CCXLVI.—*The Interchange of Alcohol Radicles in Esters. Part II.*

By AKIRA SHIMOMURA and JULIUS BEREND COHEN.

THE present investigation, which is a continuation of that previously published (this vol., p. 883), was undertaken with the object of discovering the cause which determines the interchange of alcohol radicles in esters.

The reaction, which is probably reversible, is entirely inhibited in many cases, or, in other words, the alkyl group is too firmly attached to the oxygen atom to be removed by the action of even a large quantity of a second alcohol or its sodium compound.

From the summary of results given at the end of the paper, it is clear that the alkyl group in the esters is rendered more mobile by the proximity of acidic groups. A striking illustration is that of the neutral and acid esters of dibasic acids. Ethyl oxalate readily reacts with menthol, whereas the presence of one or more intervening hydrocarbon groups (CH_2 or CH), as in ethyl malonate, ethyl succinate, and methyl phthalate, prevents the interchange.

Interchange is, however, effected if one free carboxyl group is present, for all three acid esters of the above acids react. The α -ketonic esters are all reactive; but the β -ketonic esters react only in those cases where a methylene group or a negatively substituted methylene group intervenes between the ketone and the ester group. When one or both hydrogen atoms of the methylene group are replaced by alkyl groups, as in the mono- and di-alkyl derivatives of acetoacetic ester, the action is again repressed.

Attention may be directed to the close resemblance between the inert character of the ester of the simple aliphatic acids and that of aromatic esters, as illustrated by hydroxybenzoic ester.

It should be pointed out that no deduction of a quantitative nature can be drawn from these experiments; for the very different volatility of the esters rendered it necessary to submit them to varying conditions of temperature and pressure during the reaction.

The mechanism of the interchange is still obscure and therefore we propose to continue the investigation and to examine, among other things, the effect of certain alcohols and their substitution products on the same ester.

EXPERIMENTAL.

l-Menthol and Ethyl Pyruvate.—9.1 Grams of ethyl pyruvate and 12.2 grams of *l*-menthol with 0.022 gram of sodium were heated at 130–140° for eight hours. In the course of heating, about 1 c.c. of liquid, chiefly ethyl alcohol, distilled. The product was fractionated under reduced pressure; the portion which distilled at 132–140°/14 mm. (1.9 grams) consisted chiefly of *l*-menthyl pyruvate (Cohen and Whiteley, T., 1901, **79**, 1309; b. p. 136–140°/22 mm.; McKenzie, T., 1905, **87**, 1380, b. p. 131–132°/10 mm.) and showed $[\alpha]_D^{15} -60.8^\circ$ ($c = 2.73$, $l = 2$) in alcohol.

By the above treatment, besides the interchange of groups, some sort of complex condensation seemed to take place, giving rise to a considerable amount of tarry matter (3.6 grams) which had a very high boiling point.

l-Menthol and Ethyl Oxalacetate.—(I) Nine grams of ethyl oxalacetate and 15 grams of *l*-menthol with 0.022 gram of sodium were heated at about 90° under 10–30 mm. pressure for seven hours. After the reaction was finished, the excess of menthol and unchanged ethyl ester were expelled by distillation under 20 mm. pressure, the temperature of the metal-bath being raised to 175°. The remaining liquid was subjected to steam distillation in order to remove any trace of menthol, extracted with ether, and dried over calcium chloride. The ethereal solution showed $\alpha_D -6.09^\circ$ in alcohol and gave 8.5 grams of a syrupy liquid on evaporation.

(II) A similar experiment was carried out, but without sodium. 5.2 Grams of a syrupy liquid were obtained from 9.6 grams of the ethyl ester, and showed $[\alpha]_D^{25} -45.3^\circ$ ($c = 2.68$, $l = 2$) in alcohol.

As the esters of oxalacetic acid easily decompose into carbon monoxide and malonic ester at a high temperature (Wislicenus, *Ber.*, 1894, **27**, 793), the menthyl ester could not be isolated from the mixture containing the ethyl ester by the usual method of fractional distillation in a vacuum.

l-Menthol and Ethyl Acetylpyruvate.—Ten grams of ethyl acetylpyruvate and 10 grams of *l*-menthol were heated at $155\text{--}165^\circ$ for three and a half hours, during which time 1.8 grams of ethyl alcohol distilled. The product was fractionated under reduced pressure, and the portion (6.3 grams) which distilled at $175\text{--}190^\circ/16$ mm. gave, on refractionation, 3.6 grams of a colourless liquid boiling at $185\text{--}192^\circ/12$ mm. and showing $[\alpha]_D^{25} -72.3^\circ$ ($c = 4.33$, $l = 2$) in alcohol. It was found to be the menthyl ester of acetylpyruvic acid by analysis (Found: C = 67.02; H = 9.29. $C_{15}H_{24}O_4$ requires C = 67.13; H = 9.02 per cent.).

