 mm. pressure) now gave results on analysis in agreement with the calculated numbers.

Found I. C = 57·54 ; H = 9·25. II. C = 57·61 ; H = 9·65.

$C_7H_{14}O_3$ requires C = 57·53 ; H = 9·59 per cent.

The crude ethereal salt weighed rather more than the lactate used, and the unaltered lactate contained in it, calculated from the rotations, amounted to about 10 per cent., so that, were a larger proportion of iodide used, a nearly theoretical yield would probably be obtained.

Lævo-ethoxypropionic Acid.—The acid was prepared from the ethylic salt in the same manner as the methoxy-acid from its methylic salt. Before attempting to obtain the acid in the anhydrous state by distillation in a vacuum, an experiment was first made with the inactive acid, which is known to decompose to some extent when distilled at ordinary pressure (*Annalen*, 1860, 114, 207). This distilled at 131—133° under 63—68 mm. pressure, and the following analysis shows that it does not decompose under these conditions.

Found C = 50·68 ; H = 8·21.

$C_5H_{10}O_3$ requires C = 50·85 ; H = 8·47 per cent.

The active acid was, therefore, similarly treated. It distilled at 105—106° under 16—19 mm. pressure, as a colourless syrup, which, on combustion, gave C = 50·72 ; H = 8·74 per cent. The observations on aqueous solutions of the acid, quoted below, show that its activity is not impaired by distillation.

Methylic Lævo-ethoxypropionate.—The substance was prepared from methylic iodide and silver ethoxypropionate. The liquid had the boiling point 40—41° under 10 mm. pressure, and on analysis gave :—

C = 54·42 ; H = 9·15.

$C_6H_{12}O_3$ requires C = 54·55 ; H = 9·09 per cent.

With regard to the purity of the substance, the remarks made respecting ethylic methoxypropionate apply in this case also.

The rotations of the substances described were as follows :—

	<i>l</i> .	α^{20° .	<i>d</i> 20°/4°	$[\alpha]_D^{20^\circ}$	$[\alpha]_D^{20^\circ}$ M/100.
Methoxypropionic acid.....	0·5	- 41·16°	1·0908	- 75·47°	- 78·49°
Methylic methoxypropionate.	1	95·21	0·9967	95·53	112·73
Ethylic methoxypropionate...	0·5	43·02	0·9551	90·08	118·91
Ethoxypropionic acid	0·5	34·49	1·0395	66·36	78·30
Methylic ethoxypropionate ...	0·5	39·21	0·9610	81·60	107·71
Ethylic ethoxypropionate.....	1	74·55	0·9355	79·69	116·35

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The following observations were also made at other temperatures in a 1 dm. tube.

Methylic methoxypropionate.

$$[\alpha]^{10^\circ} = -97.60^\circ, d\ 10^\circ/4^\circ = 0.9994, [\alpha]_D^{10^\circ} = -97.66^\circ.$$

$$[\alpha]^{15^\circ} = -96.28^\circ, d\ 15^\circ/4^\circ = 0.9982, [\alpha]_D^{15^\circ} = -96.45^\circ.$$

Ethylic ethoxypropionate.

$$[\alpha]^{13^\circ} = -75.72^\circ, d\ 13^\circ/4^\circ = 0.9430, [\alpha]_D^{13^\circ} = -80.30^\circ.$$

The specific rotations, therefore, decrease with rise of temperature.

With respect to the accuracy of the rotations found, that of ethylic ethoxypropionate may be a little too low, an insufficient excess of iodide having been used in its preparation, and, as has been already stated, the numbers given for the ethylic methoxy- and methylic ethoxy-salts are only approximate. The following conclusions, however, may be drawn from the observations.

The direct alkylation of the active ethereal lactates produces a remarkable rise of the rotation without altering its sign, the introduction of methyl into the hydroxyl group of methylic lactate, for example, raising the molecular rotation from 8.58° to 112.73° . The results thus confirm the conclusion previously arrived at, that the high activity of the alkyl lactates, prepared from silver lactate, is due to the production of small quantities of alkyloxypropionates.

A comparison of the rotations of the two anhydrous acids and their ethereal salts shows that the introduction of an alkyl radicle into the carboxyl group is attended with a great increase of activity. The substitution of ethyl for methyl in the carboxyl radicle, which raises the activity in the case of the lactates, whether the observed rotation, the specific rotation, or the molecular rotation be taken as its measure, lowers the first two of these constants and raises only the last in the case of the alkyloxypropionates; the same relation subsists between the ethereal malates and alkyloxysuccinates, and also between ethereal lactates and malates and their acetyl derivatives. The substitution of an ethoxy- for a methoxy-group in direct union with the asymmetric carbon atom, on the other hand, causes a fall even in the molecular rotation of both the methylic and the ethylic salts, and a similar effect is exhibited in the specific rotations of the anhydrous acids, although in this case the molecular rotations are about equal. This result is not what was to be expected from previous observations on aqueous solutions of the metallic salts of the same acids, prepared by resolution of the racemoid forms (*loc. cit.*), as these showed that the ethoxypropionates were more active than the corresponding methoxy-salts in solutions of equivalent concentration. It seemed, therefore, desirable to examine aqueous solutions of the metallic salts of the two acids obtained from active lactic acid, as described above. Aqueous solutions of the acids were also com-

pared, as the results previously found for methoxypropionic acid were unreliable.

