

CCLXXVIII.—*Optical Activity and the Polarity of Substituent Groups. Part XXI. Growing Chain Effects among the l-Menthyl Esters of n-Aliphatic Acids.*

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IN previous communications of this series it has been shown that certain electronegative substituents, I, Br, Cl, and especially OMe, which raise the rotatory powers of the *p*-substituted benzoic esters and the monosubstituted acetic esters, lower the rotations of the benzoic derivatives when they are introduced into the ortho-position. As a working hypothesis it was assumed that the abnormal effect in the ortho-position was the result of the usual substituent influence, as propagated through the chain of atoms, being reversed by that transmitted through space.

Some support was lent to this suggestion by the results of an examination of the *l*-menthyl esters of peri-substituted naphthoic acids by Bretscher, Rule, and Spence (J., 1928, 1493). Further evidence bearing on this point was sought by Rule, Hay, and Paul (J., 1928, 1347), who prepared homologous series of esters of *n*-aliphatic acids containing the substituent as a terminal group in the alkyl chain. By this means it was anticipated that, as the chain returned on itself at regular intervals, anomalies in the rotatory powers of the esters would become apparent if the hypothesis of a spatial propagation of the "ortho-effect" was correct. The periodic influence of such groups as carboxyl and methoxyl, which give rise to similar "general polar effects," but opposite types of "ortho-effects," would therefore be expected to be of opposite character in the ω -substituted aliphatic derivatives. Unfortunately, these authors instituted their comparison between the ω -carboxy-esters and a series of *n*-alkyloxyacetic esters, owing to the experimental difficulty of preparing a sufficient number of the corresponding ω -methoxy-compounds. The comparison was therefore essentially between the influence of the ω -carboxy-chain and that of a growing alkyl radical. Nevertheless, the results obtained lent some support to the original hypothesis. A subsequent investigation of the influence of *gem*-dialkyl groups on the rotatory powers of *l*-menthyl esters of the type $X \cdot CR_2 \cdot CO_2 \cdot C_{10}H_{19}$ (Rule and Harrower, J., 1930, 2319) has provided further evidence that the characteristic "ortho-influence" of the substituent X in the benzoic esters can be interpreted as a spatial influence.

Despite the laborious preparative work involved, it was decided to complete the required data by examining the series of *l*-menthyl

esters of ω -methoxy-aliphatic acids, which offer a true comparison with the ω -carboxylic derivatives already examined.

The values obtained for the rotatory powers of these esters are tabulated below.

l-Menthyl ω -methoxy-*n*-aliphatic esters, $\text{CH}_3\text{O}\cdot[\text{CH}_2]_n\cdot\text{CO}_2\text{C}_{10}\text{H}_{19}$.

Values of $[M]_{5461}^{20^\circ}$ at 20° (approx.)

<i>n</i>	1	2	3	4	5	6
Homogeneous	*-195.3°	-194.3°	-188.2°	-184.8°	-186.1°	-187.2°
Benzene (<i>c</i> = 5) ...	†-183.8	-199.1	-192.1	-190.0	-192.5	-193.7
Alcohol (<i>c</i> = 5)	†-195.8	-208.0	-204.9	-202.2	-203.7	-195.1

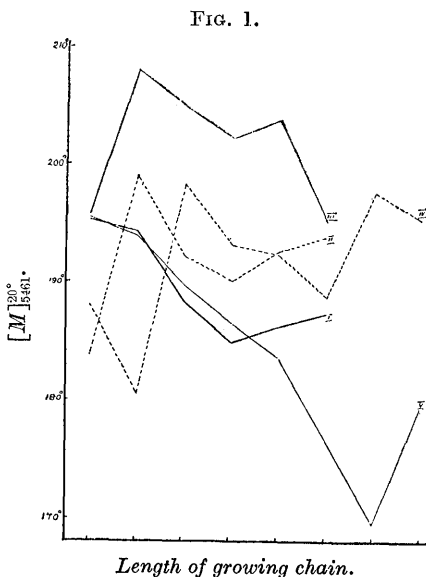
* Rule and Smith, *J.*, 1925, **127**, 2188.

