LVIII.—*Optical Activity and the Polarity of Substituent Groups. Part X. Influence of Ionisable Groups on the Rotatory Power of* l-*Menthyl Benzoate.*

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THE changes in the rotatory powers of optically active acids and bases consequent upon ionisation have been discussed in Part VI of this series (J., 1927, 54), in which attention was drawn to the fact that the characteristic influence of groups such as $\cdot CO_2H$ and NH_2 is often reversed when these are present in the ionised state. A similar reversal on ionisation occurs in the directive power of the groups upon benzene substitution (compare Flürscheim, *Chem. and Ind.*, 1926, **45**, 143; Ing and Robinson, J., 1926, 1655; Goss, Ingold, and Wilson, *ibid.*, p. 2440).

Effects of this type are of special interest in connexion with the menthyl esters of *o*-substituted benzoic acids, among which *m*-directive substituents raise, and *o*, *p*-directive groups lower the molecular rotation. One example of the influence of an ionised grouping on the rotatory power of menthyl benzoate is already available. Kenyon and Pickard (J., 1915, **107**, 54, 58), in investigating the optical rotatory powers of a number of menthyl derivatives prepared by Cohen, have recorded values for the sodium and magnesium salts of menthyl hydrogen phthalate which are much lower than those for the unsubstituted benzoate. By analogy, it has been predicted (Part VI, *loc. cit.*) that the *o*-dimethylaminobenzoic ester should exhibit an enhanced rotation in acid solution.

The present communication contains an account of the menthyl esters of hydroxy-, amino-, and dimethylamino-benzoic acids. The *o*-, *m*-, and *p*-dimethylamino-derivatives were among the large number of substituted benzoic esters prepared by Cohen (J., 1914,

105, 1892), who encountered great difficulty in their purification and finally examined them in the form of viscous, strongly coloured liquids. The rotatory powers of these liquids were not changed by solution in light petroleum, followed by precipitation as the liquid hydrochloride and subsequent removal of hydrogen chloride (Cohen, *loc. cit.*). During the present investigation the main difficulty was found in obtaining a good yield of the esters, especially of the *m*- and *p*-isomerides. The *o*-compound was prepared as a coloured product of somewhat higher rotatory power than that recorded by Cohen, the value being unaltered after attempted purification by the above method. On distillation in a high vacuum, however, the mixture separated into a colourless low-melting solid (about two-thirds of the total) and a highly coloured glass. The rotatory power of the solid was nearly double that recorded by Cohen, and was confirmed on a specimen prepared by a different method (see p. 407). The glassy residue had a correspondingly low rotation. It was not found possible to obtain the *m*- and *p*-isomerides in a state of optical purity.

The influence of ionisation was determined by measuring the rotatory powers of the four basic esters (*a*) in alcohol, and (*b*) in alcohol containing an equivalent of hydrogen chloride; the three acid esters were examined (*a*) in alcohol, (*b*) in alcohol containing an equivalent of sodium or potassium ethoxide, and (*c*) in piperidine. To complete the comparison it was necessary to know the rotatory powers of menthyl benzoate and also of menthyl hydrogen phthalate and its sodium salt in 5% alcoholic solutions. This information could not be discovered in the literature, and the preparation of these esters was therefore repeated. The rotatory power of menthyl benzoate in alcohol was found to be practically unaffected by the presence of as much as four equivalents of hydrogen chloride or of sodium ethoxide (see Table I, i). Wherever possible, the rotatory powers were determined for the wave-lengths 6708, 5893, 5461, and 4358 Å.U., and at approximately 20°.

Influence of Substituents.

As with other menthyl esters of this type, the compounds described in this communication exhibit normal and complex dispersion, the graph of $1/\alpha$ plotted against λ^2 deviating appreciably from the linear. The *salicylate*, on account of its abnormally high rotation, was examined in the homogeneous state over the temperature range 20—100°; the dispersion was complex throughout and the rotation fell slightly but continuously with rise of temperature.

From the tables it is seen that the *o*-derivatives differ considerably in rotatory power from the unsubstituted ester. In these com-

TABLE I.

