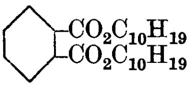
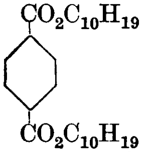
CCC.—*Optical Activity and the Polarity of Substituent Groups. Part XVI. Application of the Thorpe–Ingold Valency-deflexion Hypothesis to Optically Active Compounds.*

By H. GORDON RULE and JOHN HARROWER.

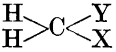
EARLIER investigations on the optically active *l*-menthyl and β-octyl esters of acetic and benzoic acids have shown that an abnormal effect is apparently produced by certain electronegative groups (Cl, Br, I, and OMe) when present in the ortho-position in the benzene nucleus. The influence of these ortho-substituents is to lower the rotation, although in the para-position they bring about the same change as in the acetic esters, where they lead to an increased rotatory power. Similarly, menthyl phthalate has been found by Cohen to exhibit a much lower rotation than the corresponding terephthalic ester (J., 1916, **109**, 225):


$[M]_D - 444°$.

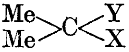

$[M]_D - 526°$.

These peculiarities of the ortho-compounds have been attributed (Rule, Hay, and Paul, J., 1928, 1347; Bretscher, Rule, and Spence, *ibid.*, p. 1493) to the spatial proximity of the substituent groups to the asymmetric complex and possibly also to their orientation relative to the latter, a conclusion which is supported by the occurrence of similar phenomena in ortho- and *peri*-substituted naphthoic esters.

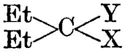
It appeared of interest, therefore, to determine whether further evidence bearing on this point could be gained by making use of the Thorpe–Ingold valency-deflexion hypothesis as applied to *gem*-dialkyl compounds. In a series such as



$\begin{matrix}H\\H\end{matrix}>C<\begin{matrix}Y\\X\end{matrix}$



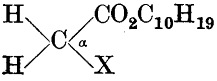
$\begin{matrix}Me\\Me\end{matrix}>C<\begin{matrix}Y\\X\end{matrix}$



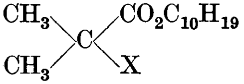
$\begin{matrix}Et\\Et\end{matrix}>C<\begin{matrix}Y\\X\end{matrix}$

the replacement of the relatively compact methylene group by *gem*-dialkyl groups of increasing bulk leads to the addenda X and Y being forced into closer contact, thus bringing about definite and predictable changes in chemical and physical properties (Ingold, J., 1921, **119**, 308; 1928, 1594; Gane and Ingold, J., 1926, 10; 1929, 1692).

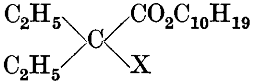
Given suitable arrangements for X and Y, these structural modifications should also become evident in the optical properties of the compounds. A simple case of this type, and one which has a direct bearing on the problem of the above ortho- and *peri*-substituted aromatic esters, is represented by the following series of *l*-menthyl derivatives in which X = OMe, CO_2R, CO_2H or $CO\overset{-}{O}(\overset{+}{Na})$:



$\begin{matrix}H\\H\end{matrix}>C\overset{\alpha}{<}\begin{matrix}CO_2C_{10}H_{19}\\X\end{matrix}$



$\begin{matrix}CH_3\\CH_3\end{matrix}>C<\begin{matrix}CO_2C_{10}H_{19}\\X\end{matrix}$



$\begin{matrix}C_2H_5\\C_2H_5\end{matrix}>C<\begin{matrix}CO_2C_{10}H_{19}\\X\end{matrix}$

The actual change in the angle α which takes place when the two hydrogen atoms are replaced by alkyl groups is assumed to be a matter of a few degrees only (Ingold, *loc. cit.*), *e.g.*, from 115° to 109°, and is certainly not of a sufficient magnitude to cause a reversal in the orientation of the dipole X relative to $CO_2C_{10}H_{19}$, as may occur in certain of the *o*-derivatives discussed above. In the corresponding series of substituted malonic acids investigated by Gane and Ingold, however, the authors have estimated that the distance between the carboxyls in the parent acid (1·54 Å.U.) becomes less in dimethylmalonic acid and is reduced to about half the original value in diethylmalonic acid. The changes in the optically active esters may conceivably be on a somewhat smaller scale owing to the larger bulk already occupied by the non-variable groups, but should nevertheless be reflected in the rotatory powers of the esters. In this respect it is to be anticipated that the introduction of *gem*-dialkyl groups into the methylene derivative will cause a displacement of the rotation in the same sense as that which occurs in the correspondingly substituted octyl or menthyl benzoates when the substituent is moved from the para- to the ortho-position.