† Rule and Harrower, *J.*, 1930, 2321.

Comparison of Rotation Curves.—In a previous communication on this subject (Rule, Hay, and Paul, *loc. cit.*) the growing chain of each series was numbered from and including the asymmetric atom; *l*-menthyl hydrogen malonate and *l*-menthyl methoxyacetate thus corresponding to $n = 6$ on this scale. It is now proposed to denote the position of the substituent by α , β , γ , etc., a simplification which does not affect the comparisons under the original numbering system.

When the rotatory powers of the ω -methoxy-esters under varying conditions are plotted (see Fig. 1) and compared with the results obtained by Rule, Hay, and Paul, a bewildering array of curves emerges which serves to emphasise the fact that the effect produced by a given substituent is to some extent dependent on the nature of the medium in which the comparison is made.

The investigation of the peri-substituted naphthoic esters (Bretscher, Rule, and Spence, *loc. cit.*) has shown that the characteristic ortho-influence of a substituent tends to be produced to its maximum extent in the presence of non-polar hydrocarbon solvents. More



Menthyl ω -methoxy-*n*-aliphatic esters: I (homog.); II (in C_6H_6); III (in EtOH); IV menthyl hydrogen dicarboxylates (in C_6H_6); V dicarboxylates (sodium salt in water).

recently, Rule and McLean (this vol., p. 675), in studying the action of solvents on the optical activity of *l*-menthyl methyl naphthalate, concluded that the solvent exerts a very definite influence which is related to its polar character. Consequently, in the present case the most trustworthy comparisons will probably result from an examination of the above methoxy-esters in dilute solution in benzene as a non-polar solvent. In addition, the values obtained for the esters in the homogeneous state may be assumed to be more normal than those observed in the presence of a highly polar solvent such as alcohol.

The nature of the curves representing the homologous ω -carboxy- and ω -methoxy-esters in benzene is in general agreement with the hypothesis of an opposite spatial influence of the two substituents in the ortho-benzoates. The two diagrams are in complete contrast, the former showing minima at the β - and ζ -positions, whereas the latter exhibits maxima at these points. Between these extremes the rotatory powers of the carboxy-compounds remain high at γ and δ , corresponding to the relatively low values of the methoxy-esters in these positions. An exact comparison is rendered somewhat difficult owing to the pronounced alternation of the curve representing the acid esters.

In the homogeneous state the opposing influences of the two terminal groups are still evident, although the contrast is neither so obvious nor so complete as when the comparison is made in the presence of benzene as solvent.

When alcohol is employed as a solvent, the maximum and minimum for the methoxy-series remain as before at the β - and δ -positions respectively, but the former maximum at ζ has now become a minimum. The latter difference is regarded as an abnormality caused by the polarity of the solvent.

The values obtained by Rule, Hay, and Paul for the rotatory powers of the sodium salts of the carboxy-esters in water* reveal, except for small deflexions at the β - and ϵ -positions, an undeviating fall to the azelate, after which the curve starts to ascend. Whilst the anomaly at the β -ester, if real, may be related to the effects already noted at this point, the pronounced minimum at the azelate is in remarkable contrast to the maximum obtaining at the corresponding point in the curve for the un-ionised carboxy-ester. This minimum can scarcely be explained except as a space effect caused by the negative ionic charge on the ionised carboxyl group. No

* The α_{5461} recorded by these authors for the sodium menthyl azelate in water gives a molecular rotation of $[M]_{5461} -169.6^\circ$ instead of -181.0° as stated in their communication, thus changing the minimum point from the suberate to the azelate.

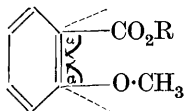
other interpretation is as probable, especially as the effect is propagated from a point a considerable distance removed from the asymmetric group. The observed changes appear to be comparable with the influence of *gem*-dialkyl groups on the rotatory powers of *l*-menthyl hydrogen malonate and its sodium salt (Rule and Harrower, *loc. cit.*). In the latter case, as the CO_2H (or COO') is forced into closer proximity to the carbomethoxy-complex by replacing the methylene hydrogen atoms by bulky alkyl groups, it is found that the characteristic increase (or decrease) in rotatory power is greatly enhanced.