(i) 1-*Menthyl benzoate.*

Solvent.	*l.*	*c.*	$[M]_{5461}$.
Benzene *	2	5·032	−280·5°
Alcohol	2	5·031	275·1
,, + 4HCl	2	5·069	274·7
,, ,, (1 hr. later)			274·7
,, + 4NaOEt	2	5·001	275·8
,, ,, (30 mins. later)...			272·7

(ii) 1-*Menthyl* o-*dimethylaminobenzoate.*

Solvent.	*l.*	*c.*	$[M]_{5461}$.
Alcohol	1	4·746	−250°
,, + HCl	1	3·736	292

(iii) 1-*Menthyl aminobenzoates.*

Isomeride.	Solvent.	*l.*	*c.*	$[M]_{5461}$.
o-	Alcohol	1	5·009	−313°
	,, + HCl	1	5·001	290
m-	Alcohol	1	3·186	281
	,, + HCl	1	1·583	271
p-	Alcohol	1	5·032	257
	,, + HCl	1	3·566	262

(iv) 1-*Menthyl hydroxybenzoates.*

Isomeride.	Solvent.	*l.*	*c.*	$[M]_{5461}$.
o-	(Homogeneous, 20°) ...	1	—	−333·2°
	(,, 100°) ...	1	—	330·5
	Alcohol	2	5·163	299
	,, + NaOEt	2	4·880	267
	,, + KOEt	2	5·680	246
	Piperidine	2	5·445	286
†*m*-	Alcohol	1	7·735	266
	,, + NaOEt	1	5·608	235
	Piperidine	1	8·815	222
†*p*-	Alcohol	1	5·144	250
	,, + NaOEt	1	4·873	241
	Piperidine	1	4·216	219

(v) 1-*Menthyl hydrogen phthalate.*

Solvent.	*l.*	*c.*	$[M]_{5461}$.
Benzene	2	4·725	399·0° ‡
Alcohol	2	5·128	345·6
,, (Na salt)	1	5·382	260·5
,, (Mg salt)		(5% approx.)	212·0 §

* Kenyon and Pickard, *loc. cit.*, record −276·5°.

† These isomerides could only be isolated in the form of somewhat coloured viscous liquids, the *p*-compound being almost a glass. There is therefore some doubt as to their purity.

‡ For λ_{5893}, $[M] = -331{\cdot}9°$ (Cohen, J., 1916, **109**, 232, records $[M]_{5893} = -332{\cdot}4°$ in benzene, $c = 5$).

§ Kenyon and Pickard, *loc. cit.*

pounds the introduction of an *o*-carboxyl group results in a marked rise in rotation, which is changed to a fall when the substituent ionises to ·COO′. On the other hand, an *o*-dimethylamino-group depresses the rotatory power of the benzoate, but raises the value when present in acid solution as $\cdot\mathrm{NMe_2H}^{\cdot}$. The optical changes are therefore related to the orienting power of the groups in benzene substitution, the *m*-directive carboxyl and dimethylammonium radicals raising the rotation and the *o,p*-directive dimethylamino-group and carboxyl anion lowering the value.

Minor changes in the *o*-carboxyl group may also be brought about by esterification. Here again the relative influence is in agreement with the directive power of the group X, as becomes evident on comparing the percentages of *m*-compound formed on nitration of C_6H_5X with the values for the rotatory powers of the menthyl alkyl phthalates recorded by Cohen, Woodruffe, and Anderson (J., 1916, **109**, 222) :

X.	CO_2H.	CO_2Me.	CO_2Et.	H.	(COO′)
m-Compound, % ...	80·2	73·2	68·4	—	(*o*, *p*)
$[M]_D$	−332°	−268°	−254°	−239°	(192°)

Among the large number of menthyl and *sec.*-β-octyl esters of *o*-substituted benzoic acids now known, the salicylic and anthranilic esters under examination are the only ones in which the presence of an *o*, *p*-directive substituent is found to raise the rotatory power. The influence in these cases may therefore be an abnormal one due to the co-ordination of the carboxylic keto-group with hydrogen of the hydroxyl or amino-group (Sidgwick, J., 1920, **117**, 402; Sidgwick and Ewbank, J., 1921, **119**, 979). This possibility appears to be supported by the low boiling points of the *o*-isomerides as compared with those of the *m*- and *p*-compounds, thus :

l-Menthyl ester.	B. p.	*l*-Menthyl ester.	B. p.
Anthranilate	156°/0·3 mm.	Salicylate	156°/0·5 mm.
m-Aminobenzoate	168°/1·8 mm.	*m*-Hydroxybenzoate	182°/1·2 mm.
p-Aminobenzoate	175°/0·2 mm.	*p*-Hydroxybenzoate ...	178°/0·1 mm.

and also by the relative insolubility of the salicylic ester in hydroxylic solvents (compare Sidgwick, *loc. cit.*). Experiment showed that menthyl salicylate at room temperature required seven times its volume of absolute methyl alcohol or six times its volume of rectified spirits (96%) for complete miscibility : it is miscible in all proportions with absolute ethyl alcohol, benzene, or light petroleum.