Since the rotatory power of menthyl phthalate is low compared with that of the terephthalate, we may expect the rotation of menthyl malonate to be diminished by the introduction of the *gem*-dimethyl group and to become still less in the *gem*-diethyl ester. Similarly, since the ionisation of the carboxyl group lowers the rotation of *l*-menthyl hydrogen malonate (see below) and to an even greater extent that of *l*-menthyl hydrogen phthalate (Rule and McGillivray, J., 1929, 401), the progressively increasing proximity of the ionised carboxyl group to the carbomenthoxy-radical in the series of sodium menthyl malonates (X = CO_2Na) should result in a progressively greater fall in rotatory power. Finally, as *l*-menthyl *o*-methoxybenzoate exhibits a low rotation and the *o*-carboxy-ester a high rotation, these specific effects of the substituent groups should be enhanced in the *gem*-dialkyl compounds if the distance between X and $CO_2C_{10}H_{19}$ is one of the chief factors governing the magnitude of the rotatory power.

The molecular rotations observed for a number of esters of this type, both in the homogeneous state and in the presence of solvents, are summarised in the following table. The dispersion of all these esters proved to be normal and approximately simple in type.

Rotatory Powers, $[M]^{20°}_{5461}$, for *l*-Menthyl Esters, $CR_2{<}\substack{CO_2C_{10}H_{19}\\ X}$.

Substit. X.	State.	R = H.	R = Me.	R = Et.
$CO_2C_{10}H_{19}$	Homog.	−311°[1]	−271·9°	−279·1°
CO_2H	,,	189·9[2]	205·0	224·7
OMe	,,	195·3[3]	197·9	—
$CO_2C_{10}H_{19}$	Benzene (*c* = 5)	324	293	259
CO_2H	,, ,,	188	199	213
OMe	,, ,,	184	190	201
$CO_2C_{10}H_{19}$	Alcohol (*c* = 5)	—	321	315
CO_2H	,, ,,	193	203	215
$CO_2(Na)$	,, ,,	185	164	166
OMe	,, ,,	196	214	—

[1] Extrapolated from values at 70°, 90°, etc., recorded by Hall, J., 1923, **123**, 110.

[2] Rule, Hay, and Paul, J., 1928, 1348.

[3] Rule and Smith, J., 1925, **127**, 2188.

Influence of the gem-*Dialkyl Groups on Rotatory Power.*—From the values recorded in the table it is seen that the modifications in rotatory power caused by the introduction of the *gem*-dialkyl groups are with one exception in agreement with the foregoing conclusions.

Dimenthyl esters. Among the di-esters an increased proximity of the ester groups leads to a fall in rotation, the molecular values in the presence of solvents diminishing continuously on passing from the methylene to the *gem*-diethyl ester. In the homogeneous state the diethyl derivative, although still much lower than the parent malonate, has a slightly higher rotation than the dimethyl compound. This small upward trend may possibly be due to the incidence of a secondary influence related to the strengths of the acids. It will be remembered that among the esters of monosubstituted acetic acids (Rule, Thompson, and Robertson, this vol., p. 1887) the higher the dissociation constant of the acid the greater is the rotation of the menthyl ester. In the series under discussion it has been shown by Gane and Ingold (*loc. cit.*) and by Vogel (J., 1929, 1476) that diethylmalonic acid ($K_1 = 63{\cdot}9 \times 10^{-4}$) is an incomparably stronger acid than either dimethylmalonic acid ($K_1 = 6{\cdot}6 \times 10^{-4}$) or the parent malonic acid ($K_1 = 14{\cdot}1 \times 10^{-4}$).

