of the plunger can easily be read to 1 mm., the instrument can be read to 0.0003 ohm.

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MENTHOL STUDIES. I. MENTHYL ESTERS OF THE NITRO- AND AMINOCINNAMIC ACIDS

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The material presented here is a preliminary study undertaken with a view to the synthesis of aromatic terpene compounds to be used in chemotherapeutic studies in tuberculosis.

The assumption is made that a chemical compound used for the purpose of destroying the *B. tuberculosis* directly, must come in contact with the bacillus. To accomplish this, since the tubercle is an avascular system, the chemical compound must penetrate the wall of the tubercle by diffusion (that is, solubility), must pass through the caseous material found in the older tubercles at least, and finally through the waxy material associated with the bacillus itself, the nature of which has been shown by chemical analyses to be compounds of the lipoidal type.[1] Opinion differs whether this waxy material is merely in close contact with the bacillus or actually encases the bacillus in an armor effect, spoken of as the "waxy capsule." Terpenes, due to their ability in general to dissolve lipoids, should be effective in penetrating such a system, or at least capable of concentration in proximity of the organism. The function of the menthol is to ascertain if such an increased solubility can be realized.

Experimental Part

General Procedure for Preparing Menthyl Esters.—The acid to be esterified was refluxed with thionyl chloride in the proportion of 0.1 mole of acid to 0.5 mole of thionyl chloride for one hour, or until solution resulted. The excess of thionyl chloride was then removed on a steam-bath at 5 mm. pressure or less. To the acid chloride 0.25 mole of menthol was added and the mixture was heated in a glycerine-bath at 130° until hydrogen chloride fumes were no longer given off. When reaction was complete the excess of menthol was removed at 110° and 5 mm. pressure. The residue was purified by crystallization from a suitable solvent or by distillation under reduced pressure.

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[1] Aronson, *Berl. klin. Wochschr.*, **47**, 1617 (1910).

TABLE I

MENTHYL ESTERS OF NITRO ACIDS

					Anal.[d] for N		
Menthyl ester of	Solvent for purification	Yield, %	M. p., °C.	Subs., g.	N_2, cc.	Calcd., %	Found, %
p-Nitrocinnamic acid	95% alcohol	82	92.5	0.4041	13.55	4.22	4.19
m-Nitrocinnamic acid	95% alcohol	80	85	.5605	18.84	4.22	4.20
o-Nitrocinnamic acid	95% alcohol	70	49.5	.3488	12.05	4.22	4.32
Cinnamic acid[a]	Frac. distn. (174°, 3 mm.)	Excellent	38				
Benzoic acid[b]	Frac. distn. (173°, 12 mm.)	Quantitative	54.5–55				
p-Nitrobenzoic acid[c]	95% alcohol	Quantitative	62				

[a] Hilditch, *J. Chem. Soc.*, **93**, 6 (1908).

[b] Gattermann and Schnitzspahn, *Ber.*, **31**, 1770 (1898).

[c] Cohen and Armes, *J. Chem. Soc.*, **87**, 1191 (1905).

[d] The nitrogen values in these tables have been reduced to standard conditions.

Menthyl *p*-Nitro-α,β-Dibromo-Hydrocinnamate.—Menthyl *p*-nitro-α,β-dibromo-hydrocinnamate was prepared according to the method of Rosenmund and Kuhnhenn.[2]

Ten g. of menthyl *p*-nitrocinnamate dissolved in 10 cc. of glacial acetic acid was treated at 3–6° with 11 g. of pyridine dibromide-hydrobromide in acetic acid suspension. After reaction had apparently ceased, the mixture was allowed to stand overnight in an incubator at 37°. The acetic acid was removed under reduced pressure, and the dibromide purified by solution in hot alcohol and treatment with charcoal. Upon cooling, the substance separated as an oil which was placed in a vacuum desiccator over sulfuric acid. After drying, a white crystalline substance resulted which melted at 48°.

Anal. Subs., 0.2064: AgBr, 0.1580. Calcd. for $C_{19}H_{25}O_4NBr_2$: Br, 32.54. Found: 32.57.

