CCLVI. — *Influence of Double Linking on Optical Activity; Some n-Propyl and Allyl Derivatives of Menthol.*

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IN connexion with the problem of ascertaining the influence of double linking on optical activity it has been shown by one of us that both in the substitution of tartramide and of malamide by *n*-propyl and by allyl respectively the resulting *n*-propylamides have higher molecular rotations than the corresponding allylamides (P. Frankland and Twiss, *Trans.*, 1906, **89**, 1854; and P. Frankland and Done, *Trans.*, 1906, **89**, 1861), which is contrary to the generally

accepted rule that unsaturated groupings bring about a higher rotation than the corresponding saturated ones. This rule is based on results obtained in a number of investigations made during the past thirteen years by Tschugaëff (*Centralbl.*, 1898, **69**, I., 875; II., 404; 1902, **73**, II., 1238), Haller, Rupe (for many references to literature see *Trans.*, 1903, **83**, 1351), Hilditch (*Trans.*, 1908, **93**, 1909, **95**, 1910, **97**, 1911, **99**; *Zeitsch. physikal. Chem.*, 1911, **77**, 482), and others.

The present communication contains data obtained in the further investigation of this subject.

The compounds which we have prepared are three pairs of *n*-propyl and allyl derivatives of menthol; they were all liquids, and their rotations were determined at a number of different temperatures between 15° and 100°. Their rotations have also been determined in methyl alcohol solution.

In the following table we have recorded the values for $[M]_D^{20}$ in the liquid state, whilst we have included for comparison the corresponding values for some other *n*-propyl and allyl compounds.

	B. p.	$[M]_D^{20}$ in liquid state.
{ Menthoxyacetic allylamide,	185—187°/14 mm.	- 192·5°
{ Menthoxyacetic propylamide	188—189°/16 mm.	193·7
{ Allyl menthoxyacetate	182°/40 mm.	234·4
{ Propyl menthoxyacetate	172°/26 mm.	234·1
{ Menthyl allylaminoacetate	155—157°/17 mm.	160·5
{ Menthyl propylaminoacetate	159—161°/17 mm.	158·3
{ Menthyl allyl ether *	--	{ $[M]_D^{19}$ - 192·5 }
{ Menthyl propyl ether †	--	{ 182·5 }
	M. p.	$[M]_D^{20}$ in pyridine solution.
{ Tartaric allylamide ‡	183°	+ 251°
{ Tartaric propylamide ‡	216	+ 289
{ Malic allylamide §	117·5	- 72·7
{ Malic propylamide §	126	90·5

* Haller and Marsch (*Compt. rend.*, 1904, **138**, 1665).

† Tschugaëff (*Centralbl.*, 1902, II, 1238).

‡ Frankland and Twiss (*loc. cit.*).

§ Frankland and Done (*loc. cit.*).

In the case of the amides of menthoxyacetic acid the allyl compound is seen to have the lower molecular rotation, but the difference is very small. This difference is practically the same over the range of temperature at which the observations were made. In this case the double linking diminishes the rotatory power, and agrees in this respect with the results obtained with the tartaric and malic amides.

The allyl and propyl esters of menthoxyacetic acid have practically identical molecular rotations at 20°, but whilst below 35° the

rotation of the allyl is very slightly in excess of that of the propyl compound, above that temperature the relation is reversed (see diagram).

In the case of the next pair, menthyl allylaminoacetate and propylaminoacetate, the allyl compound has slightly the higher molecular rotation throughout the whole range of temperature over which the observations were made.

Molecular rotation curves of the six compounds.

The results recorded in this paper lead to some general considerations:

(1) The extremely small differences between the molecular rotations of the pairs of allyl and propyl compounds described may be accounted for by the great distance of the unsaturated grouping in the allyl from the nearest asymmetric carbon atom in the menthyl radicle; thus, in menthoxyacetic allylamide, in allyl menthoxyacetate, and in menthylallylaminoacetate there are, in each case, *five atoms intervening between the unsaturated carbon atom of the allyl and the nearest asymmetric carbon atom of the menthyl*. That a constitutional change (such as passing from allyl to propyl)

made at such a great distance from the asymmetric carbon atom should have but little effect on the rotation is in accordance with the conclusions arrived at by P. Frankland and MacGregor (*Trans.*, 1896, **69**, 121), and since confirmed by many other workers.

