

ATTEMPTED SYNTHESIS OF THE OPTICAL ISOMERS OF
2,3-DIMETHYLCHOLANTHRENE.¹

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The desirability of synthesizing optically active carcinogens has been mentioned previously by Fieser and Seligman (1) who prepared 2,3-dimethylcholanthrene, III, (16,20-dimethylcholanthrene by their numbering system) for this purpose, but did not attempt to resolve it. Subsequently, this hydrocarbon was shown to be an active carcinogen when tested on mice (2). We have taken up this problem³ and report herein attempts to obtain the optical antipodes of 2,3-dimethylcholanthrene, III.

Since we knew of no good method for the resolution of III, we resolved the intermediate 1,7-dimethyl-4-hydrindenecarboxylic acid, I, converted it into active 1,7-dimethyl-4-(1-naphthoyl)hydrindene, II, and subjected II to pyrolysis at 400–420°. The resulting hydrocarbon, III, was largely, if not completely, racemized. Accordingly, this line of attack was abandoned and the inactive ketone, II, was converted to III by pyrolysis as above. It was hoped that resolution of III could be accomplished by introducing a carboxy or amino group, resolving, and then removing the functional group. A monocarboxylic acid was prepared in good yield by acetylation followed by hypochlorite oxidation, but we were unable to resolve the acid thus produced. Nitration gave in poor yield a dinitro derivative.

Attempts to resolve III by preparing an optically active polynitro compound capable of forming a complex with III are under way in this laboratory.

EXPERIMENTAL⁴

4-Chloro-7-methylhydrindone. After condensation of 385 g. each of *p*-chlorotoluene and β -chloropropionyl chloride as described (3), the crude mixture of hydrindones after a charcoal treatment was allowed to crystallize from 1 liter of benzene. Most of the 4-methyl-7-chlorohydrindone, 176 g. (35%), m.p. 122–125° after sintering at 116°, crystallized and the remaining product was vacuum-distilled to yield 165 g. (33%) of colorless 4-chloro-7-methylhydrindone, b.p. 124–130° at 4 mm., which soon crystallized to a solid, m.p. 73–77°.

4-Chloro-1,7-dimethylindene. A solution of 329 g. (1.82 mole) of 4-chloro-7-methylhydrindone in 1 l. of benzene and 500 cc. of ether was added during 90 minutes to a stirred, refluxing Grignard solution prepared from 517 g. (3.64 mole) of methyl iodide in 1.5 l. of ether. After 3 more hours the mixture was treated with ice and hydrochloric acid and the ethereal solution washed with sodium thiosulfate solution. No separate treatment was

¹ The work herein reported is taken from the Ph.D. thesis of Jack Linsk, Ohio State University, June, 1948.

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³ Professor Fieser informed us that he was no longer pursuing this research.

⁴ All melting points are corrected. Analyses marked ° by Oakwold Laboratories, Alexandria, Va.; ° by J. Polglase, O. S. U.; * by Mrs. E. Klotz, O. S. U.; and * by S. Sadtler and Sons, Philadelphia, Pa.

necessary to dehydrate the carbinol. The indene was obtained as a colorless liquid, b.p. 102–103° at 1.8 mm., n_D^{25} 1.5774, in 85.5% yield.

Anal.° Calc'd for $C_{11}H_{11}Cl$: C, 73.9; H, 6.2.

Found: C, 74.0; H, 6.3.

4-Chloro-1,7-dimethylhydrindene. In a typical experiment, a mixture of 119 g. of the pure, freshly distilled indene, 50 cc. of absolute alcohol, and 0.5 g. of Adams' platinum oxide catalyst was shaken under 3–2 atmospheres pressure of hydrogen. Reduction was complete in one hour and 113 g. (94%) of 4-chloro-1,7-dimethylhydrindene, b.p. 73–74° at 1 mm., n_D^{25} 1.5411, was obtained as a colorless liquid.

Anal.° Calc'd for $C_{11}H_{13}Cl$: C, 73.1; H, 7.3.

Found: C, 73.2; H, 7.1.

4-Cyano-1,7-dimethylhydrindene. The above chloro compound was converted into the cyano compound, b.p. 114–118° at 1.6 mm., in 88% yield using a procedure similar to that previously described (3). Redistillation for analysis yielded a sample, b.p. 105–106° at 0.6 mm., n_D^{25} 1.5489.

Anal.° Calc'd for $C_{12}H_{13}N$: C, 84.2; H, 7.7.