Even on the assumption that the two *o*-substituents are present in these esters as part of a chelate ring, it would still be anticipated that the characteristic effects of the electrical charges ($^{-}O'$ and $^{-}NH_3^{\cdot}$) would make themselves evident on ionisation. This expectation is borne out by the above figures. The amino-ester in the form of its hydrochloride has a rotation of $[M]_{5461} = -290°$, comparable with that found for the hydrochloride of the dimethylamino-ester (−292°), and considerably higher than that of menthyl benzoate (−275°). On the other hand, the salicylic ester in the presence of an equivalent of sodium ethoxide exhibits a rotatory power (−267°)

which is lower than that of the benzoate. This last figure is not so low as was anticipated by comparison with the value (−260°) recorded in Table I (v) for the alcoholic solution of sodium menthyl phthalate, possibly because part of the salicylate exists under the conditions of experiment as the free chelated hydroxy-ester or as the chelate form of the sodium derivative.

Sidgwick and Brewer (J., 1925, **127**, 2381) have concluded that potassium salts of this type are less prone to form chelate derivatives than the corresponding sodium salts. For this reason the salicylic ester was next examined in the presence of an equivalent of potassium ethoxide. In this case a much lower rotation (−246°) was observed. Hence, although the parent anthranilic and salicylic esters behave abnormally, the rotations of the ionised compounds are in agreement with the regularities previously established.

The normal effect exhibited by the *o*-dimethylamino-grouping supports the conclusions of Pfeiffer, Angern, and Wang (*Z. physiol. Chem.*, 1927, **164**, 182), who find that the keto-group in diketopiperazines co-ordinates with primary and secondary amines and with the aminobenzoic acids, but not with tertiary amines or with the dimethylaminobenzoic acids.

A discussion of these results from the standpoint of the electronic theory is reserved, pending the completion of allied lines of research.

EXPERIMENTAL.

1-*Menthyl salicylate* was prepared in the usual way from the acid chloride and menthol. The rotatory power of the crude ester rose slowly on fractionation in a high vacuum, remaining constant after the third repetition. The pure ester was obtained in better yield (60%) by dissolving the crude product in warm methyl alcohol and cooling to −15°; it is a viscous, colourless, and odourless oil, b. p. 156°/0·5 mm. (Found : C, 73·9; H, 8·9. $C_{17}H_{24}O_3$ requires C, 73·9; H, 8·7%).

1-*Menthyl* m-*hydroxybenzoate*. Thionyl chloride (2 equivs.) was added in small portions at 0° to sodium *m*-hydroxybenzoate (1 equiv.; carefully dried below 50°). When the vigorous action had ceased, the excess of thionyl chloride was removed under diminished pressure. The crude acid chloride was treated with menthol (1 mol.) and pyridine, and maintained at 120° for 24 hours. Reaction appeared slow. The mixture was diluted with water, the ester extracted with ether, and dried over sodium sulphate. After removal of the solvent, any excess of menthol was distilled off in a vacuum. The *ester* distilled as a slightly coloured oil, b. p. 182°/1·2 mm. (Found : C, 73·6; H, 8·8%) (yield, 20% of theory). The rotatory power was not altered on repeated fractionation.

l-*Menthyl* p-*hydroxybenzoate*, prepared in the same way as the *m*-compound, but in poorer yield (10%), was isolated as a pale yellow oil, b. p. 178°/0·1 mm., which solidified to a transparent glass, and could not be obtained crystalline. The rotatory power was unchanged on further fractionation (Found : C, 73·5; H, 8·9%). Both the *m*- and *p*-hydroxy-esters were miscible in all proportions with methyl or ethyl alcohol and with rectified spirits.

l-Menthyl anthranilate could not be prepared directly from anthranilic acid, nor could the chloride of the acid be isolated by means of thionyl chloride (compare McMaster and Ahmann, *J. Amer. Chem. Soc.*, 1928, **50**, 146). The ester was readily obtained in almost theoretical yield by the reduction of optically pure *l*-menthyl *o*-nitrobenzoate (Cohen, J., 1914, **105**, 1892), by means of tin and hydrochloric acid. The amino-ester was precipitated from the dried ethereal solution with gaseous hydrogen chloride, and the solid *hydrochloride* recrystallised from alcohol containing a little hydrogen chloride until of constant rotatory power; m. p. 150—170° (indefinite) (Found : Cl, 11·4. $C_{17}H_{26}O_2NCl$ requires Cl, 11·4%); it was sparingly soluble in cold alcohol, giving a violet fluorescent solution.