In this connexion, attention may be drawn to the values of $[M]_D$ recorded by Walden (*Z. physikal. Chem.*, 1896, **20**, 377) for the diamyl esters of fumaric and maleic acids, namely, $+15{\cdot}17°$ and $+11{\cdot}82°$ respectively. Here again the juxtaposition of the ester groups reduces the optical activity. As a result of spatial influences of this nature it is only in a few isolated cases that the principle of optical superposition is found to hold with any degree of accuracy.

Acid esters and their sodium salts. The observed rise of rotatory power in the carboxyl series and the fall in the values of the corresponding salts is also in accordance with the deductions drawn from the ortho-substituted benzoic esters. The actual magnitude of the change in rotation due to conversion of the acid ester into its salt becomes progressively more pronounced as the CR_2 group increases in bulk. Incidentally, it is to be expected from the work of Gane and Ingold that menthyl hydrogen diethylmalonate will be the most strongly ionised of the three ester-acids under examination. Hence, as compared with the two preceding members, the rotatory power of the diethyl compound in alcoholic solution will be relatively lowered owing to the greater proportion which is present in the ionised condition. The fall observed on conversion into the sodium salt ought, therefore, to be increased by a corresponding amount in order to institute a true comparison with the remaining two ester-acids.

Methoxy-esters. In the homogeneous state the molecular rotation of the *gem*-dimethyl derivative scarcely differs from that of the unsubstituted ester, but in benzene and still more noticeably in alcoholic solution the values of the three esters rise steadily. In this case, therefore, the presence of the *gem*-dialkyl group does not lead to a fall in rotatory power, and the parallel with the aromatic esters is not realised. Probably the most reliable index of optical rotation is given by measurements taken in the absence of strongly polar solvents, and in this connexion it may be noted that the rotations of the carboxyl derivatives increase more rapidly than those of the methoxy-compounds if the comparison is limited to determinations in benzene solution or in the homogeneous state.

The possibility may be considered that the continuous rise in the rotatory powers of the methoxy- and carboxy-esters is due in part to the normal specific influence of the alkyl groups. An examination of the annexed values of $[M]_D$ recorded by Rupe for the methyl-substituted acetic esters shows that the introduction of methyl groups does lead to an enhanced rotation, although the amount of the change is relatively small.

$CH_3{\cdot}CO_2C_{10}H_{19}$	$-158°$	$(CH_3)_2CH{\cdot}CO_2C_{10}H_{19}$	$-163{\cdot}5°$
$CH_3{\cdot}CH_2{\cdot}CO_2C_{10}H_{19}$	$-160{\cdot}2$	$(CH_3)_3C{\cdot}CO_2C_{10}H_{19}$	$-161{\cdot}5$

Another factor to be borne in mind is that the methoxyl and carboxyl groups are composite dipoles containing an oxygen atom united to the central carbon of the system, and that recent work on dipole moments indicates that the bonds of bivalent oxygen subtend an acute angle of unknown magnitude. A considerable degree of uncertainty is thus introduced owing to our lack of definite knowledge concerning the disposition of the electrical charges in these groups.

On the whole, however, it may be concluded that the influence of *gem*-dialkyl groups on the rotatory powers of the esters under discussion lends additional support to the view that the abnormal properties of ortho-substituted benzoic esters are a consequence of the proximity and relative orientation of the substituent group to the active complex.

During the preparation of these esters several peculiarities were noted which may be explained as purely steric effects due to the close packing of the various groups around the central carbon atom. When the dimenthyl esters were obtained by way of the acid chloride, the yields fell from 57% for the *gem*-dimethyl to 13% for the *gem*-diethyl compound. As a confirmatory method, these di-esters were also prepared from the corresponding dimethyl esters (in 63 and 52% yields, respectively) by heating with menthol containing a little sodium menthoxide. In this process it was found that the proportion of mixed menthyl methyl ester formed as a by-product increased continuously on passing from the malonate through the *gem*-dimethyl to the *gem*-diethyl ester. It appears, therefore, that the entry of the second bulky menthyl radical is effected less readily in the *gem*-diethylmalonate. Similar differences were observed on half-hydrolysis of the dimenthyl esters in alcoholic solution with sodium hydroxide. The malonate reacted readily at room temperature, reaction in this case being possibly facilitated by the alternative enolic structure. The *gem*-dimethylmalonate required 36 hours at 80°, and the corresponding *gem*-diethyl compound 70 hours under similar conditions of concentration and temperature, before neutrality was attained. The yields of the monosodium salts fell from 20% of the theoretical in the case of the *gem*-dimethyl ester to only 4·5% for the *gem*-diethyl ester, the remainder of the alkali forming the disodium salt.