(2) Much greater differences in the molecular rotations of the following pairs of allyl and propyl compounds have been observed:

Liquid state.	Menthyl allyl ether	$[M]_D^{19} - 192.5^\circ$	Difference = 10° .
	Menthyl propyl ether	$[M]_D^{19} - 182.5^\circ$	

In the menthylallyl ether there are only two atoms intervening between the unsaturated carbon atom of the allyl and the nearest asymmetric carbon atom of the menthyl group.

Pyridine solution.	Tartaric allylamide	$[M]_D^{20} + 251^\circ$	Difference = $38/2 = 19^\circ$.
	Tartaric propylamide	$[M]_D^{20} + 289^\circ$	
	Malic allylamide	$[M]_D^{20} - 72.7^\circ$	Difference = 17.8°
	Malic propylamide	$[M]_D^{20} - 90.5^\circ$	

In each of the two allyl compounds there are 3 atoms intervening between the unsaturated carbon of one allyl group and 4 atoms between that of the other allyl group and the asymmetric carbon atom of the tartaric and malic radicles respectively.

We do not think that any comparisons between the quantitative differences obtained in the case of the menthyl ethers on the one hand, and the amides of tartaric and malic acids respectively on the other, would be justifiable, first, because of the entirely different nature of the asymmetric nuclei concerned in the two cases, and secondly, because the rotations of the menthyl ethers were determined in the liquid state, whilst those of the tartaric and malic amides were taken in solution, and a great variation was found in the differences between the rotations of the propyl- and allyl-amides according to the particular solvent employed (pyridine, methyl alcohol, water, and glacial acetic acid) (see Frankland and Twiss, *Trans.*, 1906, **89**, 1853, and Frankland and Done, *Trans.*, 1906, **89**, 1860).

(3) It will be seen that the menthoxyacetic grouping gives rise to a much higher molecular rotation than the menthyl aminoacetate grouping, and that the propyl and allyl esters of menthoxyacetic acid again have higher rotations than the corresponding propyl- and allyl-amides.

(4) In this connexion the following relations are worthy of note:

	$[M]_D^{20}$.
Menthyl allylaminoacetate	- 160.5°
Menthyl propylaminoacetate	158.3
Menthyl propionate *	160.2
"Normal constant of the menthyl homologous fatty esters" *	157.8
Menthyl phenylpropionate *	161.9

* Tschugaeff.

Thus, such profound differences in constitution as exist between the fatty acids on the one hand and the substituted amino-fatty acids on the other are attended with practically no alteration in the molecular rotation. These changes in constitution are ineffective, because occurring at a point remote from the asymmetric grouping.

(5) Again, the greater rotatory effect of the menthyl ether than of the menthyl ester grouping which we have found is in accordance with similar results obtained by Tschugaëff, thus:

	$[M]_D^{20}$
Menthyl methyl ether	-162.6
Menthyl ethyl ether	179.0
Menthyl propyl ether	182.5
Menthyl benzyl ether	232.7
Menthyl formate	146.3
Menthyl acetate	157.3
Menthyl propionate	160.2
Menthyl <i>n</i> -butyrate	156.9
Menthyl <i>n</i> -nonoate	157.3
Menthoxyacetic allylamide	192.5
Menthoxyacetic propylamide	193.7
Menthoxyacetic allyl ester	234.4
Menthoxyacetic propyl ester	234.1
Menthyl allylaminoacetate	160.5
Menthyl propylaminoacetate	158.3

From the above figures it will be seen incidentally that the acetic allyl ester and acetic propyl ester groupings have almost exactly the same rotatory effect as is exerted by the benzyl radicle in the series of menthyl ethers.