Free l-*menthyl anthranilate* was obtained from the salt as a colourless solid, m. p. 62·5—63·5°, b. p. 156°/0·33 mm. (Found : N, 5·3. $C_{17}H_{25}O_2N$ requires N, 5·1%). It dissolves readily in alcohol, giving a violet fluorescent solution. Unlike the *m*- and *p*-isomerides, the *o*-amino-ester dissolves readily in dilute aqueous acids.

l-*Menthyl* m-*aminobenzoate*. After unsuccessful attempts to prepare the ester directly from *m*-aminobenzoic acid, it was eventually obtained from pure *l*-menthyl *m*-nitrobenzoate by reduction with titanous chloride in boiling alcoholic solution. Dry hydrogen chloride precipitated the ester from ethereal solution as the hydrochloride in the form of a yellowish-brown oil. This was treated with sodium carbonate to give the free ester, which was purified again through the hydrochloride. l-*Menthyl* m-*aminobenzoate* distilled as an almost colourless oil, b. p. 168°/1·8 mm. (yield 40%)(Found : N, 5·3. $C_{17}H_{25}O_2N$ requires N, 5·1%).

l-*Menthyl* p-*aminobenzoate* was prepared in the same way as the *m*-derivative, but only in 10% yield, probably owing to hydrolysis during reduction. The compound decomposes slightly on distillation (b. p. 175°/0·2 mm.), the yellow distillate having a slight smell of menthol (Found : N, 5·3%). The ester forms a solid hydrochloride, melting indefinitely in the neighbourhood of 200°, by means of which it was purified. The salt easily loses hydrogen chloride in aqueous-alcoholic solution.

Both *m*- and *p*-amino-ester hydrochlorides dissolve in concentrated hydrochloric acid, but are precipitated on addition of a small amount of water.

l-*Menthyl* o-*dimethylaminobenzoate* was prepared from *o*-dimethylaminobenzoic acid by way of the acid chloride (compare Cohen and Dudley, J., 1910, **97**, 1737). The product was dissolved in dilute hydrochloric acid, and any unchanged menthol extracted with ether. The aqueous liquor was made alkaline, the free ester removed with ether, and the extract dried over sodium sulphate. On evaporation of the solvent a highly coloured viscous mass resulted which had a rotatory power ($\alpha_D^{16°}$ $-51{\cdot}6°$, $l = 1$) somewhat higher than that recorded by Cohen and Dudley ($\alpha_D = -10{\cdot}24°$, $l = 0{\cdot}302$). This rotatory power was not changed when the ester in ethereal solution was kept over animal charcoal and subsequently precipitated from light petroleum as the liquid hydrochloride, as recommended by the above authors. The product was therefore distilled in a high vacuum, and thus separated into a pale yellow oil, b. p. 170—171°/0·6 mm., $\alpha_{5893}^{16°}$ $-35{\cdot}67°$ ($l = 0{\cdot}5$), forming about two-thirds of the total volume, which slowly solidified in the receiver, and a highly coloured glassy residue ($\alpha_{5893}^{16°}$ $-0{\cdot}61°$ in benzene, $l = 1$, $c = 2{\cdot}18$). The rotatory power of the original mixture was approximately the mean of the values found for the two fractions. The crude solid ester, m. p. 35—75° (mainly 35—38°), was purified with considerable loss, owing to its high solubility, from light petroleum at −15°, and then had m. p. 36—37° (Found : C, 75·3; H, 9·9; N, 5·1. $C_{19}H_{29}O_2N$ requires C, 75·2; H, 9·6; N, 4·6%). (An unidentified solid of higher m. p., and containing sulphur, was isolated as a by-product.) The somewhat high value found for nitrogen has since been traced to the tendency of the dimethylamino-esters on combustion to yield nitrogen admixed with a small amount of combustible gas, probably methane or ethane, which is exceedingly difficult to convert quantitatively into carbon dioxide and water.

In view of the unexpectedly high rotatory power of this ester, the compound was prepared by another method. Methyl *o*-dimethylaminobenzoate (14 g.) was added to *l*-menthol (25 g.) in which sodium (0·05 atom) had been dissolved (compare suggestion of Verley, *Bull. Soc. chim.*, 1927, **41**, 788). The mixture was maintained at 150—160° in a distilling flask, and a slow current of dry air drawn through the apparatus. Methyl alcohol, menthene, and menthol slowly distilled over, and after 3 hours the residue in the flask was distilled in a vacuum, giving *l*-menthyl *o*-dimethylaminobenzoate (8 g.), b. p. 170°/0·2 mm. The ester solidified on standing, and on repeated recrystallisation from light petroleum possessed the same m. p. and rotatory power as the product obtained as above. The authors wish to thank Mr. C. F. Campbell for carrying out this preparation.