A comparison between the rotation curve obtained for the *l*-menthyl alkyloxyacetates prepared by Rule, Hay, and Paul (*loc. cit.*) and that for the ω -methoxy-derivatives affords a further illustration of what Lowry (*Trans. Faraday Soc.*, 1930, **26**, 266) has described as "the fantastic idiosyncrasies of the growing chain in homologous series."

Whilst there remains the possibility that the carboxy-ester curves are entirely abnormal owing to combination between the carboxyl group and the ester half of the molecule (compare Kendall and Booge, *J. Amer. Chem. Soc.*, 1916, **38**, 1712), yet the considerable degree of uncertainty still existing concerning the electrical nature of such composite groups as the methoxyl and carboxyl is probably the chief obstacle to a satisfactory interpretation of these results.

The magnitude of the effect produced by the methoxyl substituent in the *n*-aliphatic esters compared with that obtained in the corresponding *o*-substituted benzoic derivatives shows that the influence of the group is considerably greater in the latter case than in the former. This has already been pointed out by Rule, Hay, and Paul with respect to the carboxyl substituent, and has been considered to be largely due to the predominance of a rigid structure in the *o*-substituted benzoic esters as compared with the state of constant motion of the end of the aliphatic chain. The effect in the benzoic compounds may also be increased by the smaller angles (α) in the ortho-esters (compare Mills and Nixon, *J.*, 1930, 2510), which will force the side chains closer together than would occur in the normal structure prevailing in the open-chain series (see annexed diagram).

Notwithstanding some apparent exceptions, these results afford further support for the original hypothesis, and it is concluded that the characteristic "ortho-effect" of the electronegative substituents under consideration is best explained as a spatial influence predominating over the normal effect propagated through the chain of atoms.



EXPERIMENTAL.

l-Menthyl β -Methoxypropionate.—From methyl β -iodopropionate the corresponding β -methoxy-derivative was obtained as an oil, b. p. 142—144°/760 mm. The *l*-menthyl ester was then synthesised by the sodium methoxide process (compare Rule and Harrower, *J.*, 1930, 2334). Methyl β -methoxypropionate (16 g.) gave only 3 g. of the *l*-menthyl ester, a considerable proportion of a high-boiling liquid being left in the flask. The ester boiled at 135—137°/10 mm., and after two fractionations gave $\alpha_{D_{461}}^{20} - 77.01^\circ$ ($l = 100$), which remained unchanged after a further distillation (Found : C, 69.4; H, 10.9. $C_{14}H_{26}O_3$ requires C, 69.4; H, 10.8%).

l-Menthyl γ -Methoxybutyrate.—A number of different processes recommended in the literature for the preparation of the intermediate γ -methoxybutyronitrile were tried, but none gave sufficiently large yields to enable the final stages to be carried out. Attempts included the preparation of trimethylene chlorobromide, first from allyl chloride (Bruylants, *Rec. trav. chim.*, 1909, **28**, 244) and also from trimethylene glycol (Marvel and Calvery, "Organic Syntheses," VII, 113), and conversion of this into methyl γ -chloropropyl ether by the method of Haworth and Perkin (*J.*, 1894, **65**, 597); the chloro-compound was then converted successively into the nitrile and methoxy-acid.

The method by which γ -methoxybutyric acid was eventually obtained consisted in converting trimethylene bromide (200 g.) into γ -bromobutyronitrile (Derrick and Hess, *J. Amer. Chem. Soc.*, 1918, **40**, 546) by refluxing it for 7—8 hrs. with anhydrous alcohol (500 c.c.) and dry, finely powdered potassium cyanide (32 g.). The precipitated potassium bromide was filtered off, and the alcohol removed by distillation from a brine-bath. On fractionation of the residual brown liquid, the butyronitrile, b. p. 100—104°/20 mm., was collected separately; yield 29 g. (20%). About 50 g. of trimethylene bromide were recovered.

