

CCLXII.—*Optical Activity and the Polarity of Substituent Groups. Part XX. Some Aliphatic and Aromatic Ethers of l-Menthol.*

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IN its effect upon the rotatory power of optically active compounds, the general polar influence of electropositive and electronegative substituents has been clearly demonstrated in derivatives of the type of Schiff's bases (Betti, *Trans. Faraday Soc.*, 1930, 337) and in the *l*-menthyl and β -octyl esters of aliphatic and aromatic acids (Rule, *ibid.*, p. 321). Comparatively little information is available concerning substances of other types.

The present communication deals with *l*-menthyl ethers, among which the homologous alkyl derivatives have been examined by Tschugaev (*Zentralbl.*, 1902, II, 1238) and Lander (J., 1900, 77, 731), the chloromethyl ether by Wedekind (*Ber.*, 1901, 34, 814), and menthoxyacetic acid and its propyl ester by Frankland and O'Sullivan (J., 1911, 99, 2329). The preparation of *l*-menthoxyacetic acid has now been repeated in order to determine the nature of the dispersion and the optical properties of the *methyl* and the *menthyl* ester, and of the sodium salt and *amide*; the *phenyl*, *picryl*, and 2 : 4-*dinitrophenyl ethers* have also been prepared and studied.

All the aliphatic ethers examined in the present investigation proved to have normal and simple dispersion over the range of wave-length employed. From a survey of the molecular rotations of the derivatives, $C_{10}H_{19}O \cdot CH_2X$ (Table I), it will be seen that the influence of the substituent X on the optical activity is similar to that observed among the acetic esters: the more electronegative the substituent, the higher is the negative rotation. Owing to the lack of necessary data, the polar changes in this case are not readily determined by reference to the dipole moments characteristic of the substituent groups, but some idea of the variations may be gained by making use of the dissociation constants, *K*, of the corresponding substituted acetic acids, $X \cdot CH_2 \cdot CO_2H$.

TABLE I.

Rotations, $[M]_D^{20}$, of the Homogeneous l-Menthyl Ethers,
 $C_{10}H_{19} \cdot O \cdot CH_2X$.

X =	H	CH ₃	Et	Allyl	CONH ₂	CO ₂ H	CO ₂ Me	CO ₂ Pr †	Cl †
$[M]_D$	-163°	-179°	-183°	-193°	-194°*	-218°	-233°	-234°	-353°
$K \times 10^5$	1.8	1.4	1.5	2.1	—	161	45.1 §	45.1 §	155

* In benzene, $c = 5$. † Wedekind, *loc. cit.* ‡ Frankland and O'Sullivan, *loc. cit.* § These figures refer to CO₂Et (ethyl hydrogen malonate) as no values have been recorded for the acids in question.

On this basis of comparison, the rotatory power of the methyl ether ($X = H$) occupies a slightly lower position than would be anticipated, and menthoxyacetic acid has suffered a considerable displacement in the same sense. There are, however, good grounds for believing that in the latter case the dissociation constant gives an untrustworthy estimate of the polarity. The observed rotatory power is in very good agreement with the relatively low rotation of menthyl hydrogen malonate (Rule, Thompson, and Robertson, J., 1930, 1887) and with the low dipole moments ($0.6\text{--}1.4 \times 10^{-18}$) which have been recorded for simple carboxylic acids.

As the normal influence of the carboxyl group is to increase the rotatory power, it is to be expected that ionisation of the acid will tend to produce the reverse effect. This change may be followed by converting the acid into the sodium salt and also by the addition of dry hydrogen halide to the free acid, which represses the degree of ionisation. The molecular rotations, $[M]_{5461}^{20^\circ}$, for the menthoxy-acid, its salt, amide, and methyl ester under various conditions are summarised in Table II.

TABLE II.

Values of $[M]_{5461}^{20^\circ}$ for the Ethers, $C_{10}H_{19}O \cdot CH_2X$.

Solvent.	<i>c.</i>	CO_2H .	CO_2Me .	$CONH_2$.	H.	CO_2Na .
(Homog.)	—	—258°	—276°	—	—192°	—
C_6H_6	5	—239	—255	—230°	—195	—
EtOH	5	—231	—259	—243.5	—199*	—180°
EtOH + 4HCl	5	—241	—	—245	—	—

* In MeOH.

Among menthoxyacetic derivatives, the relative polar influences of the various substituents may be expressed by $CO_2H > CO_2Me > CONH_2 > H > CO_2O^-$, this sequence representing a continuous change from strongly electron-attracting groups to one of electron-repelling type. On the whole, the rotatory powers are also in this order, the chief displacements being those of the free acid in benzene and in alcoholic solution. The low values in the latter cases appear to be due in part to partial ionisation; the rotation in alcohol (unlike those of the ester, amide, or menthyl methyl ether) is lower than in benzene, and rises considerably in the presence of dry hydrogen chloride, which may be expected to repress ionisation.

