# THE DIASTEREOMERIC MENTHYL CHLORIDES OBTAINED FROM (−) MENTHOL

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When (−) menthol (I) reacts with phosphorus pentachloride (1–4) a mixture (3), $[\alpha]_D^{20}$ −5° to −10°, of two diastereomers is obtained. If this mixture of menthyl (II) and neomenthyl (III) chlorides is treated with a dehydrohalogenating agent the less stable dextrorotatory isomer (III) is converted to menthene more rapidly than the levorotatory isomer (II).
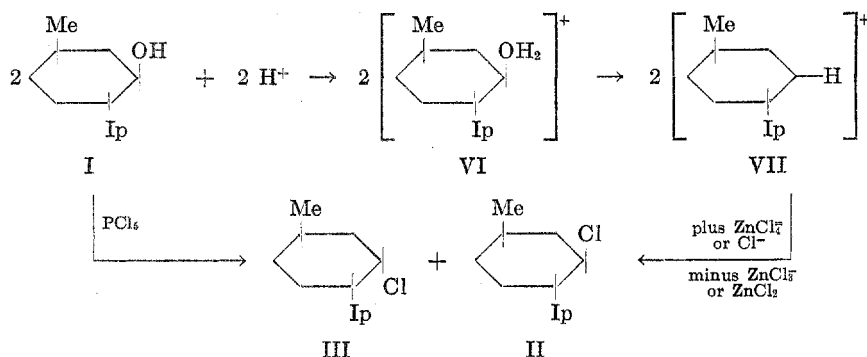
Consequently II may be obtained by this device in high enantiomeric purity (*ca.* −51°) using acetic acid and sodium acetate, or aniline (3) as the dehydrohalogenating agent.

Hückel and Pietrzok (2) increased the amount of menthyl chloride over that of neomenthyl chloride in the product by adding ferric chloride to the phosphorus pentachloride. An equimolecular mixture of these inorganic halides was reported to give a product with rotation $[\alpha]_D^{20}$ of −39.8°. We have duplicated this result using menthol of rotation $[\alpha]_D^{20}$ = −50.1° (ethanol, *c*, 7.28).

We have now further increased the levorotation of the product by treatment of menthol with the solution of zinc chloride in hydrochloric acid commonly known as the Lucas reagent (5, 6). At 35° a 3-molar excess of this reagent converts (−) menthol in 90% yield to a product with specific rotation −45°. This product has been identified as menthyl chloride by conversion *via* its Grignard reagent to the two 3-*p*-menthanecarboxylic acids, one of which has been identified by conversion to its amide (7).

The Lucas reagent as it ordinarily is prepared contains a slight molar excess of hydrogen chloride over that of zinc chloride. If the content of zinc chloride is increased the diastereomeric purity of the menthyl chloride produced from it does not suffer. On the other hand Table I shows that an increase in hydrogen chloride content over that of zinc chloride in the ordinary Lucas reagent causes a marked decrease in the levorotatory power of the product. It would seem that

this decrease in diastereomeric purity was not owing to the hydrochloric acid as such, since this acid will not convert menthol to menthyl chloride at 35°.

The menthyl chloride evidently is stable in the reaction medium, because neither the yield nor the diastereomeric purity is altered at 35° if the reaction time of five hours is increased two- or three-fold. The diastereomeric purity is also unaffected if the Lucas reagent is diluted by 5–10 mole-% more water than it ordinarily contains. Likewise replacement of all of the water in Lucas reagent by diethyl ether has no effect on enantiomeric purity, although the yield is lowered from 80 to 8%. However Table II shows both yield and diastereomeric purity are adversely affected by increase in reaction temperature.