Menthyl *o*-Nitro-α,β-dibromo-hydrocinnamate.—Sixteen cc. of a 10% bromine solution in chloroform was added to 2.9 g. of menthyl *o*-nitrocinnamate dissolved in 10 cc. of chloroform. This mixture was allowed to stand for two days at 37°, after which the chloroform and bromine were removed on the steam-bath. The dibromo compound which remained as an oil crystallized after standing a few hours in the cold. The menthyl *o*-nitro-α,β-dibromo-hydrocinnamate was obtained in a pure condition after crystallization from 95% alcohol; m. p., 93–93.5°.

Anal. Subs., 0.1914: AgBr, 0.1472. Calcd. for $C_{19}H_{25}O_4NBr_2$: Br, 32.54. Found: 32.72.

Menthyl α,β-Dibromo-hydrocinnamate.[3]—Thirty-one cc. of 10% bromine solution in chloroform was added to 5.7 g. of menthyl cinnamate dissolved in 25 cc. of chloroform and the mixture was allowed to stand overnight at room temperature. The chloroform was evaporated and the residue was crystallized from glacial acetic acid; m. p., 83.5°.

General Procedure for Reduction of Nitro to Amino Compounds and General Method of Identification

The menthylnitro esters are easily and quantitatively reduced to the amino esters with iron powder. The menthylnitro ester was intimately mixed with seven times its weight of iron powder (precipitated from alco-

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[2] Rosenmund and Kuhnhenn, *Ber.*, **56B**, 1262 (1923).

[3] Cohen and Whiteley, *J. Chem. Soc.*, **79**, 1308 (1901).

hol), and sufficient water was added to form a thick paste. This mixture was heated and mechanically stirred simultaneously. The reduction of the *p*-nitromenthyl cinnamate required eight to ten hours at 65–75°; the *m*-nitromenthyl cinnamate six hours at 47–50°; the *o*-nitromenthyl cinnamate 10 to 15 hours at 50–60°; and menthyl *p*-nitrobenzoate 20 hours at 50° to 60°. A small amount of water was added from time to time, to balance the evaporation. When reduction was complete, the mixture was allowed to evaporate to dryness and the residue extracted in a Soxhlet extractor with ether. The ether was removed through distillation and the amino ester obtained. After washing the crystals with a little petroleum ether, the amino esters were obtained in a condition pure enough for most purposes.

Method of Identification.—For identification the menthylamino esters were hydrolyzed with alcoholic sodium hydroxide and the products of hydrolysis, menthol and amino acid, were identified through their physical properties.

TABLE II

MENTHYL ESTERS OF AMINO ACIDS

				Analysis for N			
Menthyl	Solvent	Yield, %	M. p., °C.	Subs., g.	N_2, cc.	Calcd., %	Found, %
p-Aminocinnamate	Ether-ligroin	90–95	122	0.2550	9.49	4.64	4.66
m-Aminocinnamate	Frac. distn.	Good	(B. p.) 230 (2 mm.)	.2828	10.28	4.64	4.55
o-Aminocinnamate	Hot ligroin	Excellent	85	.2974	10.91	4.64	4.60
p-Aminobenzoate	Ether-ligroin	90	88	.2516	10.31	5.10	5.13

Salts of the Menthylamino Esters

Menthyl *m*-Aminocinnamate Hydrochloride.—Five g. of menthyl *m*-aminocinnamate was dissolved in ligroin and the solution was saturated with dry hydrogen chloride gas. The hydrochloride separated from the petroleum ether in a gum-like mass, which became crystalline when dried in a vacuum desiccator.

Anal. Subs., 0.4052: N_2, 15.50 cc. (23°, 746.5 mm.). Calcd. for $C_{19}H_{28}O_2NCl$: N, 4.15. Found: 4.21.

Menthyl *p*-Aminobenzoate Nitrate.—The nitrate was obtained from menthyl *p*-aminobenzoate and dil. nitric acid. This salt decomposes between 150–156°, and is insoluble in water. One g. of the menthyl *p*-aminobenzoate nitrate was suspended in dil. sodium hydroxide and the reaction mixture was extracted with ether. Upon evaporation of the solvent, menthyl *p*-aminobenzoate, m. p. 89°, was obtained.

Menthyl *p*-Aminobenzoate Hydrochloride.—Five g. of menthyl *p*-aminobenzoate was dissolved in chloroform and the solution was saturated with dry hydrogen chloride gas. Upon evaporation, a white crystalline substance, melting at 196° with decomposition, was obtained. The hydrochloride is soluble in chloroform and ether, and practically insoluble in petroleum ether.