In agreement with the theoretical sequence given above, it is found that the ionised acid in the form of its sodium salt has a definitely lower rotation than menthyl methyl ether.

As was to be anticipated, the *fall* on converting the acid into its sodium salt, $\Delta = 51^\circ$ (for alcoholic solutions), is much greater in this case than was previously observed for *l*-menthyl hydrogen

malonate, $C_{10}H_{19}O \cdot CO \cdot CH_2 \cdot CO_2H$, and its salt, for which under similar conditions, $\Delta = 8^\circ$ (Rule and Harrower, J., 1930, 2319). In the latter compound the carboxyl group is one remove further away from the active complex, and its characteristic influence is consequently diminished.

The rotatory power of the amide was also measured in the presence of hydrogen chloride, since any appreciable combination with the amino-group should become evident in a small rise in rotation (compare J., 1930, 1887). The observed increase of 1.5° , although confirmed by repetition, is of the order of the experimental error involved in the determination ($\alpha_{5461} - 5.09^\circ$, $l = 1$, $c = 5$).

l-Menthyl menthoxyacetate gave the following values for $[M]_{5461}^{20}$: in ethyl alcohol ($c = 5$), -474.2° ; in benzene ($c = 5$), -468.1° .

In spite of numerous attempts, it was not possible to prepare any of the mononitrophenyl ethers, owing to preferential formation of coloured by-products from which the ether could not be separated. The molecular rotations of the benzyl, phenyl, 2:4-dinitrophenyl, and picryl ethers are given in Table III.

TABLE III.

Values of $[M]_D^{20}$ for *l*-Menthyl Ethers, $C_{10}H_{19}O \cdot X$ (in C_6H_6 , $c = 5$).

X	$C_6H_5 \cdot CH_2$	C_6H_5	$C_6H_3(NO_2)_2$	$C_6H_2(NO_2)_3$
$[M]_D$	$-233^* $	-301°	-149°	-1082°

* In homogeneous state (Tschugaev, *loc. cit.*).

For the picryl and phenyl ethers, the dispersion appeared to be normal and simple, but the 2:4-dinitrophenyl ether exhibited strongly anomalous dispersion both in benzene and in alcoholic solution. In these circumstances no definite conclusions can be drawn from the rotatory power of the dinitro-compound. The molecular rotation of the benzyl ether is already comparatively high, and this value is considerably increased when the phenyl group is brought nearer to the menthyl radical, as in the phenyl ether. A remarkable change occurs on passing to the picryl ether, in which the powerfully electronegative picryl complex raises the rotation to $[M]_D - 1082^\circ$. The optical influence of the picryl group has also been observed by Peacock (P., 1914, 30, 275) in the case of cinchonine (cinchotoxine), $[M]_D + 165^\circ$, and of picrylcinchonicine, $[M]_D - 1968^\circ$ (both in acetone, $c = 5$).

It may therefore be concluded that the polar influences of substituents in *l*-menthyl ethers resemble those previously established in the esters, electronegative groups causing an increased negative rotation, and electropositive ones a diminished value. In both

series the ionisation of a carboxyl group results in a decreased rotation.

Solvent Influence.—Rotatory powers of the ethers were also determined in a large number of solvents. The regularities observed in the case of *l*-menthyl methyl naphthalate (Rule and McLean, this vol., p. 674) were repeated in values obtained for *l*-menthyl picryl ether, the high rotation of which is at a maximum in non-polar solvents ($[M]_{5461} - 1597^\circ$ in carbon disulphide) and at a minimum in highly polar media (-1075° in acetonitrile). A similar tendency was noted for the phenyl ether, but only small and irregular variations were obtained with the methyl ether.

The 2:4-dinitrophenyl ether, which exhibits anomalous dispersion and abnormally low rotatory power, was influenced by solvents in the reverse sense. For this compound the highest rotations were observed in highly polar solvents ($[M]_{5461} - 301^\circ$ in acetonitrile) and the lowest in those of non-polar type (-159° in carbon disulphide).

The experimental data and detailed discussion relating to solvent influence are withheld for a later communication, which will deal also with a number of other *l*-menthyl derivatives.

EXPERIMENTAL.

l-Menthoxycetic acid was prepared by the method of Frankland and O'Sullivan (*loc. cit.*) from chloroacetic acid (25 g.), sodium (20 g.), and menthol (100 g.). Instead of purifying the crude syrupy menthoxy-acid by repeated (6-fold) recrystallisation, it was found much more economical to distil it under diminished pressure. In this way a first fractionation gave an acid of $[M]_D - 195.8^\circ$ (in methyl alcohol, $c = 5$), which was obtained optically pure (-198.8°) on repeating the process; b. p. $163-164^\circ/10$ mm., yield 44 g. The alcoholic solution of the sodium salt required for polarimetric measurements was prepared by adding an equivalent of sodium ethoxide to a solution of the acid in alcohol.

