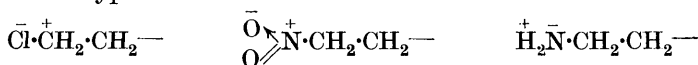


CCXLV.—*Optical Activity and the Polarity of Substituent Groups. Part XIV. Influence of Substituent Poles and Dipoles on the Rotatory Power of l-Menthyl Acetate.*

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IN an earlier communication (Rule and J. Smith, J., 1925, **127**, 2188) it was shown that the rotatory powers of the *l*-menthyl esters of a number of mono-substituted acetic acids vary with the electro-negative nature of the substituent, as determined by its influence on the dissociation constant of acetic acid: the greater the dissociation constant of the acid, the higher is the rotatory power of the ester. An attempt to relate the optical changes to the dipole character of the substituent groups was only partly successful owing to the lack of data, but with the recent development of the theory of dipoles it is now possible to discuss this problem from the more fundamental aspect of the electrical changes induced in that part of the molecule containing the substituent.

Measurements of the dipole moments of compounds, carried out chiefly by Smyth, Williams, Højendahl, and Errera, have established the fact that electronegative substituents such as NO₂, CO₂H, Cl, and OMe, represent dipoles oriented in the opposite sense to those of electropositive substituents such as Me, NH₂, and NMe₂. The experimental results indicate that the dipole may be regarded as being in the main located in the neighbourhood of the substituent itself or of the point at which it is attached to the adjacent carbon chain. Although no absolute method has yet been discovered for determining the orientation of a given type of dipole with respect to the parent molecule, it is tacitly assumed (compare Smyth, *J. Amer. Chem. Soc.*, 1929, **51**, 2380) that an electronegative substituent is responsible for a dipole oriented with its positive end towards the parent hydrocarbon chain, and an electropositive group for a dipole of inverse type:

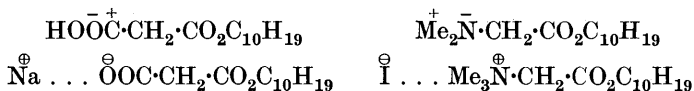


This is in agreement with the generally accepted hypothesis that electronegative substituents have the property of attracting the valency pairs of electrons in the chain of atoms towards themselves, and that electropositive substituents exert a corresponding electron repulsion. The direction of the resulting electron shift has frequently been employed to explain the influence of a substituent on properties such as ionisation, chemical reactivity, and tautomeric change, *e.g.*,



When a substituent group is introduced into a molecule, the ensuing change in the electrical state of the latter will depend primarily on the magnitude of the newly formed dipole and upon its sign. As is indicated in the above formulæ, an electronegative substituent may be regarded as creating a positive field, and an electropositive substituent a negative field, in that part of the molecule to which it is immediately attached. From this point of view the rotatory powers of the *l*-menthyl acetic esters previously investigated may be summarised in the statement that the stronger the positive field exerted at the asymmetric atom by the substituent, the greater is the increase in negative rotatory power. Hence it may be deduced that a negative field will lead to a diminished rotation.

Similar considerations may be applied to the alteration in electrical state brought about when a substituent assumes a positive or negative charge on ionisation. Among derivatives of *l*-menthyl acetate, the ionisation of a substituent carboxyl group will lead to a superimposed negative field, which will tend to reverse the original field due to the substituent. As an increasing positive field leads on the above line of reasoning to an increasing negative rotation, it would be anticipated that the sodium salt of *l*-menthyl hydrogen malonate would have a lower rotatory power than the free carboxylic acid when both are examined under the same conditions. The rotation of the dimethylamino-acetate, on the other hand, would be expected to be low compared with that of the unsubstituted ester but should tend to rise on conversion into the hydrochloride or methiodide, owing to the proximity of the positive charge on the nitrogen atom.



In order to test these conclusions, the previous investigation on *l*-menthyl esters of substituted acetic acids has now been extended to include the *dimethylamino*- and *diethylamino*-acetic esters together

with their hydrochlorides and methiodides, *l*-menthyl hydrogen malonate and its sodium salt, and sodium menthyl sulphoacetate. The manner in which the rotatory power alters with the changing sign and magnitude of the dipole is illustrated in Table I. Values (*e.s.u.*) of the dipole moments, μ , characteristic of the substituent groups are quoted from Williams (*J. Amer. Chem. Soc.*, 1928, **50**, 2350), and in order to emphasise the fundamental nature of the dipole effect, other columns have been added showing its influence upon the dissociation constant (K_a) of the acid and upon the velocity of chemical reaction. Under the last heading are given figures recorded by Tasman (*Rec. trav. chim.*, 1927, **46**, 653) for the speed with which the phthalide ring in 5-substituted phthalides is opened by alkalis: similar velocity data are available for numerous reactions, but in few other cases have amino-groups been included among the substituents.