A similar result was obtained by heating an equimolecular mixture of the ethyl ester and menthol with a little sodium at 90° under 10–30 mm. pressure for six hours.

l-Menthol and Ethyl Mesoxalate.—Twelve grams of ethyl mesoxalate and 18 grams of *l*-menthol with 0.028 gram of sodium were heated at 90° under 15–30 mm. pressure for six hours. The product was fractionated under diminished pressure; the fraction which boiled at $171\text{--}200^\circ/13$ mm. (4.3 grams) deposited a considerable quantity of crystals on standing for three weeks. The crystalline mass was pressed on a porous plate, washed with water, and recrystallised from alcohol. The colourless microprisms thus obtained melted towards 63° and showed $[\alpha]_D^{25} -58.6^\circ$. It was apparently a mixture of the *l*-menthyl ester of mesoxalic acid and a small quantity of ethyl dihydroxymalonate, judging from the result of its analysis [Found: C = 60.2; H = 8.9.

$CO(CO \cdot O \cdot C_{10}H_{19})_2$
requires C = 70.1; H = 9.6, whilst $C(OH)_2(CO \cdot O \cdot C_2H_5)_2$ requires C = 43.8; H = 6.2 per cent.]. From the residue of fractional distillation under reduced pressure, a very small quantity of crystals, melting at $67\text{--}68^\circ$, was obtained which seemed to be menthyl oxalate formed by partial decomposition.

l-Menthol and Ethyl Monoacetylmalonate.—Five grams of ethyl monoacetylmalonate and 7.8 grams of *l*-menthol with 0.015 gram of sodium were heated at 90° under 10–30 mm. pressure for six hours. The product was distilled up to $103^\circ/14$ mm. and the residue was subjected to steam distillation to remove all menthol, extracted

with ether, and dried over sodium sulphate. The ethereal solution gave a syrup after the ether had been removed, which solidified slowly to a crystalline mass when rubbed with a glass rod, with addition of a little alcohol, and cooled in ice. After recrystallisation from alcohol, *menthyl monoacetylmalonate* was obtained in colourless, long needles (0.8 gram) with m. p. 58° and showing $[\alpha]_D^{19} -77.5^\circ$ ($c = 1.18$, $l = 2$) in alcohol (Found: C = 71.46; H = 10.32. $C_{25}H_{42}O_5$ requires C = 71.04; H = 10.02 per cent.).

l-Menthol and Ethyl Diacetylmalonate.—Twelve grams of ethyl diacetylmalonate and 15.4 grams of *l*-menthol with 0.034 gram of sodium were heated at about 90° under 15–30 mm. pressure for five hours. The product was distilled up to $115^\circ/18$ mm., and the residue was distilled with steam to remove menthol, extracted with ether, and dried over sodium sulphate. The oil obtained after the ether was driven off was again fractionated under diminished pressure. It was found to undergo decomposition at a higher temperature, apparently giving off acetic acid and some other gas. The portion which distilled at 173 – $195^\circ/16$ mm., smelling strongly of acetic acid and acid to litmus paper, showed $[\alpha]_D^{19}$ about -26° ($c = 2.58$, $l = 2$) in alcohol. By heating it at a higher temperature, menthol also seemed to be split off.

l-Menthol and Ethyl Acetoxymalonate.—An equimolecular mixture of ethyl acetoxymalonate and *l*-menthol with a little sodium was heated at about 90° under 15–30 mm. pressure for six hours. The product was distilled up to $120^\circ/12$ mm. and the residue was subjected to steam distillation to remove menthol, during which distillation a slight decomposition took place, acetic acid being given off. The isolation of the menthyl ester was unsuccessful, but the residual oil, after extraction with ether and drying over sodium sulphate, showed $[\alpha]_D^{18} -10.4^\circ$ ($c = 10.2$, $l = 2$) in alcohol.