TABLE I

REACTION OF 0.025 MOLE OF MENTHOL, $[\alpha]_D^{20}$ −48.8° (ethanol) AT 35°

TIME, hrs.	ZnCl$_2$, moles	HYDROGEN CHLORIDE, moles		(−) MENTHYL CHLORIDE	
		37%	gas	YIELD, %	$[\alpha]_D^{20}$
5	0.083	0.093	—	78.1	−42.0°
21	.103	.093		79.3	−42.0°
5	.047	.093		29.8	−25.1°
18	.12	.10	0.096	80.4	−27.1°
52	0	.093	—	0	

TABLE II

REACTION OF 0.025 MOLE OF MENTHOL, $[\alpha]_D^{20}$ −48.8°, 0.083 MOLE OF ZINC CHLORIDE, AND 0.093 MOLE OF HYDROCHLORIC ACID

TIME, hrs.	TEMP., °C.	YIELD, %	$[\alpha]_D^{20}$
1.0	95	77	−31.2°
1.5	80	77	−34.8°
3.5	61	79	−38.0°
17.5	35	84	−41.7°
63.0	2	14	−42.3°

The lower yield at higher temperature may be attributed to dehydration of menthol to menthene. The decrease in diastereomeric purity must be caused by alteration of the Lucas reagent, probably in a simultaneous decrease in the zinc chloride-menthol complex and an increase in the amount of tetrachlorozincic acid. It cannot be due to the effect of high temperature alone because menthyl chloride itself is unaltered by maintenance at 100° for four hours.

Both yield and diastereomeric purity are decreased by replacement of zinc chloride in the Lucas reagent with cadmium chloride or with ferric chloride. Lowered yield (20%) and lowered diastereomeric purity are also caused by replacement of the hydrochloric acid in the Lucas reagent by phosphorus trichloride (in benzene at 25° for one day). Much menthene is formed by this latter variation.

The stereochemical configuration of menthol (I) is based largely on its resistance to dehydration (8) and on the assumed generalization that the elements of water are eliminated from apex and base of adjacent carbon atoms (9). A comparable demonstration by Hückel, Tappe, and Legutke (10) that menthyl chloride has a similar stereochemical configuration (II) is based on the general tendency toward apex-base elimination of hydrogen chloride. These authors pointed out that menthyl chloride is unaffected by aniline or quinoline and gives Δ^2-p-menthene with sodium ethoxide, whereas neomenthyl chloride (III) is dehydrohalogenated with ease to a mixture of Δ^2- and Δ^3-p-menthene. These alkenes may be identified because of the fact that the latter, but not the former, is racemized by benzenesulfonic acid (10).