Sodium (5 g.) in the form of sodium methoxide dissolved in 60 c.c. of methyl alcohol was added in four portions to the butyronitrile (29 g.) and raised to the boil for a short time after each addition (compare Haworth and Perkin, *loc. cit.*). The copious precipitate of sodium bromide was filtered off, alcohol removed by distillation, and the residue dissolved in ether and dried over sodium sulphate. This gave, on fractionation, an oily distillate, b. p. 170—175°; yield 8 g. (41%) (Schlinck, *Ber.*, 1899, **32**, 948, gives b. p. 172—175°).

The nitrile (8 g.) obtained from the preceding stage was mixed with potassium hydroxide (7.5 g.) dissolved in its own weight of water, and heated under reflux until no more ammonia was evolved

(8 hrs.). The product was acidified with concentrated hydrochloric acid, water added, the precipitated potassium chloride filtered at the pump, and the resulting clear solution extracted with ether in a continuous-extraction apparatus for 12—15 hrs. The ethereal solution, after drying over sodium sulphate, gave γ -methoxybutyric acid, b. p. 216—220°; yield 4 g. (40%).

l-Menthyl γ -methoxybutyrate was prepared from the above acid (4 g.) by dissolving it in light petroleum and adding thionyl chloride (5 g.). After the mixture had boiled gently for one hour, the solvent and excess thionyl chloride were removed by gentle heating under diminished pressure, and the residual acid chloride treated in the usual way with *l*-menthol (6 g.). The *menthyl* ester distilled at 143—145°/10 mm., being obtained as a colourless liquid, yield 6 g. (60%). The rotation of the homogeneous liquid rose to $\alpha_{5461}^{20} - 70.28^\circ$ on purification by repeated fractionation ($l = 100$) (Found: C, 70.0; H, 11.3. $C_{15}H_{28}O_3$ requires C, 70.3; H, 11.0%).

l-Menthyl δ -Methoxyvalerate.—The starting point in the preparation of this ester was ethyl γ -methoxypropylmalonate, which was obtained by the method outlined by Noyes (*Amer. Chem. J.*, 1897, **19**, 778) for the corresponding ethoxy-compound. Methyl γ -chloropropyl ether (24 g.) was added to a mixture of malonic ester (34 g.) and methyl alcohol (70 c.c.) in which sodium (5 g.) had been dissolved. After 3 hours' boiling, alcohol was removed by distillation from a brine-bath, and the residue fractionated under reduced pressure. A colourless distillate was obtained which on a second fractionation gave 7 g. of γ -methoxypropylmalonic ester (15% yield). This preparation had to be repeated several times in order to enable the next stage to be carried out.

The foregoing ester (23 g.) was hydrolysed on the water-bath with potassium hydroxide (14 g.) in water (25 c.c.). After 3 hrs., an excess of hydrochloric acid was added, and the mixture was extracted with ether in a continuous-extraction apparatus for 9—10 hrs. After the extract had been dried and the ether distilled off, the crude γ -methoxypropylmalonic acid (16 g.) was heated on an oil-bath to 170° as long as carbonic acid escaped. The impure product was fractionated after a preliminary portion boiling up to 122°/12 mm. had distilled, and the δ -methoxyvaleric acid then boiled at 124—128°/12 mm. (compare Noyes, *loc. cit.*); yield 7 g. (53%).

l-Menthyl δ -methoxyvalerate was obtained from the acid (9 g.) by way of the acid chloride, giving an oil of b. p. 155—165°/12 mm. (yield 9 g., 50%). After another fractionation, the rotatory power was $\alpha_{5461}^{20} - 64.75^\circ$ ($l = 100$), unchanged on further fractionation (Found: C, 70.7; H, 11.5. $C_{16}H_{30}O_3$ requires C, 71.0; H, 11.2%).

1-*Menthyl* ϵ -*Methoxy-n-hexoate*.—Benzoylpiperidine was prepared from piperidine by the method of Marvel and Lazier ("Organic Syntheses," IX, p. 16), and thence pentamethylene dibromide was obtained by the method of von Braun (*op. cit.*, IX, p. 70). Starting from 160 g. of benzoylpiperidine, and using the corresponding amounts of phosphorus tribromide and bromine, 91 g. of pentamethylene dibromide were obtained, b. p. 101—103°/17 mm. (yield 41%).