Found: C, 84.4; H, 7.8.

1,7-Dimethyl-4-hydrindenecarboxamide. A solution of 0.5 g. of the nitrile in 2 cc. of concentrated sulfuric acid was heated to 95°, cooled, and poured on ice. The amide, m.p. 148–150°, was obtained in 63% yield. A sample recrystallized for analysis melted at 151–152°.

Anal.° Calc'd for $C_{12}H_{13}NO$: N, 7.4. Found: N, 7.3.

1,7-Dimethyl-4-hydrindenonic acid. I. To a solution of 13.7 g. of nitrile in 35 cc. of concentrated sulfuric acid which had been heated to 105° and cooled was added a solution of 35 cc. of water and 70 cc. of acetic acid and the whole refluxed for fifteen hours. The solids were collected and the acid taken into alkali, treated with decolorizing charcoal, and precipitated with acid. On recrystallization from aqueous methanol 91 g. (60%) of acid, m.p. 175.5–177°, was obtained as colorless needles. A sample recrystallized for analysis melted at 177.0–178.0°.

Anal.° Calc'd for $C_{12}H_{14}O_2$: C, 75.8; H, 7.4.

Found: C, 75.8; H, 7.3.

Resolution of I. A solution containing 16.4 g. of racemic I and 28.1 g. of quinidine, m.p. 171.1–171.5° (purified by liberation from the sulfate and crystallization from methanol), was refluxed for one hour and treated with 150 cc. of ether. Crystallization began on cooling and seeding [the first crystal was obtained after ten days from an ether-petroleum ether (b.p. 65–70°, Skellysolve B) mixed solvent]. The first crop, m.p. 169–174°, $[\alpha]_D^{25}$ 155.2°, weighed 24.8 g. After six recrystallizations from chloroform-ether solutions, the last two of which yielded salt having the same rotation, 9.7 g. (44%) of salt, m.p. 181.4–182.8°, $[\alpha]_D^{25}$ 131.5° ± 0.4°, (c, 2.65% in chloroform, 2 dm. tube) was obtained.

Anal.° Calc'd for $C_{32}H_{36}N_2O_4$: C, 74.7; H, 7.4.

Found: C, 74.8; H, 7.7.

The free acid was liberated from the salt with hydrochloric acid and was crystallized from chloroform-Skellysolve B to yield the *l*-isomer, m.p. 136.2–137.0°, (racemic form, m.p. 177–178°), $[\alpha]_D^{27}$ –47.8° ± 0.2° (c, 2.6% in chloroform, 2 dm. tube). The over-all yield of resolved *l*-acid varied from 22 to 30% in several experiments.

When 0.4 g. of the optically active acid was sealed in a Pyrex ampoule and heated at 380–390° for twenty minutes it was partly racemized and partly decarboxylated. On recrystallization 230 mg. of acid, m.p. 155–170°, $[\alpha]_D^{25}$ –18°, was obtained.

1,7-Dimethyl-4-(1-naphthoyl)hydrindene, II. Racemic and levo forms. This ketone (1) was prepared from 1-naphthylmagnesium bromide and 4-cyano-1,7-dimethylhydrindene as a viscous oil, b.p. 220–225° at 1.5 mm., in 90% yield by a method used for a closely related compound (3). No attempt was made to crystallize this ketone; it was pyrolyzed to III as described below.

To prepare optically active II, the Grignard reagent from 10.4 g. (0.05 mole) of 1-bromo-

naphthalene in 75 cc. of ether was treated with 4.58 g. (0.025 mole) of finely divided cadmium chloride. After stirring and warming for one hour, 20 cc. of benzene was added and to this was added during 15 minutes a solution of the acid chloride, prepared from 2.6 g. (0.014 mole) of *l*-acid, I, and purified (4) thionyl chloride, in 50 cc. of benzene. The mixture was stirred and held at reflux for one hour and the neutral fraction of the hydrolyzed reaction product was distilled at 0.3 mm to yield 4.0 g. (97%) of an amber viscous oil. Crystallization from Skellysolve B yielded the pure *l*-ketone, II, as colorless plates, m.p. 124.0–125.8° [the racemic ketone (1) melted at 112–114°], $[\alpha]_D^{25} -132.2^\circ \pm 1^\circ$, (c, 0.98% in chloroform, 2 dm. tube).

Anal.^o Calc'd for $C_{22}H_{20}O$: C, 88.0; H, 6.7.

