[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

# An Improved Method for the Synthetic Preparation of Methylcholanthrene

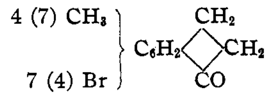
BY LOUIS F. FIESER AND ARNOLD M. SELIGMAN

Numerous requests for supplies of methylcholanthrene and inquiries concerning the two methods of preparation developed in this Laboratory have caused us for some time to give attention to the problem of producing the hydrocarbon in quantity sufficient to meet the wide-spread demand for material required for various forms of biological experimentation. The preparation from cholic acid[1] affords a fairly simple and rapid method of obtaining a few grams of the carcinogenic hydrocarbon, but the purification of the material obtained in this way is somewhat troublesome, the yield amounts to less than 4 g. from 100 g. of the bile acid, and the process becomes cumbersome when working on a large scale. The synthetic method[2] affords a better yield (11%, over-all) and a more easily purified product, but the process as originally described had the disadvantage of being rather lengthy, involving eight separate steps.

As the synthesis seemed to offer more possibility for improvement than the degradative method, a search was made for a shorter route to the required intermediates. In the initial stages of the original process, $p$-bromotoluene was converted into 4-bromo-7-methylhydrindene through a mixture of hydrindones (I) obtained through the following sequence of reactions

$$p\text{-}CH_3C_6H_4Br \longrightarrow CH_3C_6H_3(Br)CH_2Cl \longrightarrow CH_3C_6H_3(Br)CH_2CH(COOR)_2$$

$$\xrightarrow{\text{(2 steps)}} CH_3C_6H_3(Br)CH_2CH_2COOH \longrightarrow$$



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As an alternate route to the ketone mixture I we investigated the hydrindone synthesis of Mayer and Müller,[3] but all attempts to cyclize the chloro ketone mixture (II) obtained from $p$-bromotoluene and $\beta$-chloropropionyl chloride were unsuccessful. No trace of either of the two previously described[2] (crystalline) methylbromohydrindones (I) was observed and the only substance isolated as a solid is an isomer of these compounds and probably is a vinyl ketone (III).[4]

$$\underset{\text{II}}{CH_3C_6H_3(Br)COCH_2CH_2Cl} \longrightarrow \underset{\text{III}}{CH_3C_6H_3(Br)COCH{=}CH_2}$$

This unfavorable result was rather surprising, for Mayer and Müller report that the corresponding chloro ketone from $p$-chlorotoluene can be cyclized readily. On trying the latter reaction for comparison, the results were so generally satisfactory that it seemed worth while to investigate the use of a chlorohydrindene in place of a bromo compound in the methylcholanthrene synthesis, and eventually a very convenient process was evolved.

The Friedel and Crafts reaction with $\beta$-chloropropionyl chloride can be conducted easily with as much as one-half kilogram of $p$-chlorotoluene in one lot and the cyclization of the crude chloro ketone mixture (oil) likewise proceeds well on a large scale. A purified mixture of the hydrindones IV and V was obtained in over-all yield of 61%. Although Mayer and Müller report the isolation of only one isomer (m. p. 128°), two compounds actually are formed and a fairly sharp separation can be accomplished by fractional distillation in vacuum. Dr. W. F. Bruce has kindly informed us that he has synthesized both isomers by another method and established the fact that the higher melting compound of Mayer and Müller is 4-methyl-7-chlorohydrindone-1 (IV), while the isomer is 7-methyl-4-chlorohydrindone (V). On this basis, and from the results of our fractionation, it appears that in the original Friedel and Crafts reaction substitution ortho to the methyl group predominates in the ratio of about 2:1. The course of the reaction seems to be quite similar to that observed by Wahl[5] in a careful study of the chlorination of $p$-chlorotoluene (58% substitution ortho to the methyl group). It is interesting that in the Blanc reaction with