EXPERIMENTAL.

l-Menthyl malonate was found to be much more readily accessible by the sodium menthoxide process than by any of the methods given in the literature. Methyl malonate (1 mol.) was treated with *l*-menthol (4 mols.) in which sodium (0·05 g.-atom) had been dissolved. The mixture was maintained at 140—150° in a distillation flask, and a slow current of dry air drawn through the apparatus for 30 minutes to remove methyl alcohol. The product was washed and distilled in steam. Yield, 63%. After being three times crystallised from methyl alcohol, it gave $\alpha_{5461}^{20^\circ}$ — 9·30°, $l = 2$, in chloroform, $c = 5$ (Hall, J., 1923, **123**, 109, records —9·32°). The majority of the following esters were prepared by the same method.

l-*Menthyl dimethylmalonate.* Dimethylmalonic acid (m. p. 185°) was converted into the acid chloride, which was fractionated and treated with methyl alcohol. The methyl ester so obtained (1 mol.) was then heated with menthol ($2\frac{1}{2}$ mols.) and a small amount of sodium for 4—5 hours at 120—130°. After being washed, the product was dried, and menthol removed by distillation (b. p. 100—112°/12 mm.). The crude menthyl *ester* distilled at 208—215°/2 mm.; yield, 57% of the theoretical. On refractionation, the pure ester, b. p. 210—212°/2 mm., was obtained as an almost odourless oily liquid having a pale yellow tint (Found: C, 73·3; H, 11·1. $C_{25}H_{44}O_4$ requires C, 73·5; H, 10·9%).

l-*Menthyl hydrogen dimethylmalonate* was prepared by heating the normal ester (in portions of 25 g.) with 1 mol. of sodium hydroxide in 1200 c.c. of 96% alcohol, the course of the reaction being followed by titrating 2 c.c. of the mixture with *N*/250-acid. The mixture was maintained at 80° and reached the neutral point in 36 hours. The acid ester was purified by the method previously described (J., 1928, 1357) until the optical rotation underwent no further change, being obtained as an odourless but slightly yellow syrup. Yield, 4 g. from each 25 g. of di-ester (Found: C, 66·3; H, 9·8. $C_{15}H_{26}O_4$ requires C, 66·6; H, 9·7%).

l-*Menthyl diethylmalonate* was first prepared from diethylmalonic acid (B.D.H.), which was purified by recrystallisation from a mixture of benzene, ether, and light petroleum (compare Vogel, J., 1929, 1478). This was converted into the acid chloride by means of thionyl chloride, and after excess of the reagent had been distilled off, the crude chloride was treated directly with *l*-menthol, and the mixture heated at 130—140° for 4 hours. The product was washed and dried, and menthol distilled off at 100—110°/12 mm. The bulk of the dimenthyl ester was not distilled, for this led to partial decomposition as indicated in the variable rotatory power. On being allowed to stand, it gradually solidified, and on crystallisation from alcohol gave colourless needles, m. p. 52—53°, $[M]^{20°}_{5461} - 315°$, in alcohol, $c = 5$. Yield, 13% calculated on acid used.

A further supply of the dimenthyl ester (27 g.) was obtained from the corresponding dimethyl ester by use of menthol and sodium menthoxide (see above). After removal of menthol and a mixed menthyl methyl ester fraction (b. p. 130—180°/2 mm.), the residual dimenthyl ester solidified, forming a white crystalline mass. This was twice crystallised from alcohol and gave $[M]^{19°}_{5461} - 318°$, in alcohol, $c = 5$ (Found : C, 74·3; H, 11·3. $C_{27}H_{48}O_4$ requires C, 74·2; H, 11·1%).