Found: C, 88.1; H, 6.5.

2,3-Dimethylcholanthrene, III. The hydrocarbon was obtained pure, *i.e.*, m.p. 169–170° (1), in 13.4% yield by heating 21.4 g. of the above described viscous ketone (racemic) at 400–415° for 20 minutes. Purification was effected mainly by recrystallization of the picrate. In a similar experiment with 2.18 g. of *l*-ketone (see above) there was isolated 0.2 g. (10%) of III, m.p. 165.6–167.2°, after more extensive purification. This material had possibly a very slight levo rotation but, since this experiment was so unpromising, we made no further attempt at pyrolysis. If a way could be found to lower the temperature of the Elbs reaction, possibly the active ketone would yield active hydrocarbon.

Complexes were prepared from III and several polynitro compounds. The *trinitrotoluene complex* formed red elongated plates from benzene, m.p. 152.6–154.4°.

Anal.^o Calc'd for $C_{23}H_{23}N_3O_6$: C, 68.4; H, 4.6; N, 8.2.

Found: C, 68.5, 68.9; H, 4.3, 4.4; N, 7.9, 8.1.

The *trinitrofluorenone complex* (5), greenish-black crystals from a large volume of benzene, m.p. 235–239.5°, contained benzene of crystallization.

Anal.^k Calc'd for $C_{32}H_{23}N_3O_7 \cdot C_6H_6$: N, 6.2. Found: N, 6.1.

The *2,4,2',4'-tetranitrobiphenyl complex* was formed with more difficulty and contains two molecules of the biphenyl to one of III. It formed small red plates from methanol, m.p. 145.8–147.2°.

Anal.^k Calc'd for $C_{46}H_{30}N_8O_{16}$: C, 58.1; H, 3.2; N, 11.8.

Found: C, 58.1, 58.4; H, 3.3, 3.5; N, 11.1, 11.4.

?-Acetyl- and ?-carboxy-2,3-dimethylcholanthrene. To a solution of 1.10 g. of III and 0.34 g. of acetyl chloride in 5 cc. of carbon disulfide and 15 cc. of nitroethane was added 0.85 g. of aluminum chloride during ten minutes. After one hour at room temperature the mixture was treated with dilute hydrochloric acid and the organic solvents were removed by steam distillation. The reaction products were taken into benzene and passed through a short chromatographic column of alumina. The eluate was concentrated to 20 cc. and further chromatographed to yield a total of 836 mg. of yellow needles, m.p. 173–180° (70% based on III not recovered) and 66 mg. of III. A sample recrystallized from benzene for analysis melted at 178.6–180.4°.

Anal.^k Calc'd for $C_{24}H_{20}O$: C, 88.8; H, 6.2.

Found: C, 88.5; H, 5.9.

A solution of 0.5 g. of acetyl compound in 120 cc. of pyridine was treated with 75 cc. of a solution of potassium hypochlorite (containing a small excess) during 15 minutes. The temperature rose to 36°. After standing at room temperature for one hour, the mixture was poured into water containing 5 cc. of acetone to destroy excess oxidizing agent. Acidification after fifteen minutes afforded 469 mg. (93%) of acid, m.p. 285–295°, which was insoluble in hot aqueous alcoholic sodium hydroxide. Recrystallization was effected from a large volume of hot toluene and yielded a yellow microcrystalline solid.

Anal.^k Calc'd for $C_{23}H_{18}O_2$: C, 84.1; H, 5.6.

Found: C, 84.1; H, 5.6.

Decarboxylation by refluxing for one hour in quinoline containing copper-bronze powder yielded III.

Attempts to resolve this acid with the aid of quinidine, brucine, cinchonine, and strychnine failed. The only crystalline product obtained was acid.

Dinitro-2,3-dimethylcholanthrene. A solution of 223 mg. of III in 12 cc. of benzene was treated with 0.2 cc. of concentrated nitric acid in 2 cc. of acetic acid, the temperature being maintained at 0-5° for 42 hours. The reaction product was crystallized once from aqueous acetone and three times from chloroform-petroleum ether, b.p. 65-70°, to yield a few milligrams of small orange needles, m.p. 215-218.5°.

Anal.^k Calc'd for C₂₂H₁₆N₂O₄: N, 7.5. Found: 7.4.

SUMMARY

The synthesis of 2,3-dimethylcholanthrene by an improved procedure is described. The Elbs reaction on an optically active ketone intermediate leads to an optically inactive hydrocarbon.

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