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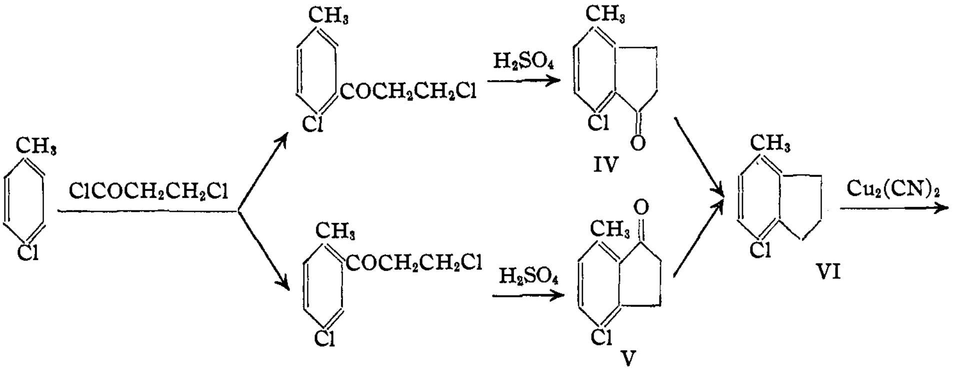
[1] Fieser and Newman, THIS JOURNAL, **57**, 961 (1935). Difficulty may be experienced in effecting the hydrogenation of dehydrocholic acid unless this material is reasonably free from impurities. An adequate purification of the crude oxidation product of cholic acid consists in precipitation of the acid from a solution in dilute alkali and crystallization from acetone. Four 40-g. lots of the purified acid have been hydrogenated in succession with one 3-g. charge of catalyst.

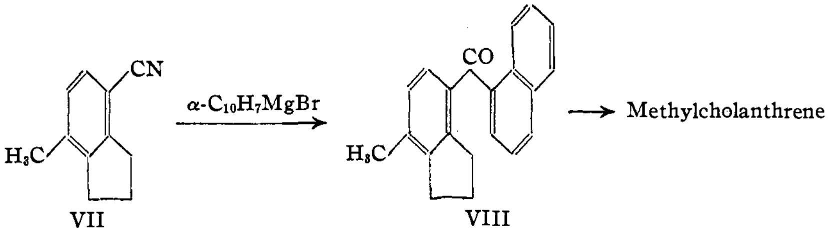
[2] Fieser and Seligman, *ibid.*, **57**, 228, 942 (1935).

[3] Mayer and Müller, *Ber.*, **60**, 2278 (1927).

[4] This substance, m. p. 129–132° (from alcohol), was obtained in small amounts by heating crude II with concentrated sulfuric acid at 100° for one-half hour (found: C, 53.61; H, 4.35), the bulk of the product being an oil. Steam distillation of II gave a viscous oil which polymerized on standing (probably a mixture of the vinyl ketones III) and which could not be cyclized with sulfuric acid or aluminum chloride.

[5] Wahl, *Compt. rend.*, **202**, 2161 (1936).





*p*-bromotoluene the situation is reversed, substitution occurring chiefly adjacent to the bromine atom in the ratio 1.8:1.[2]

For the purpose of the present synthesis a separation (or distillation) is not required, and 4-chloro-7-methylhydrindene (VI) was obtained in 95% yield from the mixture of hydrindones. For the preparation of the ketone VIII the chloro compound VI was first converted into the nitrile VII by the Rosenmund-von Braun method. Fairly satisfactory results were obtained using cuprous cyanide without a solvent[6] at 265°, but a better procedure was encountered by Dr. E. B. Hershberg in the course of work on a related problem and applied by him to the present reaction. Using pyridine as solvent, as suggested in the patent literature,[7] the reaction took place at a lower temperature (220–230°) and the nitrile was obtained (pure) in 78% yield. The condensation of the nitrile with α-naphthylmagnesium bromide proceeded very smoothly and the ketimine was obtained as a crystalline yellow hydrochloride. This was hydrolyzed in the presence of toluene, and on vacuum distillation the ketone VIII was obtained in a satisfactory condition in 89% yield, based on the nitrile. The yield of the ketone is about twice as great as that obtained from 7-methyl-4-bromohydrindene and α-naphthoyl chloride,[2] and the yield in two steps from the chloro compound (69%) is better than in the single step previously employed.

No difficulty was experienced in conducting the pyrolysis of the ketone VIII on a large scale. The bulk of the methylcholanthrene was obtained in a very pure condition after one or two crystallizations of the crude distillate and the remainder was purified as the picrate, the total yield being 49%. In working with large quantities of material it was observed that the hydrocarbon invariably is accompanied by an oily substance. This was collected from the mother liquors and purified by removing traces of methylcholanthrene by its preferential reaction with sulfuric acid. The resulting pale yellow oil, b. p. 221–226° (4 mm.), had the composition of a tetrahydro derivative of methylcholanthrene, but, as it proved to be quite resistant to dehydrogenation with selenium, such a structure is unlikely. The hydrocarbon, which unfortunately yielded no picrate, more probably is 4-methyl-7-(1-naphthylmethyl)-hydrindene, formed by the reduction of the carbonyl group of the starting material (VIII). That some form of reduction process occurs during the pyrolysis is clear from the composition of the hydrocarbon, and it is interesting that products both of reduction and of oxidation[8] (anthrones) have been observed as by-products in the Elbs reaction, suggesting a process of disproportionation as a side reaction.