l-*Menthyl hydrogen diethylmalonate* was prepared in the same manner as the previous acid ester, the alkaline mixture in this case requiring to be boiled for 70 hours before hydrolysis was complete. From 22 g. of diester only 0·6 g. of the desired product was isolated. Better yields were obtained by making use of the crude fraction, b. p. 130—180°/2 mm., which was separated during the purification of the diester. 25 G. of the crude mixed ester gave 4 g. of menthyl hydrogen diethylmalonate after 36 hours' hydrolysis, the product having the same rotatory power as that prepared from the dimenthyl ester. The acid ester was isolated as an odourless faintly yellow and very viscous syrup (Found : C, 68·4; H, 10·4. $C_{17}H_{30}O_4$ requires C, 68·4; H, 10·2%).

l-Menthyl methoxyacetate, for which the rotatory power in alcoholic and benzene solutions has not previously been recorded, was prepared by the method of Rule and Smith (J., 1926, 2188).

l-*Menthyl α-methoxy*iso*butyrate*. Acetonecyanohydrin, prepared by the very convenient process of Welch and Clemo (J., 1928, 2629), was hydrolysed by treatment with five times its volume of fuming hydrochloric acid. After four days at room temperature the mixture (with deposited ammonium chloride) was evaporated on the water-bath to one-third of the original bulk and allowed to cool, the voluminous deposit of ammonium chloride being then filtered off. The filtrate was extracted with ether for 20 hours in a continuous-extraction apparatus, and the extract dried over sodium sulphate. On removal of ether, a mass of white crystals remained, m. p. 77—78°, which was purified either by sublimation or by recrystallisation from light petroleum. From 30 g. of cyanohydrin were obtained 23 g. of pure hydroxy*iso*butyric acid, m. p. 79° (62% yield).

The pure hydroxy-acid (25 g.) was methylated with methyl iodide (205 g.) and dry silver oxide (167 g.), a mercury-sealed mechanical stirrer and a reflux condenser being used. The mixture was cooled in ice, and the oxide added in small portions during 6 hours. Stirring was continued for 3 hours with the addition of a further 10 c.c. of methyl iodide, and the product then kept at room temperature for 3 days. The mixture was thoroughly shaken with ether, filtered, and the filtrate dried over calcium chloride. On removal of ether, methyl methoxy*iso*butyrate was obtained as a clear sweet-smelling liquid, b. p. 134—137° (corr.)/755 mm. Yield 22 g., 70% of the theoretical.

l-*Menthyl* α-*methoxy*iso*butyrate* could not be prepared from the free acid by way of the acid chloride, owing to the excessive darkening and decomposition which ensued on treatment with thionyl chloride. It was therefore obtained (see previous esters) from the above methyl ester (8 g.) and menthol in the presence of a small amount of sodium menthoxide. The crude ester (8 g.) so obtained boiled between 118° and 128°/10 mm., and after fractionation at 124—126°/10 mm. The rotatory power was not altered by further treatment (Found : C, 70·2; H, 11·2. $C_{15}H_{28}O_3$ requires C, 70·3; H, 11·0%).

l-*Menthyl* α-*methoxy*-α-*ethylbutyrate* was prepared from the ester of α-hydroxy-α-ethylbutyric acid, which is readily obtained by the interaction of ethyl oxalate (1 mol.) and magnesium ethyl bromide (2 mols.), as described by Hepworth (J., 1919, **115**, 1203). The ethyl ester was hydrolysed to give α-hydroxy-α-ethylbutyric acid, and the latter was then recrystallised from light petroleum and methylated as indicated above under the methoxy*iso*butyric ester. The hydroxy-acid (20 g.) gave methyl α-methoxy-α-ethylbutyrate (7 g.), b. p. 165—168°, $n_D^{18°} = 1·4194$. In order to ascertain whether methylation was complete, this product was again treated with methyl iodide and silver oxide, after which $n_D^{18°}$ was unchanged at 1·4193.

The methyl ester was converted into the menthyl derivative by the sodium menthoxide method, giving a 20% yield. *l*-Menthyl α-methoxy-α-ethylbutyrate, b. p. 139—141°/8 mm., was obtained as a clear liquid, $\alpha_{5461}^{18°}$ — 76·23° (in the homogeneous state, l = 100 mm.). A second fractionation raised this rotation to —76·58°, after which further treatment produced no change. Only a small amount of this ester was obtained (Found: C, 71·6; H, 11·5. $C_{17}H_{32}O_3$ requires C, 71·8; H, 11·4%).