Methyl l-menthoxyacetate was obtained from the acid (20 g.) by converting it into the acid chloride (22 g.) and treating this with methyl alcohol. The methyl ester, b. p. $131^\circ/8$ mm., was fractionated until of constant rotation in the homogeneous state (yield 30%) (Found: C, 68.3; H, 10.6. $C_{13}H_{24}O_3$ requires C, 68.4; H, 10.5%).

A portion of the acid chloride in dry benzene was treated with dry ammonia gas to give *l-menthoxyacetamide*, which was recrystallised from light petroleum (b. p. $60-80^\circ$) until of constant rotation. It forms white needles, m. p. 93° , dissolving readily in alcohol, ether,

acetone, and carbon tetrachloride. It is less soluble in light petroleum or benzene, and practically insoluble in water [Found : N, 6.50 (ter Meulen). $C_{12}H_{23}O_2N$ requires N, 6.57%].

l-Menthyl *l*-menthoxyacetate was obtained in 70% yield from the acid chloride and *l*-menthol. It is sparingly soluble in methyl alcohol, from which it separates in colourless prisms (Found : C, 75.0; H, 11.4. $C_{22}H_{40}O_3$ requires C, 75.0; H, 11.4%).

In the preparation of *l*-menthyl picryl ether, hot toluene solutions of picryl chloride (1 mol.) and potassium menthoxide (2 mols.) were mixed. A considerable evolution of heat occurred, and after being cooled, the mixture was filtered and the solid product washed thoroughly with benzene. The resulting dark red complex of *l*-menthyl picryl ether and potassium menthoxide (compare Jackson and Boos, *Amer. Chem. J.*, 1898, **20**, 449) was dried and decomposed by careful trituration with dilute hydrochloric acid and ether, whereupon the colour changed to orange. After the ethereal solution was dried and the solvent removed, the picryl ether was obtained as a yellow solid. After preliminary solution in hot benzene and precipitation with light petroleum, the compound was purified by several recrystallisations from the latter solvent, giving pale yellow needles, m. p. 133° (violent decomp. at 150°). The ether is moderately soluble in light petroleum or alcohol, and readily soluble in acetone, benzene, or chloroform. From benzene or acetone, it separates as yellow plates (Found : N, 11.2. $C_{16}H_{21}O_7N_3$ requires N, 11.4%).

Light appears to effect decomposition of the picryl ether, leading to the formation of a dark brown substance. A small amount of the latter is also a normal by-product when the ether is recrystallised under ordinary conditions; it is soluble in alcohol and acetone, but insoluble in benzene or light petroleum. Unfortunately, the solutions in acetone or alcohol possessed such an intensely red colour that it was not possible to examine them polarimetrically. Probably they were inactive, for a thin layer of the powdered ether, when placed between glass plates and exposed to sunlight, rapidly turned brown and viscous; at the same time a strong odour of menthone became apparent. On account of the difficulty of preparing reasonably large quantities of the ether, this decomposition was not further investigated.

l-Menthyl 2 : 4-dinitrophenyl ether was prepared from chlorodinitrobenzene (20 g.) and a cold benzene solution of potassium menthoxide (2 mols.). A brownish precipitate of potassium chloride was deposited, and the pale yellow mother-liquors were then removed and concentrated. On extraction with cold light petroleum, the

crystalline product gave the required ether (8 g.) as pale yellow fibrous crystals, m. p. 88° (Found: N, 8.65. $C_{16}H_{22}O_5N_2$ requires N, 7.0%). This ether resembles the picryl compound in turning brown on exposure to light. It dissolves readily in benzene and acetone, but is only sparingly soluble in alcohol.

l-Menthyl Phenyl Ether.—Potassium (7.8 g.) was dissolved in menthol (100 g.) at 100°, and iodobenzene (40 g.) added. The mixture was maintained at 100° for 18 hours, and subsequently raised to 180° until no further deposition of potassium iodide occurred. The product was then filtered and distilled in a vacuum. After a preliminary fractionation, a second distillation gave the *phenyl ether*, b. p. 144°/12 mm., which solidified on cooling (yield 5 g.). It was recrystallised from alcohol until optically pure, $[\alpha]_{5461} - 154^\circ$ (in benzene, $c = 5$). It forms colourless needles, m. p. 49.5°, dissolves freely in benzene, ether, and acetone, and is less soluble in alcohol and light petroleum (Found: C, 82.7; H, 10.4. $C_{10}H_{24}O$ requires C, 82.8; H, 10.35%).