TABLE I.

Homogeneous l-menthyl esters of monosubstituted acetic acids,
 $X \cdot CH_2 \cdot CO_2H$.

X.	$\mu \times 10^{18}$.	$K_a \times 10^5$.	$[M]_D^{20^\circ}$.	Phthalide opening.
NEt ₂	—	} Small	—154·6°	—
NMe ₂	+1·4		156·9	0·31 (NH ₂)
H	—	1·8	157·3	1·00
CH ₃	+0·4	1·4	160·2	—
CO ₂ H	—0·9	160	160·2	—
OC ₂ H ₅	—	23	160·6	—
OCH ₃	—1·2	33	165	—
OH	—1·7	15	165 (at 94°)	—
Br	—1·5	138	169	1·53
Cl	—1·5	155	171	1·32
CN	—3·8	370	174	5·71

Many of these rotatory powers have already been discussed in a previous communication (Rule and J. Smith, *loc. cit.*). For *l*-menthyl propylaminoacetate, Frankland and O'Sullivan (*J.*, 1911, **99**, 2332) find $[M]_D^{20^\circ} = -158·3^\circ$.

Although the range of rotatory powers recorded above is relatively small and the values have been found in some cases to undergo minor fluctuations with temperature, it is evident that a close correspondence exists between the magnitude and sign of the dipole moment of the substituent group and its influence on the rotatory power. The expected lowering of the rotatory power by the electropositive basic groups is confirmed.

In Table II will be found the rotatory powers $[M]_{5461}^{20^\circ}$ in alcoholic solution of amino- and carboxy-esters, both in the free state and in the form of salts. The rotation of *sodium l-menthyl sulphoacetate* is also included, the solvent in this case being water as the salt is almost insoluble in alcohol. Values of rotatory powers are given

for the wave-length λ_{5461} , as being more accurately measured than those for the D line.

TABLE II.

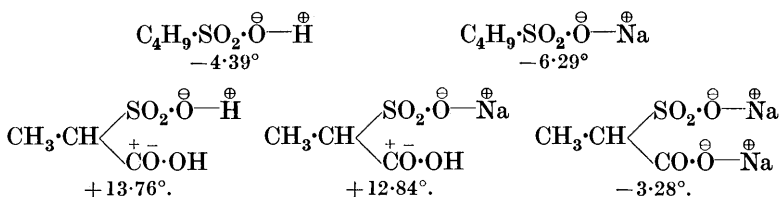
Values of $[M]_{5461}^{20}$ for *l*-menthyl esters, $X \cdot CH_2 \cdot CO_2 C_{10}H_{19}$ in alcohol.

X.	c.	$[M]_{5461}^{20}$.	X.	c.	$[M]_{5461}^{20}$.
NMe ₂	5	-201°	CO ₂ H*	5	-193°
NMe ₂ .HCl.....	5	207	CO ₂ Na*	5	-185
NMe ₃ I	2	208	(CO ₂ Na†	5, in H ₂ O	-195)
NEt ₂	5	203	(SO ₃ Na	3, in H ₂ O	-210)
NEt ₂ .HCl	5	208			
NEt ₂ .MeI	4	208			

* Unpublished values determined by J. Harrower.

† Rule, Hay, and Paul, J., 1928, 1348.

From this table it will be seen that the negative field due to the ionisation of the carboxyl group leads to a definite lowering of the rotatory power.* The ionisation of the basic groups in the form of their hydrochlorides or methiodides results, on the other hand, in a small rise in rotation. These changes are in the direction anticipated from the previously established influence of electronegative dipoles on the rotatory power of *l*-menthyl acetate, although, owing to the distance separating the ionic charges from the asymmetric atom, the observed effects are small. Unfortunately, not only was the free sulphonic derivative found to be too unstable for preparation in the optically pure state, but the sodium salt is too sparingly soluble in alcohol for its rotation to be determined in this solvent. In aqueous solution the sodium sulphonate has a somewhat high rotation, as compared with, *e.g.*, sodium menthyl malonate (see table). On theoretical grounds, however, it is improbable that the free sulphonic acid has a rotation differing in any marked degree from the sodium salt, since the sulphonic acid, unlike the carboxyl derivative, is already highly ionised in aqueous solution. Confirmation of this point may be obtained from the following figures recorded by Levene and Mikeska (*J. Biol. Chem.*, 1924, **59**, 45; *Chem. Reviews*, 1925, **2**, 205) for sulphobutane and sulphopropionic acid :