l-Menthol and Ethyl Phenoxymalonate.—8.6 Grams of ethyl phenoxymalonate and 10.7 grams of *l*-menthol with 0.029 gram of sodium were heated at about 90° under 15–30 mm. pressure for seven hours. The reaction product was distilled up to $107^\circ/16$ mm. and the residue was subjected to steam distillation to remove every trace of menthol. The oil, thus freed from menthol, solidified very slowly and, on repeated recrystallisation from alcohol, the *menthyl* ester was obtained in colourless micro-needles (1.5 grams) with m. p. 96° , and $[\alpha]_D^{17} -55.5^\circ$ ($c = 0.613$, $l = 2$) in alcohol (Found: C = 73.56; H = 9.32. $C_{19}H_{44}O_5$ requires C = 73.68; H = 9.39 per cent.).

l-Menthol and Ethyl Methylenemalonate, $CH_2:C(CO_2Et)_2$.—Two grams of ethyl methylenemalonate and 4.3 grams of *l*-menthol with a little sodium were heated at 130 – 150° for seven hours.

The product was distilled with steam to remove all menthol, extracted with ether, and dried over sodium sulphate. The viscous liquid obtained from the ethereal solution showed $[\alpha]_D^{20} -20.4^\circ$ ($c = 1.37$, $l = 2$) in alcohol.

A similar experiment was carried out under reduced pressure at 90° , and the product, after all the menthol had been removed by steam distillation, gave a lævorotatory syrupy liquid.

The isolation of the pure menthyl ester was not successful in either case.

l-Menthol and Ethyl Ethoxymethylenemalonate, $\text{OEt}\cdot\text{CH}\cdot\text{C}(\text{CO}_2\text{Et})_2$.—Ten grams of ethyl ethoxymethylenemalonate and 14.5 grams of *l*-menthol with 0.026 gram of sodium were heated at about 90° under 10–30 mm. pressure for six and a half hours. The product was fractionated under diminished pressure, and the portion which distilled at $185\text{--}224^\circ$ (mainly $215\text{--}220^\circ/12$ mm.) gave, on redistillation, a colourless, viscous oil (3.9 grams) with b. p. $215\text{--}221^\circ/10$ mm. and $[\alpha]_D^{20} -39.6^\circ$ ($c = 2.16$, $l = 2$) in alcohol. This oil was found to be the *l*-menthyl ester, containing a little unchanged ethyl ester (Found: C = 68.30; H = 9.98. $\text{C}_{26}\text{H}_{44}\text{O}_5$ requires C = 71.51; H = 10.16 per cent.).

l-Menthol and Ethyl Hydroxymethylenemalonate.—6.1 Grams of ethyl hydroxymethylenemalonate and 10.1 grams of *l*-menthol with 0.021 gram of sodium were heated at $80\text{--}90^\circ$ under 20–30 mm. pressure for six hours. The product distilled mostly below $145^\circ/17$ mm. The small remaining quantity of oil was distilled with steam to remove any menthol and the residue was extracted with ether. The dried ethereal solution showed a very small rotation of $\alpha_D -0.28^\circ$ in alcohol. It is rather doubtful if the interchange of groups had actually taken place in this case, and if so, it must have been to a very small extent.

l-Menthol and Ethyl Hydrogen Malonate.—10.6 Grams of ethyl hydrogen malonate and 12.5 grams of *l*-menthol with 0.026 gram of sodium were heated at about 90° under 15–30 mm. pressure for five hours. The product was distilled with steam to remove menthol and the residue was extracted with ether. The ethereal extract gave a small quantity of viscous oil, which was dissolved in a dilute solution of sodium carbonate; after the solution had been extracted with ether to remove any insoluble matter, the oil was reprecipitated by the careful addition of acetic acid. The oil thus obtained showed $[\alpha]_D^{15} -46.8^\circ$ ($c = 1.54$, $l = 2$) in alcohol and consisted undoubtedly of the menthyl ester formed by interchange of the ethyl group.

l-Menthol and Methyl Hydrogen Succinate.—Ten grams of methyl hydrogen succinate and 11.9 grams of *l*-menthol with 0.03 gram

of sodium were heated at 90—100° under 17—20 mm. pressure for five hours. The product was distilled up to 150°/20 mm. and the remaining syrupy oil was dissolved in a warm dilute solution of sodium carbonate. The solution was extracted with ether to remove any impurity, the oil, reprecipitated by careful addition of acetic acid, was distilled with steam to remove any trace of menthol and the excess of acetic acid. The residue was extracted with ether and dried over sodium sulphate. The ethereal extract gave a little oil, which, after three weeks' standing at the ordinary temperature, solidified to a crystalline mass. On recrystallisation from alcohol, the substance was obtained in colourless prisms, m. p. 57—59°, showing $[\alpha]_D^{17} -61.0^\circ$ ($c = 0.50$, $l = 2$) in alcohol. It was found to be the *menthyl hydrogen* ester of succinic acid by analysis (Found: C = 65.23; H = 9.66. $C_{14}H_{24}O_4$ requires C = 65.58; H = 9.44 per cent.).