Since menthol and menthyl chloride thus seem to be identical in configuration the addition of aluminum chloride or ferric chloride by Hückel and Pietrzok (2) to phosphorus pentachloride has enhanced direct replacement of hydroxyl by chlorine. Hückel and Pietrzok attributed this to increase in the amount of tetrachlorophosphorylium ion (PCl_4^+) in the presence of the superacid anions tetrachloroaluminate or tetrachloroferrate rather than chloride. They considered that menthol coördinated with the cation and the complex ion then decomposed to menthyl chloride, phosphorus oxychloride, and hydrogen ion. They believed that such inclusion of menthol into a ten-electron shell thus reduced the tendency for replacement by inversion of hydroxyl in menthol by chloride ion. Substantiation for this concept was afforded by the addition of pyridine to the phosphorus pentachloride-menthol system which caused exclusive formation of the inversion product, neomenthyl chloride. This behavior was attributed to appropriation of the tetrachlorophosphorylium ion by the pyridine, thus leaving the menthol free for attack with inversion by the chloride ion.
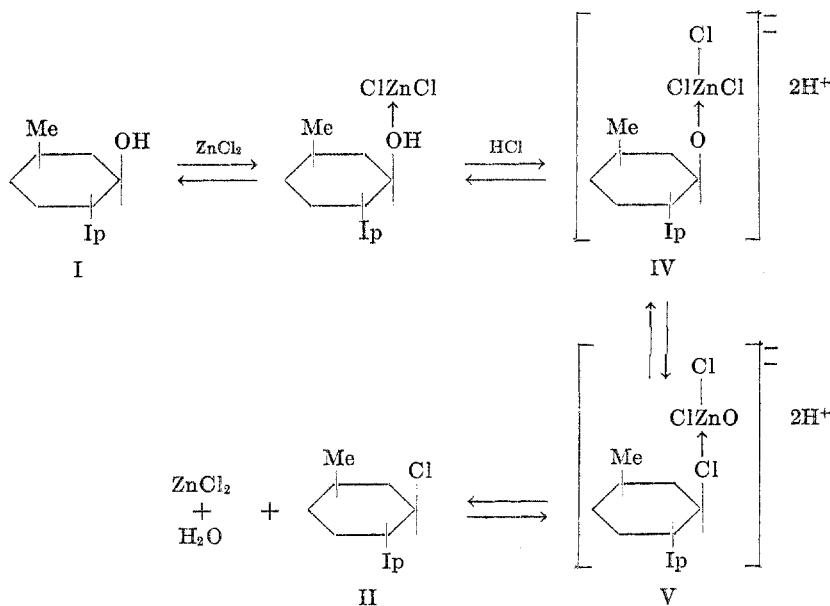
It is apparent that such a postulated mechanism cannot account for the behavior of zinc chloride and hydrochloric acid with menthol which we have observed. However some coördination mechanism is indicated for our reaction since it is unlikely that the high diastereomeric purity which we obtained could arise either by direct replacement of hydroxyl by chlorine or *via* an intermediate carbonium ion. We suggest that the reaction which we have observed proceeds *via* a complex anion such as IV, which may undergo intra-ionic direct replacement of hydroxyl by chlorine with subsequent decomposition of V to menthyl chloride.
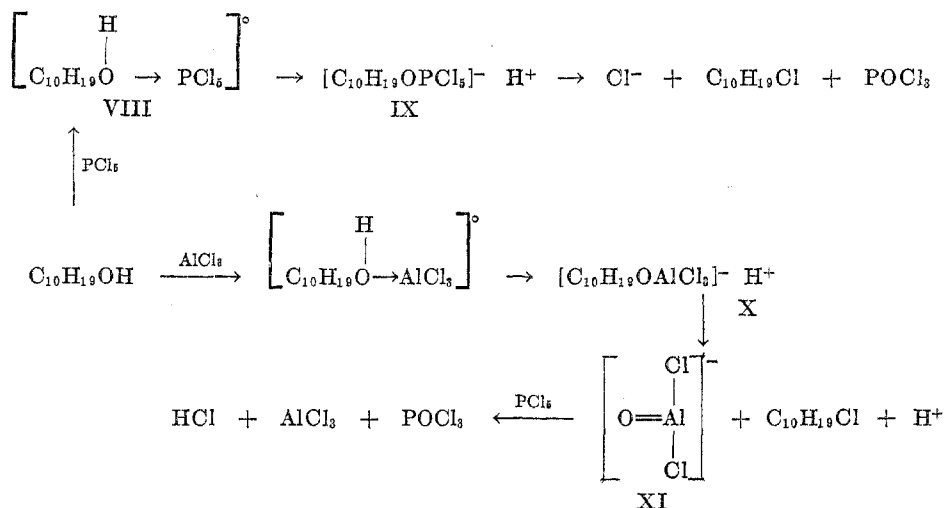
Such a mechanism permits that an excess of hydrogen chloride would prevent the formation of the tetragonal menthoxytrichlorozincate ion IV by preferential formation of the chlorozincate ion $[ZnCl_4]^=$. The "superacid" related to $[ZnCl_4]^=$ should be capable of forming from menthol a menthyloxonium ion (VI) and, perhaps, a menthylcarbonium ion (VII) which would be expected to react with chloride ion with loss of configuration. Such a scheme is presented in the first formulation in this report. We suggest that the reaction conditions for optimum production of menthyl chloride (II) and minimum formation of neomenthyl chloride (III) depend on the relative extent to which IV rather than the tetrachlorozincate ion exists in the reaction system.