Each of the six steps of the new synthesis can be carried out rapidly and on a reasonably large scale, and the over-all yield (20%) is quite satis-

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(6) Von Braun and Manz, *Ann.*, **488**, 111 (1931).

(7) Ger. Pat. 271,790 (1914), 293,094 (1916).

(8) Morgan and Coulson, *J. Chem. Soc.*, 2551 (1929); Fieser and Peters, THIS JOURNAL, **54**, 3742 (1932).

factory. Using ordinary equipment, 75 g. of methylcholanthrene can be prepared conveniently from 176 g. of *p*-chlorotoluene, and the first three reactions can be conducted easily with amounts three times as great. The β-chloropropionic acid required as starting material can be prepared readily from trimethylene chlorohydrin in 79% yield by a modification of the usual method[9] for which we are indebted to Professor E. H. Huntress and Dr. E. B. Hershberg. Also included in the experimental part is a procedure developed by Dr. M. S. Newman for the preparation of methylcholanthrene-choleic acid,[10] a compound of interest for biological experimentation in the form of the water-soluble sodium salt.

The modifications reported in this paper widen somewhat the scope of the general synthesis, and various further applications are at present under investigation. We are indebted to Drs. Hershberg and Newman for the contributions noted, and to Mr. Phillip A. Shaffer, Jr., for able assistance in conducting the experiments.

## Experimental Part[11]

**β-Chloropropionyl Chloride.**—Following the procedure recommended by Huntress and Hershberg, 250 g. of trimethylene chlorohydrin was added gradually from a dropping funnel to 775 cc. of concentrated nitric acid (sp. gr. 1.42) contained in a 3-liter long-necked flask provided with a mechanical stirrer and a thermometer suspended in the liquid, and cooled in an ice-bath (hood). The temperature of the reaction mixture was carefully controlled to 25–30° throughout the addition, which required about three hours. Stirring was continued for a short time, and after standing overnight the mixture was heated for one-half hour on the steam to complete the reaction. The solution was combined with that from a second oxidation of the same amount of material and the nitric acid was removed by distillation up to about 100° at 25 mm. The β-chloropropionic acid then distilled at 115° (25 mm.), or 120° (30 mm.); yield 445–465 g. (78–81%).

The acid prepared in this way (465 g.) was refluxed with 800 g. of purified thionyl chloride (all-glass apparatus) for three hours and the excess thionyl chloride was removed by careful fractionation from a modified Claisen flask at the pressure of the water pump. The β-chloropropionyl chloride then distilled at 53° (23 mm.) or 87° (95 mm.); yield 525 g. (96%).

**Friedel and Crafts Reaction.**—A 5-liter three-necked flask provided with a mercury-sealed Hershberg wire-stirrer[12] and a calcium chloride tube was charged with 525 g. of β-chloropropionyl chloride, 525 g. of *p*-chlorotoluene and 2100 cc. of carbon bisulfide, and 1050 g. of aluminum chloride was added to the stirred solution in 100-g. portions over a period of three hours. Stirring was then continued at room temperature for ten hours, by which time the greater part of the aluminum chloride had been converted into a liquid complex. To complete the reaction the mixture was warmed to 40–45° and stirred for two hours without further heating. It was then cooled thoroughly by stirring in an ice-bath and the liquid was decanted into dry flasks and then poured cautiously through a funnel into a stirred mixture of ice and concentrated hydrochloric acid, using in all 12 liters of ice and 1.5 liters of acid distributed among several beakers. The residue in the reaction flask, containing aluminum chloride, was decomposed separately with ice and acid. The aqueous liquor was separated in portions and washed once with ether. The carbon bisulfide layer was extracted once with water, combined with the ethereal extract and, without drying, evaporated at the pressure of the water pump. The residual red-brown oil containing a mixture of the two β-chloropropionyl derivatives and weighing about 910 g. (theoretical, 897 g.) was used at once or else stored in the ice box.