This greater rotatory effect of the menthyl ether than of the menthyl ester grouping is in reality a further illustration of what has been pointed out by Purdie and Irvine (Trans., 1901, **79**, 964) in respect of ethyl malate, ethyl monomethoxysuccinate, and ethyl acetylmaleate on the one hand, and in respect of ethyl tartrate, ethyl dimethoxysuccinate, and ethyl diacetyltartrate on the other, and by P. Frankland and Gebhard (Trans., 1905, **87**, 864) in respect of the alkyl glycerates, alkyl dimethoxypropionates, and alkyl diacetylglycerates. In all of these cases the effect on molecular rotation of alkylating the OH-group attached to an asymmetric carbon atom is much greater than that produced by acetylating the same group.

EXPERIMENTAL.

Menthoxyacetic Acid, $C_{10}H_{19}O \cdot CH_2 \cdot CO_2H$.—Two hundred grams of menthol (Kahlbaum) were dissolved in about 500 c.c. of sodium-dried benzene in a 3-litre, round-bottom flask. Forty grams of

sodium cut up into thin plates were then added, and the flask was heated under a reflux condenser on a boiling-water bath for four hours. The excess of sodium was then removed (only 30 grams being required by 200 grams of menthol), and 50 grams of chloroacetic acid, dissolved in about 400 c.c. of dry benzene, were then added gradually, the flask being well shaken during the addition to keep the precipitated sodium chloroacetate in a finely divided state, and cooled when necessary to prevent violent boiling due to the reaction. The result of this is to produce a gelatinous precipitate of sodium chloroacetate, on which the sodium menthoxide is able to react to form the sodium salt of menthoxyacetic acid. It is apparent that two molecules of sodium menthoxide must be present for every molecule of chloroacetic acid, as the reaction takes place in two stages:

In the actual preparation the quantities taken were in the proportion of $2\frac{1}{2}$ molecules of sodium menthoxide to 1 molecule of chloroacetic acid. At first sight it would seem to be more economical were the sodium chloroacetate prepared in some other way instead of utilising sodium menthoxide as in the first equation, but this is practically the only serviceable way, and the excess of menthol is easy to recover.

The flask was then heated under a reflux condenser for twenty-five hours on a boiling-water bath. During this time the pasty sediment was periodically broken up by vigorous shaking, and dry benzene to the extent of $1\frac{1}{2}$ litres added at intervals to keep the mixture in a sufficiently liquid condition.

The sodium menthoxyacetate was then washed out with water, which also dissolves the sodium chloride, sodium hydroxide, and any free chloroacetic acid. The menthol remains in the benzene layer, as well as any tarry products if formed. The aqueous solution of sodium menthoxyacetate was acidified with sulphuric acid, and the free menthoxyacetic acid extracted with ether. This extract after being dried was concentrated to a syrup, which crystallised out in the refrigerator. The crystals were washed free from mother liquor with a little ether, and dried on porcelain.

This product was almost colourless, and melted only 3° below that of the purified acid. The total yield of this crude acid was 85 grams, which is 75 per cent. of the theoretical quantity obtainable from the chloroacetic acid used.

The acid is very soluble in all organic solvents; it was purified by repeated recrystallisation from ether. After six such crystallisa-

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tions, the melting point was 53—54°, and the rotation in methyl alcohol at 20° was:

<i>l.</i>	<i>p.</i>	D_4^{20}	<i>c.</i>	α_D	$[\alpha]_D^{20}$	$[M]_D^{20}$
2-dcm.	5.253	0.8030	4.218	-7.84°	-92.93°	-198.8°

For the following preparations the acid was used after one crystallisation.

Menthoxyacetic Allylamide.—Ethyl menthoxyacetate was prepared by esterifying 60 grams of menthoxyacetic acid in an excess of absolute alcohol by saturation with dry hydrogen chloride. After heating for an hour, hydrogen chloride was again passed in, and the heating continued for another hour, after which the mixture was washed with a dilute solution of sodium carbonate, and the ester extracted with ether. After drying the extract, the ether was distilled over, and the ester distilled in a vacuum. The yield was 50 grams.