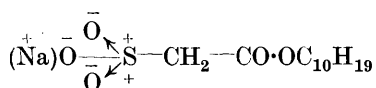


It is interesting to note that although the conversion of the sulphonic acids into the sodium salts produces little change in the

* A much greater decrease has been observed in the case of dialkylmalonic derivatives (Part XVI, Rule and Harrower, to be published shortly).

rotation, the ionisation of the carboxyl group in sulphopropionic acids leads to a depression which brings about a change of sign. In the latter case, salt formation corresponds to the creation of a new negative pole, thus exerting an electrical influence at the asymmetric atom which is the reverse of that due to the original carboxyl dipole(s).

The relatively high rotatory power of sodium menthyl sulphoacetate may be due in part to the powerfully electronegative character of the sulphonic group, which contains two semipolar double bonds arranged with their positive poles directed towards the menthyl radical. The optical behaviour of the sulphonic group in these esters is apparently in accordance with investigations on the



orienting power of this group in benzene substitution as carried out by Robinson (J., 1927, 2785), who concludes that, despite the free negative charge on the ion, the sulphonic group still retains a higher electron affinity than the hydrogen atom which it has replaced.

In the foregoing discussion it has been assumed that the modification in rotatory power due to the introduction of a substituent is related to the alteration in the electrical field at the asymmetric centre, or, more precisely, to the resulting displacements of the valency electrons in the neighbourhood of the asymmetric atom. This interpretation is employed as a simple means of correlating the dipole character of the substituent with the alteration in rotatory power rather than as suggesting a physical cause of optical rotation. The extensive investigations on the application of the Drude equation carried out by Lowry and others (see also Pickard and Hunter, J., 1923, **123**, 434) indicate a very definite relationship between the optical activity and the absorption bands of a compound, a connexion which is also a feature of certain recent theories of optical activity (compare Kuhn, *Trans. Faraday Soc.*, 1930, in the press). Attempts have been made by Dadiou (*Z. Elektrochem.*, 1929, **35**, 288) and Scheibe (*Ber.*, 1926, **59**, 2617) to establish a general agreement between the polar character of substituent groups and their effect on the absorption spectra of compounds, and researches on these lines may eventually show that the nature and position of absorption bands are intimately dependent on the dipoles present in the molecule. In any case, the changes in the rotatory powers of the menthyl derivatives under discussion support the more general hypothesis developed in these communications, that the molecular rotation is a function of the signs, magnitudes, and relative positions of the poles and dipoles present in the molecule.

E X P E R I M E N T A L.

l-Menthyl diethylaminoacetate was prepared from optically pure *l*-menthyl chloroacetate and diethylamine (Einhorn and Jahn, *Arch. Pharm.*, 1902, **240**, 646). It was isolated as a colourless liquid which boiled over a very narrow range, 142.5—143°/9 mm., and had a slight fishy odour (Einhorn and Jahn record b. p. 160—162°/20 mm.). After a second fractionation, the rotatory power, $\alpha_{5461}^{20^\circ} - 62.79^\circ$ ($l = 1$), was unchanged by further treatment. In view of the tendency of the ester to acquire a yellow tint in air, it was examined at once for the rotatory power (α) in the homogeneous state, (b) in alcoholic solution, and (c) in alcohol containing 1 mol. of hydrogen chloride. It was then precipitated from dry ether as the hydrochloride, and the colourless salt dried in air over calcium chloride, m. p. 127° (Einhorn and Jahn, 108°).

Some of the diethylamino-ester was converted into the methiodide by heating it for a short time with methyl iodide, and the salt was recrystallised from ethyl acetate until of constant rotatory power; m. p. 161—162° (Einhorn and Jahn, m. p. 157°).

l-Menthyl dimethylaminoacetate was similarly prepared from menthyl chloroacetate (37 g.) and dimethylamine (25 g.), the reaction being allowed to proceed in a tightly stoppered bottle for $2\frac{1}{2}$ days at 2°. The mixture was poured into an excess of dilute hydrochloric acid, and any unchanged chloro-ester extracted with ether. Alkali was added to the aqueous solution, the basic ester extracted with ether, and dried over anhydrous potassium carbonate. The *hydrochloride* of the ester was then precipitated from the dry ethereal extract by means of hydrogen chloride. The salt was finally recrystallised rapidly from acetone containing a little hydrogen chloride; yield 24 g., m. p. 169° (Found: Cl, 12.8. $C_{14}H_{28}O_2NCl$ requires Cl, 12.7%). The hydrochloride is readily soluble in water, alcohol, ethyl acetate, and acetone.