**Cyclization.**—Approximately one-half of the above oil (910 g.) was added from a separatory funnel with efficient stirring (wire stirrer) to 2600 cc. of concentrated sulfuric acid contained in a 5-liter flask and preheated to 105° (hood). The addition was completed in thirty minutes, and the solution was kept at 105–110° with stirring for twenty-five minutes longer. The mixture was then carefully cooled by applying wet towels, then water, then ice, while stirring, and after reaching a temperature of 25° (twenty minutes) it was poured onto about 12 liters of cracked ice and the volume was made up to about 16 liters with water. The reaction product separated as a crystalline, tan precipitate, and this was collected on a large Büchner funnel and washed thoroughly with water. The washing removed a considerable amount of very dark tar (which is reprecipitated by the dilute acid in the filtrate) and left a light tan, granular product. This was combined with the material obtained in the same manner from the second half of the chloro ketone mixture and the product without being dried was dissolved in boiling alcohol, using a considerable excess of the solvent. For clarification the dark solution was filtered by suction through a 2-cm. pad of Norite, changing the pad frequently, as required. After a second filtration the solution was light yellow, and after suitable concentration and cooling there was deposited a first crop of nearly colorless crystals (390 g.). A second crop was obtained after clarification and concentration of the solution, and finally the remainder was precipitated with water. The total yield of light colored hydrindone mixture suitable for the next step was 460 g. (61%).

In another experiment the crude, tan hydrindone mixture from 490 g. of *p*-chlorotoluene was taken up while wet in benzene and the solution was washed with aqueous sodium chloride solution, dried and after removing the solvent the product was distilled at reduced pressure from a modified Claisen flask. There was obtained in the first fraction, b. p. 152–157° (8 mm.), 213 g. of colorless solid melting at 75–79° and consisting very largely of **7-methyl-4-chlorohydrindone-1** (V). Recrystallized several

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[9] "Organic Syntheses," Coll. Vol. I, 1932, p. 162.

[10] Fieser and Newman, THIS JOURNAL, **57**, 1602 (1935).

[11] All melting points are corrected. Analyses by Mrs. G. M. Wellwood.

[12] Hershberg, *Ind. Eng. Chem., Anal. Ed.*, **8**, 313 (1936).

times from alcohol, a sample of the substance formed long needles, m. p. 82–82.4°.

*Anal.* Calcd. for $C_{10}H_9OCl$: C, 66.47; H, 5.03. Found: C, 66.31; H, 5.10.

The second fraction distilled largely at 172–180° (8 mm.), and the colorless distillate weighed 112 g. and melted at 110–120°. Crystallization from alcohol afforded pure **4-methyl-7-chlorohydrindone-1**(IV), which formed leaf-like prisms melting at 128° as recorded by Mayer and Müller.[3] The substance is considerably less soluble than the isomer. As the total yield in this experiment was low (46%), and as a considerable residue remained from the distillation, it is probable that much material was lost during the prolonged process of fractionation, possibly through biindone formation under the influence of impurities in the crude material. For this reason the approximate ratio of the isomers V and IV (66:34) in the total distillate may be only a rough indication of the course of the original substitution. In an earlier small-scale experiment in which the distillation was carried out more rapidly without attention to the separation of isomers, the yield from 140 g. of *p*-chlorotoluene was 59%. Purification of the crude hydrindone mixture by rapid distillation thus appears to be satisfactory when handling small quantities, but in large-scale operation it is safer to crystallize the material.

**4-Methyl-7-chlorohydrindene** (VI).—For the Clemmensen reduction the 460-g. batch of mixed hydrindones described above was divided into three portions, each of which was dissolved in 750 cc. of alcohol. The solutions were kept hot on the steam-bath and in the course of four to five hours each solution was added in portions through a reflux condenser to a gently boiling mixture prepared by shaking 1600 g. of granulated zinc with a warm solution of 80 g. of mercuric chloride, decanting, washing once with water, and adding 500 cc. of water, 200 cc. of alcohol and 1100 cc. of concentrated hydrochloric acid. After the addition the mixtures were kept boiling for ten hours, during which time 900 cc. of concentrated hydrochloric acid was added in portions to each flask. After standing overnight to cool, the aqueous liquors were decanted, diluted with water to twice the original volume and extracted twice with ether. The greater part of the reaction product was recovered from the zinc residues by thorough extraction with ether, taking care to break up any lumps of metal. The various ethereal extracts were combined, the solvent was removed by distillation and the residual oil was steam distilled from a solution of sodium hydroxide. The colorless oil in the distillate, together with that extracted from the aqueous layer with ether, was dried and distilled, the yield of colorless, mobile liquid, b. p. 132–133° (25 mm.), being 403 g. (95%).

*Anal.* Calcd. for $C_{10}H_{11}Cl$: C, 72.09; H, 6.66. Found: C, 71.76; H, 6.98.