ϵ -Bromo-*n*-hexonitrile was prepared by a method similar to that adopted for γ -bromobutyronitrile. Methyl alcohol (200 c.c.) was refluxed on the water-bath for 7—8 hrs. with finely powdered, dry potassium cyanide (13 g.) and pentamethylene dibromide (91 g.). The precipitated potassium bromide was filtered off, and the alcohol removed by distillation. The residue was carefully fractionated, and the portion of b. p. 125—135°/14 mm. collected separately; yield of ϵ -bromo-*n*-hexonitrile 28 g. (78%).

ϵ -Methoxy-*n*-hexonitrile was synthesised from the above bromo-derivative by a process similar to that for the production of the γ -methoxy-nitrile, sodium (5 g.), in the form of sodium methoxide dissolved in methyl alcohol (60 c.c.), being added in separate portions to ϵ -bromo-*n*-hexonitrile (38 g.). After separation of potassium bromide and removal of alcohol, the brownish oily residue was fractionated under reduced pressure. Practically all the liquid distilled at 98—102°/23 mm., giving a yield of 16 g. (58%) of the methoxy-compound.

The methoxy-acid was obtained by the hydrolysis of the nitrile (16 g.), which was heated on a brine-bath with potassium hydroxide (10 g.) dissolved in 15 c.c. of water, till no further evolution of ammonia took place (about 8 hrs.). The cooled product was acidified and extracted with ether, dried, and fractionated. A colourless liquid distilled between 135° and 145°/15 mm., yield 12 g. (87%). The ϵ -methoxy-*n*-hexoic acid so obtained was further purified and analysed; b. p. 140—142°/15 mm. (Found: C, 57.5; H, 9.6. $C_7H_{14}O_3$ requires C, 57.5; H, 9.7%).

1-*Menthyl* ϵ -methoxy-*n*-hexoate was obtained from the ϵ -methoxy-acid (5 g.) by way of the acid chloride (see valerate); yield 8.5 g. (85%). Two fractionations gave an optically pure product, α_{5461}^{20} — 61.56° ($l = 100$); b. p. 181—182°/16 mm. (Found: C, 71.8; H, 11.6. $C_{17}H_{32}O_3$ requires C, 71.8; H, 11.4%).

1-*Menthyl* ζ -Methoxy-*n*-heptoate.—Methyl ϵ -bromo-*n*-amyl ether was the starting point for this ester. Pentamethylene dibromide (175 g.) was boiled for 1½ hours with sodium (3.5 g.) dissolved in absolute methyl alcohol (60 c.c.). The products of reaction were

distilled from the precipitated sodium bromide, and fractionated under reduced pressure. A considerable proportion of dibromide was recovered and 25 g. of a liquid, b. p. 75—78°/12 mm., were collected. This fraction was found to be the required bromo-ether. The yield (25 g.) calculated on the dibromide used (61 g.) represented 51% of the theory. Repeated fractionation gave the pure bromo-ether, b. p. 70.5°/10 mm. (Found: Br, 43.6. $C_6H_{13}OBr$ requires Br, 44.1%).

Sodiomalonic ester (ethyl malonate, 25 g.; sodium, 3.5 g.; absolute alcohol, 40 c.c.) was condensed with methyl ϵ -bromo-*n*-amyl ether (16 g.) as in the preparation of γ -methoxypropylmalonic ester. After 6 hours' boiling, water was added; the ϵ -methoxy-*n*-amylmalonic ester separated as an oil, which was extracted with ether, washed, and dried over calcium chloride. Removal of the ether left a clear liquid, b. p. 150—155°/10 mm.; yield 22 g. (60%). Hydrolysis of this ester (22 g.) was effected by heating with water (25 c.c.) containing potassium hydroxide (15 g.) to 120° on an oil-bath for 3 hrs. Excess of hydrochloric acid was added, and the mixture placed in a continuous ether extraction apparatus for 15 hrs. The extract was dried over anhydrous sodium sulphate, the ether removed, and the free dicarboxylic acid treated as in the preparation of δ -methoxyvaleric acid. On fractionation, a considerable volume distilled between 120° and 145°/12 mm., but a definite fraction was collected at 155—160°/12 mm.; this corresponded to the required heptoic acid; yield 4.5 g. (33% calculated on the ester used). The ζ -methoxy-*n*-heptoic acid was purified by further fractionation (Found: C, 59.8; H, 10.0. $C_8H_{16}O_3$ requires C, 60.0; H, 10.1%).