Fifteen grams of allylamine (Kahlbaum) were added, and the mixture heated under a reflux condenser on a water-bath for eight hours. The liquid product was purified by vacuum distillation until the observed rotation was constant. The yield was about 20 grams. After four distillations, the liquid boiled at 185—187°/14 mm., and gave $[\alpha]_D^{20}$ -76.11°.

The amide is a colourless, odourless, oily liquid, soluble in all organic solvents, but not in water or acids:

0.1466 gave 7.3 c.c. N_2 (moist) at 19° and 744.7 mm. $N=5.61$.

$C_{15}H_{27}O_2N$ requires $N=5.53$ per cent.

Densities:

t°	20°.	30°.	50°.	70°.	97°.
D_4^t	0.9667	0.9590	0.9442	0.9290	0.9082

Menthoxyacetic Allylamide.

Rotations in a 1-dcm. tube:

t°	D_4^t (from curve).	α_D^t	$[\alpha]_D^t$	$[M]_D^t$
20	0.9667	-73.58°	-76.11°	-192.5°
49	0.9445	71.72	75.93	192.1
58	0.9376	70.97	75.70	191.5
68	0.9304	70.31	75.57	191.2
99	0.9070	68.20	75.19	190.2

Rotation in methyl alcohol solution. (Substance slightly impure through being kept a year.)

<i>p.</i>	<i>c.</i>	D_4^{20}	α_D^{20} (<i>l</i> =2).	$[\alpha]_D^{20}$	$[M]_D^{20}$
2.3759	1.887	0.7944	-3.03°	-80.27°	-203.1°
3.9200	3.132	0.7990	5.02	80.13	202.7
7.1802	5.772	0.8039	9.14	79.18	200.3

Menthoxycetic Propylamide.—This was prepared in an identical manner to the allylamide from 45 grams of the ester and 12 grams of propylamine (Kahlbaum). After five distillations the observed rotation not being constant, and there being only 12 grams of the purest fraction, a second preparation of the amide was commenced, and after five vacuum distillations was added to the first preparation. When the whole had been distilled three more times, the observed rotation became constant. The yield from the two preparations was 20 grams.

This pure substance boiled at 188—189°/16 mm., and gave $[\alpha]_D^{20} - 75.96^\circ$. It is a colourless, odourless, oily liquid, similar in properties to the allylamide:

0.1410 gave 7.0 c.c. N_2 (moist) at 17.5° and 748.6 mm. $N = 5.66$.
 $C_{15}H_{29}O_2N$ requires $N = 5.49$ per cent.

Densities:

t° .	20°.	30°.	50°.	70°.	97°.
$D_4^{t^\circ}$	0.9545	0.9469	0.9320	0.9174	0.8958

Menthoxycetic Propylamide.

Rotations in a 1-dm. tube:

t° .	$D_4^{t^\circ}$ (from curve).	$\alpha_D^{t^\circ}$.	$[\alpha]_D^{t^\circ}$.	$[M]_D^{t^\circ}$.
20.0	0.9545	-72.51°	-75.97°	-193.7°
33.5	0.9445	71.60	75.80	193.3
60.0	0.9240	69.83	75.57	192.7
99.0	0.8840	67.09	75.04	191.4

Rotation in methyl alcohol solution. (Substance slightly impure through being kept a year.)

p .	c .	D_4^{20} .	α_D^{20} ($l=2$).	$[\alpha]_D^{20}$.	$[M]_D^{20}$.
2.3051	1.835	0.7960	-2.98°	-81.20°	-207.1°
4.5327	3.625	0.7997	5.88	81.11	206.8
6.0106	4.818	0.8016	7.79	80.84	206.1
7.3065	5.875	0.8041	9.44	80.34	204.9

Allyl Menthoxyacetate.—Sixty-five grams of menthoxyacetic acid (1 mol.) and 57 grams of allyl alcohol (3 mols.) were mixed in a flask and saturated with dry hydrogen chloride. After heating on a water-bath for a short time, more hydrogen chloride was passed in, and the mixture again heated for an hour. The mixture was then washed with a solution of sodium carbonate, and the ester and excess of allyl alcohol extracted with ether. This extract was dried, and the ether and alcohol distilled off. The ester was then distilled in a vacuum until the observed rotation was constant at 15° in a 0.5-dm. tube. After seven distillations the ester boiled at 182°/40 mm., and gave $[\alpha]_D^{15} - 93.04^\circ$. The yield was 20 grams.