Attempts to repeat the preparation of the *m*- and *p*-dimethylaminobenzoic esters (see Cohen and Dudley, *loc. cit.*) were unsuccessful, leading to the formation of inseparable mixtures of varying rotatory power.

Menthyl hydrogen phthalate was prepared according to the method of Arth (*Ann. Chim. Phys.*, 1886, **7**, 485).

Measurements of Rotatory Power.

The rotatory powers (determined as in previous papers) are given in Table II. An asterisk attached to the first column indicates $l = 2$; otherwise $l = 1$. Where sodium or potassium ethoxide or hydrogen chloride is mentioned, one equivalent was employed.

TABLE II.

l-*Menthyl salicylate* (homogeneous).

t.	*d*.	$[M]_{6708}$.	$[M]_{5893}$.	$[M]_{5461}$.	$[M]_{4358}$.
20°	1·0467	208·9°	278·8°	333·2°	590·3°
40	1·0319	208·6	278·3	332·4	588·3
60	1·0170	208·3	277·7	331·9	586·4
80	1·0022	207·8	277·1	331·2	584·2
100	0·9877	207·4	276·5	330·5	582·1

l-*Menthyl hydroxybenzoates* (at 20° approx.).

Isomeride.	Solvent.	*c*.	$[M]_{6708}$.	$[M]_{5893}$.	$[M]_{5461}$.	$[M]_{4358}$.
**o*-	Alcohol	5·163	192°	253°	299°	500°
	,, + NaOEt	4·880	176	228	267	(412)
	,, + KOEt	5·680	—	—	246	—
	Piperidine	5·445	183	241	286	498
m-	Alcohol	7·735	—	—	266	—
	,, + NaOEt	5·608	—	—	235	—
	Piperidine	8·815	—	—	222	—
p-	Alcohol	5·144	—	—	250	—
	,, + NaOEt	4·873	—	—	241	—
	Piperidine	4·216	—	—	219	—

Rotations of the above esters measured in the presence of ethoxide showed no decrease in value during the period of measurement or the succeeding half-hour.

l-*Menthyl aminobenzoates.*

Isomeride.	Solvent.	*c*.	$[M]_{6708}$.	$[M]_{5893}$.	$[M]_{5461}$.	$[M]_{4358}$.
o-	Alcohol	5·009	210°	261°	313°	511°
	,, + HCl	5·001	187·5	240	289	483
m-	Alcohol	3·186	182	238	276	466
	,, + HCl	1·583	181	231	272	451
p-	Alcohol	5·032	175	224	257	—
	,, + HCl	3·566	176	227	262	—

l-*Menthyl dimethylaminobenzoate.*

o-	Benzene	5·243	—	206	—	—
	Alcohol	4·746	151	206	250	419
	,, + HCl	3·736	192	251	292	482
	N/1·HCl aq.	5·006	—	230	269	449

For rotatory powers of *l*-menthyl benzoate and *l*-menthyl hydrogen phthalate see Table I, (i) and (v).

Summary.

An investigation has been made of the alteration in the rotatory power of *l*-menthyl benzoate following nuclear substitution by dimethylamino-, amino-, hydroxy-, and carboxy-groups and their corresponding ionised forms.

The most definite variations are those found among the *o*-substituted esters. The optical properties of these derivatives are in agreement with the regularities previously established among *o*-esters of this kind. The groups CO_2H, $NMe_2H^{\bullet}$, and $NH_3^{\bullet}$, which orient to the *m*-position in benzene substitution, lead to an increased rotatory power, whereas the groups COO', NMe_2, and O', which are *o*,*p*-directive in type, lead to a fall in rotation. Minor changes in the *o*-carboxy-group, due to formation of methyl or ethyl esters (Cohen, Woodruffe, and Anderson, *loc. cit.*), also affect the rotation in the sense anticipated from this relationship, the rotatory power diminishing as the substituent becomes less *m*-directive in power.

Exceptional behaviour is exhibited by the hydroxyl and amino-groups in the un-ionised salicylic and anthranilic esters, both of which have abnormally high rotations. This is ascribed to the chelated condition of these compounds.

The authors wish to express their gratitude to the Ritchie Bequest for a grant which has covered most of the expenses incurred in this investigation.

UNIVERSITY OF EDINBURGH. [*Received, January 15th,* 1929.]