1-Menthyl ζ -methoxy-*n*-heptoate was obtained by treating the acid (4g.) in the usual way with thionyl chloride dissolved in light petroleum and adding menthol to the crude acid chloride. The ester (yield 5.5 g., 73%) had b. p. 178—183°/10 mm. after the usual purification and fractionation. Two further fractionations altered the rotatory power by only +0.02°, so the value $\alpha_{5461}^{20} - 58.82^\circ$ ($l = 100$) was regarded as representing the pure substance; b. p. 183—184°/10 mm. (Found: C, 72.4; H, 11.4. $C_{18}H_{34}O_3$ requires C, 72.4; H, 11.5%).

Observed Rotatory Powers.—The rotations were all observed in a 1-dcm. tube, and the densities determined in a pycnometer holding 1—2 c.c. of liquid. The reciprocals of the observed rotations in the homogeneous state plotted against the squares of the wave-lengths of the light employed gave in all cases a straight line. The dispersions may therefore be assumed to be normal and simple over the range of wave-length employed.

Rotations in homogeneous state.

Ester (ω -methoxy)	β	γ	δ	ϵ	ζ
t°	20°	19.5°	19.5°	18°	20°
$D_{4^\circ}^\circ$	0.9600	0.9565	0.9463	0.9406	0.9350
α_{8708}°	-51.39°	-45.22°	-41.65°	-39.80°	-37.99°
α_{5893}°	-65.20	-59.53	-54.80	-52.12	-49.78
α_{5461}°	-77.01	-70.28	-64.76	-61.56	-58.82
α_{4368}°	-127.99	-116.66	-107.52	-101.86	-97.68

Rotations in solution at 20° (approx.) ($\lambda = 5461$).

<i>l</i> -Menthyl ester.	Solvent.	<i>l</i> .	<i>c</i> .	<i>a</i> .
β -Methoxypropionate	$\{ C_6H_6$	100	5.206	-4.28°
	$\{ C_2H_5OH$	100	5.264	-4.52
γ -Methoxybutyrate	$\{ C_6H_6$	100	5.012	-4.01
	$\{ C_2H_5OH$	100	5.000	-3.75
δ -Methoxyvalerate	$\{ C_6H_6$	100	5.130	-3.60
	$\{ C_2H_5OH$	100	5.106	-3.82
ϵ -Methoxyhexoate	$\{ C_6H_6$	100	5.156	-3.49
	$\{ C_2H_5OH$	100	5.316	-3.81
ζ -Methoxyheptoate	$\{ C_6H_6$	100	4.926	-3.20
	$\{ C_2H_5OH$	100	4.586	-3.00

Summary.

A number of *l*-menthyl esters of the type $CH_3O \cdot [CH_2]_n \cdot CO_2 \cdot C_{10}H_{19}$ have been prepared and their rotatory powers examined in the homogeneous state and in solution in benzene and alcohol.

It is found that, for benzene solution, the maxima and minima in the rotation curve of the series correspond to minima and maxima respectively in the rotation curve obtained by Rule, Hay, and Paul (J., 1928, 1347) for the *l*-menthyl hydrogen dicarboxylates. It is also pointed out that the curve showing the variation of the values for the ionised sodium salts of the ω -carboxy-esters in water exhibits a pronounced minimum at the azelate, which corresponds to a maximum in the rotation curve for the un-ionised hydrogen esters at the same point. This evidence is considered to support the hypothesis of a space effect exerted by these substituents when present in the ortho-position in the active benzoic esters (compare Rule, Hay, Numbers, and Paterson, J., 1928, 178).

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