Observed Rotatory Powers.

On plotting the reciprocals of the rotations of the following esters against the squares of the wave-lengths of light employed, a straight line is obtained within the limits of experimental error. The dispersion in every case may therefore be assumed to be normal and simple over the region investigated. Values for λ_{5461} will be found on p. 2321. Rotations for the sodium salts were measured by using acid solutions of the concentrations indicated in the presence of an equivalent of sodium ethoxide.

Solvent.	*c.*	*l.*	*t.*	$[M]_{6708}$.	$[M]_{5893}$.	$[M]_{4358}$.
l-*Menthyl dimethylmalonate.*						
Homog.	($d_{4^\circ}^{14\cdot5^\circ}$ 0·9712)	100	14·5°	−177·5°	−230·9°	−438·7°
Alcohol	5·462	200	15	211	273	527
Benzene	5·012	100	20	194	246	473
l-*Menthyl hydrogen dimethylmalonate.*						
Homog.	($d_{4^\circ}^{17\cdot5^\circ}$ 1·029)	25	17·5	131	172	342
Alcohol	5·094	100	18	133	173	338
Benzene	4·980	100	18	135	168	333
(Na salt in alcohol)	4·671	100	17	117	139	266
l-*Menthyl diethylmalonate.*						
Homog.	($d_{4^\circ}^{20^\circ}$ 0·9705)	100	20	181·0	236·2	452·3
Alcohol	4·944	100	19	202	266	516
Benzene	5·000	100	19	170	222	410
l-*Menthyl hydrogen diethylmalonate* * ($d_{4^\circ}^{20^\circ}$ 1·013).						
Benzene	4·940	100	19	138	181	355
Alcohol	5·072	100	20	141	182	352
(Na salt in alcohol) ...	4·534	100	20	103	141	272
l-*Menthyl malonate.*						
Benzene	5·000	100	20	—	278	—
l-*Menthyl hydrogen malonate.*						
Benzene	5·005	200	20	—	159	—
Alcohol	5·022	100	20	—	164	—
(Na salt in alcohol) ...	3·670	100	20	—	156	—
l-*Menthyl* α-*methoxy*iso*butyrate.*						
Homog.	($d_{4^\circ}^{20^\circ}$ 0·9466)	100	20	127·9	168·1	328·2
Benzene	5·017	200	17	123	163	312
Alcohol	5·004	200	17	141	182	353
l-*Menthyl* α-*methoxy*-α-*ethylbutyrate.*†						
Benzene	4·892	100	18	134	171	336

* Owing to the yellow colour, this ester could only be examined in the homogeneous state for λ_{5461}.

† The small yield of this ester only sufficed for the determination of $[M]_{5461}$ in the homogeneous state, observed during the process of purification, and the above rotations in benzene solution.

The additional rotatory powers of menthyl malonate, menthyl hydrogen malonate, and menthyl methoxyacetate in benzene and alcoholic solutions were only measured for λ_{5461} and are given in the table on p. 2321.

Summary.

The influence of *gem*-dialkyl groups, CR_2, on the rotatory power of *l*-menthyl esters of the type $X{\cdot}CR_2{\cdot}CO_2C_{10}H_{19}$ has been examined. The increasing proximity of X and $CO_2C_{10}H_{19}$ resulting from the changes $CH_2 \longrightarrow CMe_2 \longrightarrow CEt_2$ leads to a marked fall in the rotations of the menthyl malonates ($X = CO_2C_{10}H_{19}$), to a rise in the values of the hydrogen malonates ($X = CO_2H$), and to a fall in those of the corresponding sodium salts ($X = CO_2Na$). The depression following the conversion of the acids into their sodium salts increases continuously in magnitude from the malonate to the diethylmalonate. These observations are in agreement with the known influence of the substituents X in the para- and ortho-substituted benzoic esters, on the assumption that the characteristic ortho-effects are related to the proximity of X to the ester grouping.

The methoxy-esters ($X = OMe$) exhibit a continuous rise from the methylene to the *gem*-diethyl compound, and thus present no parallel to the characteristic depression occasioned by the methoxyl group in *l*-menthyl *o*-methoxybenzoate.

UNIVERSITY OF EDINBURGH.

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