Rotatory Powers of Methoxy- and Ethoxy-propionic Acids and of their Metallic Salts in Aqueous Solution.

The concentrations of the solutions of the acids were ascertained by titration with a decinormal solution of barium hydroxide. As the salts, with the exception of calcium ethoxypropionate, cannot be obtained in a state of definite hydration, and as their complete dehydration involved the risk of racemisation, the concentrations of the solutions were determined by estimating the metals in the residues left after the evaporation of known volumes; the results of these analyses, in percentage numbers, are given below.

The sodium and calcium salts were similar in appearance to those of the active acids obtained by resolution of the racemic forms.

Methoxypropionates.

Sodium salt.—Found, 18·27; calculated, 18·25.

Calcium salt.—Found, 16·21; calculated, 16·26.

Barium salt.—Very soluble, radiating needles. Found, 40·06; calculated, 39·94.

Zinc salt.—A gum crystallising with difficulty in rectangular plates. Found, 23·81; calculated, 24·10.

Magnesium salt.—Very soluble, microscopic prisms. The salt was not constant in weight at 120°, and it then contained about 1 per cent. over the calculated quantity of magnesium.

Ethoxypropionates.

Sodium salt.—Found, 16·54; calculated, 16·43.

Calcium salt.—Found, $H_2O = 11·55$; Ca in anhydrous salt = 14·65; calculated, $2H_2O = 11·61$; Ca = 14·60.

Magnesium salt.—A gum, which could not be freed from water without decomposition.

Zinc salt.—A gum, solidifying to a glassy mass which, when dried at 120°, gave Zn = 22·12; calculated, 21·84 per cent.

The respective concentrations of the solutions of the two acids and their corresponding salts are approximately equivalent, with the one exception that the solution of the sodium methoxypropionate has a considerably higher molecular concentration than that of the ethoxy-compound. The molecular concentrations of the different salts are also, for the most part, comparable with each other. The observations were made at 20°, and in a 1 dm. tube unless the rotations were small, when a 2 dm. or 4 dm. tube was employed. For the sake of brevity, the molecular rotations only are given. In the column headed N, the concentrations are expressed in fractions of a normal solution.

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	1-Methoxypropionic Acid.			1-Ethoxypropionic Acid.		
	c.	N.	$[\alpha]_D^{20} \text{ M}/100.$	c.	N.	$[\alpha]_D^{20} \text{ M}/100$
Acid	26.726	2.57	-66.6°	30.572	2.59	-61.5°
	17.552	1.69	66.5	20.122	1.70	60.5
	8.776	0.84	66.4	10.061	0.85	60.6
	3.510	0.34	66.4	4.025	0.34	61.0
,, (distilled).....	8.522	0.82	66.1	9.612	0.81	60.6
Sodium salt	32.460	2.58	54.5	23.700	1.69	62.1
	16.230	1.29	60.1	11.850	0.84	64.7
	6.492	0.52	61.5	4.740	0.34	65.9
	3.212	0.25	62.8	2.396	0.17	66.6
Calcium salt	24.095	1.96	27.7	26.790	1.96	50.2
	12.0475	0.98	42.7	—	—	—
	9.6380	0.78	47.1	10.716	0.78	60.9
	4.8190	0.39	53.6	5.358	0.39	64.1
Barium salt	36.580	2.13	39.7	—	—	—
	18.290	1.06	53.8	—	—	—
	7.316	0.43	59.8	—	—	—
	3.658	0.21	65.2	—	—	—
Magnesium salt...	21.9760	1.91	35.2	20.964	1.62	51.9
	10.9880	0.96	43.8	10.482	0.81	55.0
	5.4940	0.48	47.8	5.241	0.40	57.4
Zinc salt	29.96	2.21	+23.1	30.972	2.07	14.0
	14.98	1.10	+6.2	15.486	1.03	28.9
	7.49	0.55	-8.2	7.743	0.51	39.1
	3.745	0.28	-22.1	3.8715	0.25	44.8
	1.8725	0.14	-33.3	—	—	—

The molecular rotations are somewhat lower than those previously found, the difference being partly due to the higher temperature at which they were observed, but on the whole the numbers exhibit the same relations. We believe the numbers now given for the methoxy-acid are correct, as on recovering it from its salts, the rotation was found to be unaltered. The molecular rotations of the salts increase in every case in the *lævo*-direction with dilution, and the order of the values found in the most dilute solutions is such as might be expected from the probable degree of electrolytic dissociation, the order of decreasing values for the salts of both acids being sodium, barium, calcium, magnesium, zinc. On plotting the results in curves (see diagram), the abscissæ representing molecular concentrations and the ordinates molecular rotations, it is seen that the magnesium and zinc salts, like the other salts previously examined, conform in general to the law of Oudemans and Landolt, the rotations of the zinc salts increasing very rapidly with dilution. The curves of the methoxy-

propionates lie invariably below those of the corresponding ethoxy-salts, and excepting those of the nearly completely dissociated sodium salts, which are parallel, they are in general much steeper.