l-Menthol and Ethyl o-Nitrobenzoate.—Ten grams of ethyl *o*-nitrobenzoate and 8 grams of *l*-menthol with 0.04 gram of sodium were heated at about 90° under 10—30 mm. pressure for five and a half hours. A vigorous reaction was observed at the beginning of heating. The product was distilled up to 202°/13 mm., and the residual dark syrupy mass (3.2 grams) was dissolved in alcohol and boiled with animal charcoal for one hour and filtered hot. The menthyl ester separated in an oily state at first, but on seeding, it solidified at once. When recrystallised from alcohol, it was obtained in large, colourless prisms (2.6 grams), m. p. 64—65°, showing $[\alpha]_D^{15} -152.2^\circ$ ($c = 1.58$, $l = 2$) in alcohol. It was found to be identical with the menthyl ester formerly obtained by Cohen and Armes (T., 1905, **87**, 1190) by a direct synthesis.

l-Menthol and Ethyl m-Nitrobenzoate.—Ten grams of ethyl *m*-nitrobenzoate and 8 grams of *l*-menthol with 0.04 gram of sodium were treated in the same way as the ortho-compound. The product was fractionated under diminished pressure; the portion which distilled at 223—224°/13 mm. gave, on redistillation, a pale greenish-yellow, viscous oil (6.4 grams) with a weak fluorescence, boiling at 228°/10 mm. and showing $[\alpha]_D^{15} -77.5^\circ$ ($c = 1.58$, $l = 2$) in alcohol. It was found to be identical with the menthyl ester of *m*-nitrobenzoic acid obtained directly by Cohen and Armes (*loc. cit.*).

l-Menthol and Ethyl p-Nitrobenzoate.—Ten grams of ethyl *p*-nitrobenzoate and 8 grams of *l*-menthol with 0.04 gram of sodium were treated in the same way as its isomerides. The product was distilled up to 210°/12 mm. The residue, which solidified on cooling, was dissolved in alcohol, boiled with animal charcoal for one and a half hours, and filtered hot. On cooling, almost colourless

crystals of menthyl *p*-nitrobenzoate (7.5 grams) were obtained, m. p. 63°, $[\alpha]_D^{25} -75.0^\circ$ ($c = 1.58$, $l = 2$) in alcohol. The substance was identical with that prepared by Cohen and Armes (*loc. cit.*).

l-Menthol and Ethyl *m*-Aminobenzoate.—Eight grams of ethyl *m*-aminobenzoate and 7.6 grams of *l*-menthol with 0.032 gram of sodium were heated at 90° under 10–30 mm. pressure for five hours, and the product was fractionated. The portion which distilled above 200°/16 mm. (1.6 grams), when dissolved in alcoholic hydrochloric acid, solidified after some time to a colourless, crystalline mass, which, after being pressed on a porous plate, was recrystallised from alcohol, containing a little hydrogen chloride, and was obtained in colourless prisms, melting indefinitely towards 190°, and showed $[\alpha]_D^{18} -72.9^\circ$ ($c = 0.288$, $l = 2$) in alcohol. It was undoubtedly the hydrochloride of menthyl *m*-aminobenzoate (Found: Cl = 12.06. $C_{17}H_{25}O_2N.HCl$ requires Cl = 11.37 per cent.) containing probably a very small quantity of the hydrochloride of the unchanged ethyl ester.

l-Menthol and Methyl Hydrogen Phthalate.—Ten grams of methyl hydrogen phthalate and 8.7 grams of *l*-menthol with 0.022 gram of sodium were heated at about 90° under 15–30 mm. pressure for six and a half hours. The dark syrupy product was directly distilled with steam to remove menthol. When the contents of the flask were evaporated on a water-bath, a solid, consisting of fine prisms, separated with some oil which also solidified when cooled. The whole, which was evidently a mixture of two products, was filtered and the two substances were separated mechanically from one another. The crystals with the higher m. p. (6.5 grams) were found to be chiefly phthalic acid, which was obtained in a pure state [4.8 grams; m. p. 210–211° (decomp.)] by recrystallisation from a large bulk of hot water. In order to ascertain the origin of this phthalic acid, methyl hydrogen phthalate alone was heated with water at 100° for several hours, and was found to decompose very readily into phthalic acid and methyl alcohol.