This ester is a colourless, odourless, oily liquid, soluble in all organic solvents:

0.2758 gave 0.7130 CO₂ and 0.2559 H₂O. C=70.51; H=10.31.

C₁₅H₂₆O₃ requires C=70.87; H=10.23 per cent.

Densities:

<i>t</i> °.	15°.	20°.	30°.	40°.	60°.	80°.	99°.
D ₄ ^t	0.9726	0.9682	0.9610	0.9528	0.9384	0.9222	0.9094

Allyl Menthoxyacetate.

Rotations in a 0.5-dcm. tube:

<i>t</i> °.	D ₄ ^t (from curve).	<i>a</i> _D .	[<i>a</i>] _D ^t .	[M] _D ^t .
14	0.9720	-45.28°	-93.15°	-236.6°
25	0.9640	44.11	91.51	232.4
30	0.9605	43.66	90.91	230.9
33	0.9580	43.31	90.42	229.7
42	0.9515	42.45	89.23	226.6
85	0.9193	38.18	83.06	211.0

Rotation in methyl alcohol solution:

<i>p</i> .	D ₄ ^t .	<i>c</i> .	<i>l</i> .	<i>a</i> _D .	[<i>a</i>] _D ²⁰ .	[M] _D ²⁰ .
4.025	0.8003	3.221	2-dcm.	-5.40°	-83.81°	-212.9°
8.912	0.8067	7.189	2-dcm.	12.06	83.87	213.0

Propyl Menthoxyacetate.—The propyl alcohol used had to be fractionated, as it boiled over a range of ten degrees, 93–103°. The fraction boiling at 96.5–97.5° was used for this preparation.

This ester was prepared in a similar manner to the above, excess of the alcohol to the extent of 3 molecules to 1 molecule of the menthoxyacetic acid being taken.

Seventy grams of the acid were esterified with 60 grams of propyl alcohol by means of dry hydrogen chloride, as for the above ester.

The crude ester, after seven distillations in a vacuum, had a constant rotatory power, [*a*]_D²⁰ -91.46°, and boiled at 172°/26 mm. The yield was 19 grams.

The ester is a colourless, odourless, oily liquid, soluble in all organic solvents, but not in water:

0.2588 gave 0.6660 CO₂ and 0.2558 H₂O. C=70.18; H=10.98.

C₁₅H₂₈O₃ requires C=70.31; H=10.93 per cent.

Densities:

<i>t</i> °.	15°.	20°.	40°.	70°.	99°.
D ₄ ^t	0.9577	0.9547	0.9381	0.9144	0.8901

Propyl Menthoxyacetate.

Rotations in a 0.5-dcm. tube:

t°	D_4^t (from curve.)	α_D	$[\alpha]_D^t$	$[M]_D^t$
8.0	0.9638	-44.78°	-92.92°	-237.9°
20.0	0.9547	43.66	91.46	234.1
30.0	0.9461	42.71	90.30	231.2
53.0	0.9275	40.42	87.16	223.1
57.0	0.9240	40.15	86.91	222.5
89.5	0.8973	37.02	82.50	211.2

A 10.2 per cent. solution in methyl alcohol gave $[\alpha]_D^{20} - 82.64^{\circ}$.

p	D_4^t	c	l	α_D	$[\alpha]_D^{20}$	$[M]_D^{20}$
10.250	0.8057	8.258	2-dcm.	-13.65°	-82.64°	-211.5°

Menthyl Allylaminoacetate.—Forty grams of menthyl chloroacetate, prepared from menthol and chloroacetic acid by esterification with dry hydrogen chloride, were dissolved in 100 c.c. of sodium-dried ether, and 20 grams of allylamine were added. The mixture was heated under a reflux condenser for three hours on a water-bath. The interaction takes place readily, as after a few seconds crystals of allylamine hydrochloride were seen. It is necessary to take twice the quantity of amine required to replace the chlorine in the menthyl chloroacetate in order to combine with the hydrogen chloride split off.