Hydrolysis of the Hydrochloride of Menthyl *p*-Aminobenzoate.—The hydrochloride of menthyl *p*-aminobenzoate did not go into solution when added to water but changed immediately in appearance, indicating hydrolysis. The suspended substance was collected and identified as menthyl *p*-aminobenzoate. Silver nitrate added to the aqueous filtrate gave a precipitate of silver chloride.

Menthyl *p*-Dimethylaminocinnamate.—Thirty g. of *p*-dimethylaminobenzaldehyde was dissolved in 200 g. of menthyl acetate. Five g. of sodium wire was added and heat applied to the well-stirred mixture until a reaction commenced. This reaction raised the temperature to about 160°. Vigorous stirring was continued until most of the sodium had reacted, after which the mixture was placed in an oven at 70° overnight. Upon cooling to room temperature, 13 g. of glacial acetic acid and 400 cc. of ether were added to the gelatinous mass, and the dissolved portion was separated from a brown, gelatinous residue by filtration. The ether was removed by distillation on a water-bath and the residue was distilled under reduced pressure. The excess of menthyl acetate distilled at 73° and 2 mm., and the menthyl *p*-dimethylaminocinnamate distilled as a yellow, sirupy substance at 230° and 2 mm., and solidified upon standing. For purification the ester was crystallized first from petroleum ether, then alcohol and obtained as faintly green-tinged crystals; m. p., 99°; yield 15 g.

Anal. Subs., 0.2639: N_2, 10.6 cc. (25°, 743.6 mm.). Calcd. for $C_{21}H_{31}O_2N$: N, 4.25. Found: 4.37.

Menthyl *p*-Dimethylaminocinnamate Methyl Iodide.—Ten g. of menthyl *p*-dimethylaminocinnamate was dissolved in 60 cc. of methyl iodide. This solution was refluxed for seven hours, after which the unused methyl iodide was removed by distillation and the residue was crystallized from hot alcohol. Pale yellow crystals, decomposing above 140°, were obtained after the first crystallization. Repeated crystallizations from benzene, chloroform, hot water and alcohol did not change the properties of this substance; yield, almost quantitative.

Anal. Subs., 0.3078: AgI, 0.1545. Calcd. for $C_{22}H_{34}O_2NI$: I, 26.93. Found: 27.10.

General Procedure for Diazotizing and Forming Dyes

The amino group in the reduced menthylnitro esters was recognized through the usual diazotization process and coupling with β-naphthol or some of its derivatives to form dyes. The dyes prepared were obtained through the following combinations: menthyl *p*-aminocinnamate and β-naphthol (Dye I); menthyl *p*-aminocinnamate and sodium 2-naphthol-3,6-disulfonic acid (R salt, Dye II); menthyl *m*-aminocinnamate and β-naphthol (Dye III); menthyl *p*-aminobenzoate and β-naphthol (Dye IV); menthyl *p*-aminobenzoate and sodium 2,7-naphtholsulfonic acid (F salt, Dye V).

TABLE III

DIAZO DYES OF MENTHYL ESTERS

			Anal.				
Dye no.	Color	Solvents used in purification	Subs., g.	Measured as		Calcd., %	Found, %
I	Red	Ether	0.1906	N_2, 9.16 cc.		6.14	6.00
II	Maroon	Residue insoluble in ether and acetone	.0988	$BaSO_4$, 0.0744 g.	*S*,	10.37	10.24
III	Orange	Ether	.1372	N_2, 7.09 cc.		6.14	6.46
IV	Orange-red	Ether-alcohol	.2447	N_2, 12.74 cc.		6.72	6.51
V	Orange	Fraction from alcohol melting 287–288°	.2430	$BaSO_4$, 0.1070 g.	*S*,	6.03	6.05

Molecular Rotation of Menthyl Esters

Solvent, benzene; 5 g. of substance dissolved in 100 cc. of solution.