Although the monomethyl ester was so easily hydrolysed with water, the corresponding menthyl ester survived steam distillation, and the product with the lower m. p. (2.9 grams) was found to be the crude menthyl ester. It was dissolved in a hot dilute solution of sodium carbonate, filtered, extracted with ether to remove any impurity, and the acid menthyl ester was reprecipitated by careful addition of acetic acid. It was obtained in colourless micro-needles, m. p. 110° (2.7 grams), showing $[\alpha]_D^{17} -102.3^\circ$ ($c = 0.988$, $l = 2$) in benzene; Arth (*Ann. Chim. Phys.*, 1886, [vi], 7, 485) found $[\alpha]_D^{20} -105.55^\circ$, and Cohen, Woodroffe, and Anderson (T., 1916, 109, 230) found $[\alpha]_D^{20} -109.32^\circ$ in the same solvent.

l-Menthol and Methyl Terephthalate; *l*-Menthol and Methyl Hydrogen Terephthalate.—Owing to their high m. p. and their insolubility in fused menthol, these methyl esters proved unsuitable for our experiments.

The Interchange of Alcohol Radicles in Esters. Replacement of an Alkyl Group by the *l*-Menthyl Group.

Alkyl esters of monobasic aliphatic acid derivatives.	Ethyl acetate	—
	„ bromoacetate	—
	„ α -cyanopropionate	—
	Methyl phenylacetate	+
	Ethyl phenylacetate	+
	Methyl phenylchloroacetate	+
	„ phenylbromoacetate	—
	„ α -bromo- β -phenylpropionate	—
	Ethyl trichloroacetate	—
	„ atrolactinate	—
	„ α -cyano- β -phenylpropionate ..	—
	Ethyl cinnamate	—
Alkyl ester of unsaturated aliphatic acid.		
Alkyl esters of α -ketonic acids.	Ethyl acetoacetate	+
	„ methylacetoacetate	+
	„ methylethylacetoacetate	—
	Ethyl pyruvate	+
	„ oxalacetate	+
	„ acetylpyruvate	+
	„ mesoxalate	+
Neutral alkyl esters of dibasic aliphatic acids.	Ethyl oxalate	+
	„ malonate	—
	„ succinate	—
	Ethyl monoacetylmalonate	+
	„ diacetylmalonate	+
	„ monobromoacetate	—
	„ acetoxymalonate	+
	„ phenoxymalonate	+
	„ mononitromalonate	—
	„ methylenemalonate	+
unsaturated	„ allylmalonate	—
	„ ethoxymethylenemalonate	+
	„ hydroxymethylenemalonate ..	?
Acid alkyl esters of dibasic aliphatic acids.	Ethyl hydrogen malonate	+
	Methyl hydrogen succinate	+
Alkyl esters of benzoic acid derivatives.	Ethyl benzoate	+
	Methyl <i>o</i> -toluate	—
	„ <i>m</i> -toluate	+
	„ <i>p</i> -toluate	—
	Ethyl <i>o</i> -nitrobenzoate	+
	„ <i>m</i> -nitrobenzoate	+
	„ <i>p</i> -nitrobenzoate	+
	„ <i>o</i> -aminobenzoate	—
	„ <i>m</i> -aminobenzoate	+
	„ <i>p</i> -aminobenzoate	—
	Methyl salicylate	—

Alkyl ester of hydrogenated benzoic acid.	Ethyl <i>cyclohexanecarboxylate</i>	—
Acid and neutral alkyl esters of benzenedicarboxylic acids.	Methyl hydrogen phthalate	+
	„ phthalate	—
	„ hydrogen terephthalate	?
	„ terephthalate	?

Note.—The names in italics are those of substances referred to in the previous paper.

Summary of the Results.

(I) The acid nature of an alkyl ester seems to promote the interchange of groups. The introduction of the following groups generally helps the reaction: phenyl, acetyl, acetoxy, phenoxy, carboxyl, nitro.

(II) Introduction of halogens does not materially influence the interchange.

(III) In some cases, a double bond assists the reaction.

(IV) Most of the esters of α -ketonic acids undergo interchange, due, undoubtedly, to the presence of the carbonyl group in the α -position to the carboxyl group.

(V) Introduction of the hydroxyl group is not favourable to the interchange.

(VI) In the case of esters of benzoic acid derivatives, *o*- and *p*-compounds behave similarly, but differ from the *m*-compound.

THE ORGANIC CHEMICAL LABORATORIES,
THE UNIVERSITY, LEEDS.

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