The amine hydrochloride was quickly collected, and washed with a little dry ether. The weight—15 grams—showed that the interaction was complete. The ether and any excess of amine was distilled off, and the crude ester distilled in a vacuum until the observed rotation became constant. After four distillations the ester boiled at 155—157°/17 mm., and gave $[\alpha]_D^{20} - 63.47^{\circ}$. The yield was 12 grams.

The ester is a colourless, odourless liquid, soluble in all organic solvents:

0.3552 gave 0.9206 CO₂ and 0.3374 H₂O. C=70.70; H=10.56.

0.2570 „ 12.9 c.c. N₂ (moist) at 20° and 739.4 mm. N=5.58.

C₁₅H₂₇O₂N requires C=71.15; H=10.67; N=5.53 per cent.

Densities:

t°	12°.	20°.	40°.	69°.	100°
D_4^t	0.9565	0.9488	0.9347	0.9133	0.8903

Menthyl Allylaminoacetate.

Rotations in a 0.5-dcm. tube:

t .	D_4^t (from curve).	α_D .	$[\alpha]_D^t$.	$[M]_D^t$.
16.2	0.9518	-30.27°	-63.60°	-160.9°
20.5	0.9488	30.09	63.43	160.5
46.5	0.9295	29.49	63.45	160.5
48.5	0.9280	29.41	63.38	160.35
69.0	0.9133	28.76	62.98	159.3
99.8	0.8903	27.95	62.79	158.8

Rotations in methyl alcohol in a 2-dcm. tube at 20°:

D_4^t	p .	c .	α_D .	$[\alpha]_D^{20}$.	$[M]_D^{20}$.
0.7945	1.5009	1.192	-1.70°	-71.28°	-180.33°
0.7979	3.0045	2.398	3.35	69.87	176.77
0.7993	4.1738	3.336	4.52	67.74	171.38

Menthyl Propylaminoacetate.—This was prepared in the same way as the above allylaminoacetic ester. Thirty-nine grams of menthyl chloroacetate were dissolved in 50 c.c. of dry ether, and heated with 20 grams of propylamine. After seven distillations in a vacuum the observed rotation was constant, the ester boiling at 159—161°/17 mm., and having $[\alpha]_D^{20}$ -62.03°. The yield was 6 grams.

This ester is colourless and odourless, and is soluble in all organic solvents:

0.3698 gave 0.9464 CO₂ and 0.3832 H₂O. C=69.80; H=11.51.

0.2590 „ 12.8 c.c. N₂ (moist) at 21° and 742.4 mm. N=5.47.

C₁₅H₂₉O₂N requires C=70.59; H=11.37; N=5.49 per cent.

Densities:

t° .	12°.	20°.	40°.	69°.	100°.
D_4^t .	0.9406	0.9330	0.9185	0.8976	0.8753

Menthyl Propylaminoacetate.

Rotations in a 0.5-dcm. tube:

t° .	D_4^t (from curve).	α_D .	$[\alpha]_D^t$.	$[M]_D^t$.
14.5	0.9368	-29.14°	-62.21°	-158.6°
20.0	0.9330	28.96	62.08	158.3
38.0	0.9195	28.55	62.10	158.4
44.5	0.9152	28.40	62.06	158.3
58.0	0.9052	28.08	62.04	158.2
66.0	0.8995	27.86	61.95	158.0
99.0	0.8756	27.10	61.90	157.8

Rotations in methyl alcohol in a 2-dcm. tube at 20°:

D_4^t	p .	c .	α .	$[\alpha]_D^{20}$.	$[M]_D^{20}$.
0.7969	2.9900	2.383	-3.32°	-69.67°	-177.6°
0.7989	4.5608	3.644	5.04	69.16	176.3
0.8057	8.9275	7.193	9.87	68.61	174.9

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