Substance Menthyl	$[M]^{30}_{D}$	Substance Menthyl	$[M]^{30}_{D}$
(Menthol)	− 72.01	*o*-Aminocinnamate	−182.32
Benzoate	−238.17	*m*-Aminocinnamate	−209.14
p-Nitrobenzoate	−271.13	*p*-Aminocinnamate	−219.30
p-Aminobenzoate	−250.53	*p*-Dimethylaminocinnamate	−220.67
Cinnamate	−218.46	*p*-Dimethylaminocinnamate methyl iodide	−177.68
o-Nitrocinnamate	−209.75		
m-Nitrocinnamate	−233.61	α,β-Dibromo-hydro-cinnamate	−202.11
p-Nitrocinnamate	−224.00	*o*-Nitro-α,β-dibromo-hydrocinnamate	− 76.03

Discussion

The hydrochloride salts of the menthyl esters of aminocinnamates are not stable in water and hydrolyze immediately and completely, due particularly to the very insoluble character of the free amino esters in water.

The specific rotation of the menthol compounds described was determined in a benzene solution which contained 5 g. of the substance per 100 cc. of solution. Observations were made in a 2dcm. tube. In general the findings have corroborated those of earlier investigators with respect to the enhanced activity associated with the phenyl group, the nitro group and the double bond. In regard to the effect of the amino group, it appears from the cinnamate series that the amino group lowers the rotation and, as usual, the *ortho* position has the greatest influence and the *para* position least. The rotation of menthyl *p*-aminobenzoate, while lower than the corresponding nitro compound, was higher than that of menthyl benzoate. Here the substituted amino group appears to increase the rotation.

The very low rotation of the menthyl *o*-nitro-α,β-dibromo-hydrocinnamate as compared with the menthyl α,β-dibromohydrocinnamate and the corresponding unbrominated compounds was not anticipated, and may be due to the disturbing effect of the solvent upon this compound. Much confusion results in an attempt to explain the change in rotation of an optically active substance by the introduction of optically inactive groups on the basis of a definite effect for a definite group and a definite position.

If the effect upon rotation of a solvent which may result in association, dissociation, or solvation is neglected, the change observed in the rotation of an optically active substance by the introduction of an optically inactive group is probably the result of a shift (a tilting) of the plane of polarization of the optically active group caused by a shift in the center of gravity of the molecule following the introduction of the optically inactive group. The center of gravity of the molecule will be determined first, by the number, size and formal arrangement of the atoms within the molecule with respect to the other atoms to which they are attached; second, by the spatial disposition of the groups which make up the molecule. This latter effect could be largely influenced by the electrical nature of the individual groups and atoms. Thus, if the change in the position of the plane of polarization of the optical group with respect to the polar axes passing through the center of gravity of the molecule could be determined following the introduction of inactive groups, it is believed that the many "exceptions" to the rule, in regard to the effect of optically inactive groups upon the rotation of an optically active substance, would disappear.

The menthol used in this work was the ordinary, C. P., Japanese menthol of commerce. The molecular rotation in benzene of several samples was found to be 72°.

Summary

1. Nineteen new compounds have been prepared and studied. This group includes the menthyl esters of *o*-, *m*- and *p*-nitrocinnamic acids, *o*-, *m*- and *p*-aminocinnamic acids, *p*-dimethylaminocinnamic acid and *p*-aminobenzoic acid.
2. Menthyl cinnamate was obtained for the first time as a crystalline substance.
3. Rotation values of eleven new menthol compounds have been reported.
4. The effect of the amino group upon rotation has been observed.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF BROWN UNIVERSITY]

SOME PHENYLGERMANIUM DERIVATIVES

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I. Introduction

For many years, tetra-ethylgermanium[2] has been the only known representative of the organic derivatives of germanium. Recently, Morgan and Drew[3] prepared tetraphenylgermanium and some of its derivatives, and Tabern, Orndorff and Dennis[4] prepared the same compound as well as a number of other quaternary organic germanium derivatives.

The chemistry of the organic germanium compounds is of particular interest since, in its chemical properties, germanium probably approaches carbon more nearly than does any other element. Comparing germanium with other elements of the fourth group, the properties of organic germanium compounds, for the most part, appear to lie intermediate between

[1] Metcalf Fellow in Chemistry at Brown University.

[2] Winkler, *J. prakt. Chem.*, **36**, 177 (1887).

[3] Morgan and Drew, *J. Chem. Soc.*, **127**, 1760 (1925).

[4] Tabern, Orndorff and Dennis, THIS JOURNAL, **47**, 2039 (1925).