The greater part of the purified salt was dissolved in water at 0°, treated with alkali, and the oily ester extracted with ether. *l*-Menthyl dimethylaminoacetate, b. p. 132°/9 mm., was obtained as a colourless and almost odourless liquid. The rotatory power, $\alpha_{5461}^{20^\circ} - 71.96^\circ$ ($l = 1$), remained unchanged on repeated fractionation (Found: N, 5.85. $C_{14}H_{27}O_2N$ requires N, 5.8%). The *methiodide* of the ester, prepared by boiling equal weights of the constituents for 1 hour, was recrystallised from ethyl acetate, in which it is only sparingly soluble, even at the boiling point; it melts above 250° (Found: I, 33.4. $C_{15}H_{30}O_2NI$ requires I, 33.2%).

Sodium l-menthyl sulphoacetate was readily formed by heating optically pure *l*-menthyl chloroacetate (25 g.) with crystalline sodium sulphite (25 g.) in aqueous-alcoholic solution. After being boiled

gently for 5 hours, the mixture was poured into 500 c.c. of water, and unchanged chloro-ester removed by extraction with ether. The aqueous liquid on concentration gave a practically quantitative yield of sodium *l*-menthyl sulphoacetate. Prolonged boiling in aqueous solution leads to decomposition with formation of menthol. After being twice recrystallised from water, the salt was obtained as a white odourless mass of fibrous needles. It was very readily hydrolysed with warm aqueous alkali. The sulphonate is only sparingly soluble in water and is almost insoluble in alcohol. It contains 2 mols. of water of crystallisation (Found: loss at 100° with subsequent standing in a vacuum over sulphuric acid, 10.67; Na, 6.88. $C_{12}H_{21}O_5SNa \cdot 2H_2O$ requires loss, 10.71; Na, 6.85%). This water is rapidly reabsorbed in air, and the salt cannot be accurately weighed in an open vessel.

Attempts were made to obtain the free sulphonic acid, both by precipitating the lead salt and treating it with hydrogen sulphide, and also by shaking the precipitated and dried barium salt for 3–4 hours with an exact equivalent of dilute sulphuric acid. The resulting free acid was readily soluble in water and to a smaller extent in alcohol. Recrystallisation, even at low temperatures, always led to decomposition with liberation of menthol. Decomposition also occurred when the acid was dried in a vacuum desiccator, and it was therefore not further examined.

The following rotatory powers were measured in a 2-dcm. tube, except where marked by an asterisk, in which case $l = 1$. The alcohol employed was dried over sodium, and densities were determined in a pycnometer holding about 3 c.c.

When the reciprocals of the rotatory powers are plotted against λ^2 the values lie approximately on a straight line.

l-Menthyl diethylaminoacetate.

Solvent.	c.	$[M]_{16708}^{20^\circ}$.	$[M]_{5893}^{20^\circ}$.	$[M]_{5461}^{20^\circ}$.	$[M]_{4358}^{20^\circ}$.
Homog.*	($d_4^{20^\circ}$ 0.9251).	-117.4°	-154.6°	-182.7°	-301.8°
Alcohol	4.532	—	171	203	—
Hydrochloride in alcohol	4.929	133	175	208	344
Methiodide in alcohol	3.947	141	175	208	339

l-Menthyl dimethylaminoacetate.

Homog.*	($d_4^{20^\circ}$ 0.9357)	—	156.9	185.5	—
Alcohol	5.559	—	170	201	—
Hydrochloride in alcohol	5.007	134	175	207	346
Methiodide in alcohol	2.062	140	177	208	346

Sodium *l*-menthyl sulphoacetate.

Water	3.283	139	181	210	341
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l-Menthyl malonate.

Alcohol	5.022	—	164	193	—
Na salt in alcohol	3.976	—	156	185	—

Summary.

The *l*-menthyl esters of dimethylamino- and diethylamino-acetic acids and their hydrochlorides and methiodides have been examined polarimetrically; also sodium *l*-menthyl malonate and sodium *l*-menthyl sulphaacetate.

The free basic esters have relatively low rotatory powers, which rise when the compounds are converted into the hydrochlorides or methiodides. *l*-Menthyl hydrogen malonate, on the other hand, has a lower rotation in the form of its sodium salt.

The influence of substituents in general, including the above basic groups, agrees closely with the sign and magnitude of their characteristic dipoles, and the direction of the change in rotation following upon the ionisation of a basic or acidic group is in the sense predicted from a knowledge of the effect of these dipoles.

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