Preparation of Sodium and Potassium Menthoxides.—The alkali menthoxides used in the above preparations were at first obtained by Beckmann's method (*J. pr. Chem.*, 1897, 55, 16), in which equivalent proportions of sodium and *l*-menthol are heated at a temperature not exceeding 200° in an atmosphere of pure dry hydrogen. About 3 hours' heating is necessary before the bulk of the metal passes into solution as menthoxide.

By working in the following manner, the reaction may be completed in about half the time, and at a temperature of 150° or lower. Menthol (4 or 5 mols.) is placed in a distilling flask, the side tube of which is stoppered, and the neck fitted to a long air-condenser; the flask is heated to 150° in an oil-bath, and the metal (1 mol.) added in small pieces through the condenser. In this way 8 g. of potassium may be dissolved in about 35 minutes. The excess of menthol is then distilled off in the usual way under diminished pressure and in a current of hydrogen. After 45 minutes, with the oil-bath at 150—160°, the contents of the flask suddenly solidify. Subsequent weighing of the distilled menthol shows that little free menthol remains in the flask. This process not only saves time, but diminishes the risk of chemical change.

Measurements of Rotatory Power.

The following determinations were made at 20° in a 1-dcm. tube. In a few cases (marked with an asterisk) a 2-dcm. tube was employed. Values for $[M]_D$ and $[M]_{5461}$ will be found in Tables I, II, and III. Figures in parentheses are somewhat uncertain owing to the absorption of light.

l-Menthoxycetic acid (d_4^{20} 1.033).

Solvent.	<i>c.</i>	α_{6708}	α_{5893}	α_{5780}	α_{5461}	α_{4355}
Homog.	—	-79.72°	-105.3°	-109.8°	-124.5°	-207.3°
EtOH	5.165	-3.67	-4.70	-4.93	-5.57	-9.28
MeOH*	5.285	-7.36	-9.81	-10.16	-11.49	-19.10
C ₆ H ₆ *	5.135	-7.40	-9.66	-10.14	-11.45	-18.91
EtOH + 4HCl	5.335	—	—	—	-6.01	—
EtOH + EtONa	5.220	—	—	—	-4.40	—

l-Menthoxycetamide.

EtOH	4.45	-3.42	-4.25	-4.49	-5.09	(-8.03)
C ₆ H ₆	3.73	-2.64	-3.39	-3.53	-4.02	(-6.59)

Methyl *l*-menthoxyacetate (d_4^{20} 0.9804).

EtOH	5.115	-3.69	-4.83	-5.14	-5.81	-9.64
C ₆ H ₆	5.020	-3.67	-4.72	-4.99	-5.62	-9.28
Homog.	—	-76.25	-100.0	-104.5	-118.5	-197.1

l-Menthyl *l*-menthoxyacetate.

EtOH*	5.000	-8.79	-11.46	-11.89	-13.47	-22.42
C ₆ H ₆ *	5.000	-8.48	-11.29	-11.74	-13.30	-22.01

l-Menthyl phenyl ether.

C ₆ H ₆	5.000	-5.00	-6.49	-6.80	-7.69	-12.38
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l-Menthyl 2 : 4-dinitrophenyl ether.

C ₆ H ₆	5.000	-1.88	-2.31	-2.35	-2.41	+1.08
EtOH*	2.340	-2.68	-3.29	-3.36	-3.68	-2.69
COMe ₂	5.00	-3.14	-3.72	-3.89	-4.21	-3.70

l-Menthyl picryl ether.

C ₆ H ₆	4.400	-9.00	-12.98	-13.90	-16.68	—
COMe ₂	2.340	-5.89	-8.44	-8.92	-10.53	—

Summary.

A number of *l*-menthyl ethers have been examined, with the following results.

1. Among ethers of the type, C₁₀H₁₉O·CH₂X, the influence of X upon the rotatory power is given by Cl > CO₂Pr > CO₂Me > CO₂H > CONH₂ > Allyl > Et > Me > H > COO'. This sequence is in close agreement with the polarity of the substituents, *e.g.*, as deduced from the dissociation constants of the correspondingly substituted acetic acids, or from dipole moments. The optical changes therefore resemble those previously established among the menthylacetic esters, strongly electronegative substituents producing the maximum rise in value.

2. Sodium *l*-menthoxyacetate has a rotation considerably lower than that of the unsubstituted methyl ether. When, however, the degree of ionisation of the acid in alcoholic solution is repressed by the addition of hydrogen chloride, the rotation rises. These changes are in agreement with the polar changes involved.

3. The comparatively high rotation of the phenyl ether becomes

very much greater in the picryl compound. *l*-Menthyl 2 : 4-dinitrophenyl ether has anomalous dispersion and an abnormally low rotatory power.

4. Polar solvents depress the rotatory power of the phenyl and picryl ethers, but raise that of the 2 : 4-dinitrophenyl ether.

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