This is particularly noticeable in the case of the presumably least dissociated zinc salts, the rotation of zinc methoxypropionate passing in a remarkable manner from $+23.15^\circ$ in a $2.2N$ solution to -33.34° in a $0.14N$ solution. It is evident that the cause which lowers the rotations of the barium, calcium, and more particularly of the zinc, salts in the more concentrated solutions, whether it be retarded electrolytic dissociation or molecular association or some other factor, has a greater effect on the methoxy- than on the ethoxy-salts.

Metallic Alkyloxypropionates.

NOTE.—Dotted lines represent ethoxy-compounds. The magnesium salts have been omitted.

A comparison of the sodium salts in dilute solution shows that the ethoxy-ion is decidedly more active than the methoxy-ion, our previous results being thus confirmed.

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The curves of the acids are nearly horizontal for the range of concentrations examined, but the higher rotations of the anhydrous substances show that the first addition of water must produce a considerable fall, and that this is probably due to the breaking up of molecular aggregates of higher activity than the single molecules or ions. The rotatory powers of the single molecules can, in fact, be very little higher than that of the ions, as in a 26 per cent. solution, which must be very far from a state of complete electrolytic dissociation, the rotatory power of the methoxy-acid approaches that of its sodium salt. In contradistinction to the relation which prevails in the salts, the curve of the methoxy-acid is the higher of the two, the explanation of the anomaly probably being that the methoxy-acid, like its salts, is more subject to molecular aggregation than its homologue. It may be noted that the ethoxy-acid presents an exception to the general law that the change of rotation produced by dilution is always in the direction of the ionic rotation; the rotation of the sodium salt in a 23·7 per cent. solution is already above that of the acid, and the same remark applies to the calcium salt in dilute solution.

If, then, ionic rotations are considered the most reliable measure of activity and molecular rotations are compared throughout, the ethoxy-molecule is the more active of the two, and the greater activity of the methoxy-molecule in the condition of aqueous acid or ethereal salt is due to its greater tendency to form molecular aggregates of higher activity. If, on the other hand, specific rotations, calculated for the ion in the case of metallic salts, be compared, the relations are somewhat simpler. The methoxy-molecule is then the more active of the two, whether in the ethereal salts, anhydrous and aqueous acids, or the fully dissociated sodium salts; the fact that the specific rotations of the methoxypropionates of divalent metals are less than those of the corresponding ethoxy-compounds may be explained on the assumption that they are less dissociated.

In the case of methoxy- and ethoxy-succinic acid, the methoxy- as compared with the ethoxy-group has a similar effect in lowering the rotations of the salts. The specific rotations of the acids, which vary little with concentration, are both about 33° ; those of the ions calculated from the normal alkali salts are $14\cdot86^\circ$ and $22\cdot41^\circ$ respectively, and the effect is still more pronounced in the salts of the divalent metals.

Some observations have been made on the effect of alcohol and varying temperature on the rotations of the salts. Calcium ethoxypropionate in alcoholic solution undergoes a still more striking fall in rotation than the sodium salt, which we examined previously. Thus the specific rotations $-44\cdot42^\circ$ ($c=10\cdot716$) and $-46\cdot75^\circ$ ($c=5\cdot358$), determined in aqueous solution, become in alcohol $-9\cdot53^\circ$ ($c=11\cdot02$)

and -10.34° ($c=5.51$). The rotation of the methoxy-acid, like that of its homologue, is raised by alcohol. The following observations show that the rotation of calcium ethoxypropionate falls with rise of temperature, and that its behaviour therefore is not in accordance with the general rule, that rise of temperature and dilution produce similar effects.

$$p = 24.434, \quad d \ 10^\circ/4^\circ = 1.0993, \quad [\alpha]_D^{10^\circ} = -37.75^\circ \\ d \ 30^\circ/4^\circ = 1.0912, \quad [\alpha]_D^{30^\circ} = -35.48.$$

To the distinctive points in the optical behaviour of lactic and the alkyloxypropionic acids previously indicated (Trans., 1898, 73, 877 ; 1899, 75, 160), we may now add the phenomena exhibited by the zinc and magnesium salts. A N/10 solution of zinc lactate, despite its comparatively slight electrolytic dissociation, gives a rotation which is not much short of the maximum rotation of the alkali salts; the rotations of the zinc alkyloxypropionates at similar concentration, though increasing rapidly, are still far short of the maximum. The molecular rotations of the lactates of the zinc group increase with molecular weight; the converse holds true for the alkyloxypropionates.

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