We do not consider that this complex-anion mechanism suggested for the reaction of the Lucas reagent with menthol either supports or contradicts the complex cation mechanism of Hückel and Pietrzok. On the other hand an entirely adequate explanation of Hückel and Pietrzok's results need not at all involve the questionable 10-electron shell which phosphorus compounds seem to avoid in favor of 8- or 12-electron valence shells. This avoidance is typified by the tendency (11) of phosphorus pentachloride to assume two alternate states.

$$[PCl_4]^+ \; + \; [PCl_6]^- \; \longleftarrow \; PCl_5 \; \longrightarrow \; PCl_4^+ \; + \; Cl^-$$
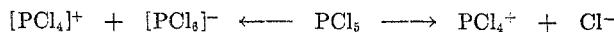
One may, then, extend an alternative suggestion of Hückel and Pietrzok [that menthol and phosphorus pentachloride form a neutral complex (VIII) with 12-electron shell about the phosphorus] by assuming the dissociation of this complex into hydrogen ion and menthoxypentachlorophosphorus anion (IX). According to this concept internal rearrangement and decomposition of this anion would lead to menthyl chloride, phosphorus oxychloride, and chloride ion. The formation of the postulated pyridine-phosphorus pentachloride complex (12-electron shell) would prevent this mechanism and thus allow complete inversion replacement of hydroxyl by chloride ion. The latter inversion replacement is, at any rate, proceeding during the reaction of menthol with phosphorus pentachloride alone because of the dissociation of the latter substance into tetrachlorophosphorylium ion and chloride ion.

If the behavior of menthol with phosphorus pentachloride were to be explained in this way, one may further presume that aluminum chloride or ferric chloride would coördinate so much more readily with menthol than does phosphorus pentachloride that the formation of a tetragonal complex anion [*e.g.* menthoxytrichloraluminate ion (X)] would exclude phosphorus pentachloride from any function other than that of decomposing the penultimate dichloroöxoaluminate ion, (XI).

$$\left[\begin{array}{c} \text{H} \\ | \\ C_{10}H_{19}O \end{array} \rightarrow PCl_5 \right]^{o} \rightarrow [C_{10}H_{19}OPCl_5]^- \ H^+ \rightarrow Cl^- + C_{10}H_{19}Cl + POCl_3$$

VIII   IX

$$\uparrow PCl_5$$

$$C_{10}H_{19}OH \xrightarrow{AlCl_3} \left[\begin{array}{c} \text{H} \\ | \\ C_{10}H_{19}O \rightarrow AlCl_3 \end{array} \right]^{o} \rightarrow [C_{10}H_{19}OAlCl_3]^- \ H^+$$

X

$$HCl + AlCl_3 + POCl_3 \xleftarrow{PCl_5} \left[\begin{array}{c} Cl \\ | \\ O=Al \\ | \\ Cl \end{array} \right]^- + C_{10}H_{19}Cl + H^+$$

XI

The authors wish to thank Dr. M. Bergmann for help in the experimental work.

EXPERIMENTAL

Melting points have been corrected with respect to reliable standards.

(−) *Menthyl chloride.* A quantity of the Lucas reagent was prepared by dissolving 226 g. (1.66 moles) of anhydrous zinc chloride in 154 ml. of 37% hydrochloric acid (1.86 moles of HCl) with cooling. To this solution was added 78 g. (0.50 mole) of (−) menthol [[α]$_D^{20}$ −49.6° (ethanol, c, 8.38)]. The heterogeneous mixture was stirred vigorously for five hours at 35 ± 2°.

The mixture was then cooled and extracted with 150 ml. of petroleum ether (b.p. 40–60°). This extract was washed with 25 ml. of water and then with 25-ml. portions of concentrated sulfuric acid until the latter was no longer discolored (about 5-fold washing). The petroleum ether solution was then washed five times with 25-ml. portions of water and was dried with magnesium sulfate.

The dried solution was distilled from a Claisen flask with indented side-neck 40 cm. in length, finally to obtain 2 g., b.p. 70–100° (22 mm.) n_D^{20} 1.4587, d_4^{20} 0.909; [α]$_D^{20}$ −31.8° and then 81.8 g. (93.6%) boiling at 101–101.5° (21 mm.), n_D^{20} 1.4637, d_4^{20} 0.936, [α]$_D^{20}$ −45.0°, m.p. −20.1° to −16.5°.

3-p-Menthane carboxylic acid. A Grignard reagent was prepared [in 55% yield according to titration (12)] from 4.36 g. (0.025 mole) of (−) menthyl chloride, [α]$_D^{20}$ −45.0°, in 50 ml. of absolute ether. The solution was added during one hour to a nitrogen-filled flask equipped with a stirrer and reflux condenser, containing 1.82 g. (0.075 atom) of sublimed magnesium, after reaction with the first several ml. had commenced within 20 minutes. This Grignard reagent was siphoned under nitrogen into a 250-ml. flask which was then connected with a 3-litre flask containing carbon dioxide at a pressure 20 mm. above that of the atmosphere. The 250-ml. flask was shaken until the solution gave a negative Gilman test.

After hydrolysis with 25 ml. of 5% hydrochloric acid the ether layer was separated, washed once with water, and then extracted with dilute aqueous sodium hydroxide. The residual ether, dried and distilled, was shown to contain 0.5 g. of menthene, b.p. 106–112° (141 mm.), n_D^{20} 1.4395 and 0.4 g. of liquid, b.p. 170–180° (15 mm.), n_D^{20} 1.4822, probably bi-menthyl. The menthene rapidly absorbed bromine in carbon tetrachloride solution.

The alkaline wash liquors were filtered and acidified with concentrated hydrochloric

acid. The oil which separated slowly crystallized partially. The solid was filtered off, wt. 1.20 g., m.p. 53–59°. This crude 3-*p*-menthanecarboxylic acid (high-melting diastereomer, 29% yield) was purified by crystallization from water-methanol (1.85:2.50 ml. per g.), m.p. 60–63°, $[\alpha]_D^{20}$ −42.6° (ethanol, *c*, 8.16). Sublimation of this acid at 60° and 10 mm. raised the m.p. to 62.0–64.0° (4).

The oily filtrate from which the high-melting 3-*p*-menthanecarboxylic acid was separated was extracted with ether. This extract was dried with magnesium sulfate and distilled, finally at 125–130° (0.2 mm.), n_D^{20} 1.4653, $[\alpha]_D^{20}$ −18.2°. This *p*-menthanecarboxylic acid, weighing 1.31 g. (31.7%), contained some of the high-melting diastereomer, since the acid amide of the latter could be isolated from it.

High-melting 3-p-menthanecarboxylic acid amide. A solution of 4.9 g. (0.027 mole) of the high-melting acid in 3.0 ml. (0.042 mole) of thionyl chloride was boiled under reflux for two hours. The excess of thionyl chloride was evaporated *in vacuo.* Slow addition of the residue to 25 ml. of ice-cold concentrated aqueous ammonia yielded 4.38 g. (89%) of crude acid amide, m.p. 141–147°. Repeated crystallization from 1:4 water-ethanol (4.5 ml. per g., 90% recovery) raised the melting point to 147–148.5°, $[\alpha]_D^{20}$ −50.4° (ethanol, *c*, 6.73). (7).

SUMMARY

1. The preparation from menthol of menthyl chloride having a specific rotation higher than that previously reported has been accomplished by the use of the Lucas reagent.

2. An optimum temperature and optimum ratio of zinc chloride to hydrochloric acid is required for maximum yield and rotation.

3. It is believed that this replacement occurs without inversion as a result of an intermediate complex anion.

4. The structure of the menthyl chloride has been confirmed by its conversion to 3-*p*-menthanecarboxylic acid.

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