**4-Methyl-7-cyanohydrindene** (VII).—In the most satisfactory experiment (by E. B. H.) 27.8 g. of thoroughly dry, powdered cuprous cyanide was poured into a 30-mm. Pyrex bomb tube constricted near the top, and 49.3 g. of 4-methyl-7-chlorohydrindene was added. After shaking vigorously to wet all of the powder, 40 cc. of dry pyridine was added, taking care not to mix the layers. The tube was then sealed and given a few quick shakes to mix the contents. A pyridine–cuprous cyanide complex forms with much evolution of heat and the mixture sets to a solid mass. On being heated in a furnace to 220–230° this dissolves to a clear, dark brown solution. After twenty hours at this temperature the tube was cooled and opened and, after adding 20–30 cc. of pyridine, warmed over a flame until the solid had dissolved. The hot solution was poured into a separatory funnel containing water and the mixture was extracted with ether. The filtered ethereal extract was washed with concentrated ammonia solution to remove copper salts, then with water, and finally with dilute hydrochloric acid. The ethereal solution was filtered to remove some precipitated solid, washed with saturated salt solution, filtered and evaporated. The residue on distillation gave 36.2 g. (78%) of distillate, b. p. 162–164° (21 mm.), which solidified at once to a colorless solid. This material was suitable for use in the Grignard reaction.

When no solvent was employed (A. M. S.), the best results were obtained by heating 80 g. of 4-methyl-7-chlorohydrindene and 41 g. of dry cuprous cyanide at 265° for eighteen hours. Before the tube was sealed it was evacuated several times to mix the reagents, and after the first ten hours of heating the tube was removed and shaken well. It was found convenient to isolate the reaction product by vacuum distillation (2 mm.) directly from the bomb-tube, and for this purpose an end section of the tube was drawn down to a diameter of 6 mm. and bent upward so that it subsequently could be cleaned easily and sealed to a delivery tube leading to a bulb receiver. The reaction product, together with some starting material, distilled readily in a colorless condition and was accompanied by only a small amount of inorganic sublimate (56 g.). The material was collected and dried in ether and on fractionation there were obtained 7.5 g. of starting material and 46.5 g. of nitrile (3° range); yield 68%, based on the chloro compound actually consumed. At the above temperature the conversion invariably was incomplete, and at higher temperatures considerable material was destroyed. The collection of the product by distillation from the bomb tube seemed to give yields just as good as the very tedious process of extraction with benzene.

4-Methyl-7-cyanohydrindene crystallizes well from petroleum ether, and a dilute solution deposits large, flat, rectagonal prisms with a characteristic design resembling the section of an hourglass. The pure substance melts at 72.9–73.2°.

*Anal.* Calcd. for $C_{11}H_{11}N$: C, 84.01; H, 7.06. Found: C, 83.80; H, 7.21.

The corresponding **amide** was obtained by refluxing the nitrile with concentrated hydrochloric acid. It formed colorless needles from alcohol, m. p. 176–177.4°.

*Anal.* Calcd. for $C_{11}H_{13}ON$: C, 75.40; H, 7.48. Found: C, 75.35; H, 6.85.

Hydrolysis of the amide with alkali gave **4-methylhydrindene-7-carboxylic acid**; irregular prisms from alcohol, m. p. 227–229°.

*Anal.* Calcd. for $C_{11}H_{12}O_2$: C, 74.97; H, 6.87. Found: C, 74.82; H, 6.87.

**4-Methyl-7-(α-naphthoyl)-hydrindene** (VIII).[2]—To the Grignard reagent prepared from 195 g. of α-bromonaphthalene, 37 g. of magnesium and 800 cc. of dry ether, 100 cc. of dry benzene was added and about half of the ether was removed by distillation. A solution of 120 g. of 4-methyl-7-cyanohydrindene in 650 cc. of benzene was then added rapidly with stirring, the heat of the reaction bringing the mixture nearly to the boiling point. After refluxing overnight, the mixture was poured onto 1 kg. of ice and 500 cc. of concentrated hydrochloric acid, when the ketimine hydrochloride separated as fine yellow crystals. The organic solvents were removed with steam and, after cooling, the yellow solid was collected on a Büchner funnel and transferred to a 5-liter flask. To effect hydrolysis 1 liter of water, 500 cc. of concentrated hydrochloric acid, 500 cc. of glacial acetic acid, and 600 cc. of toluene were added and the mixture was refluxed until the ketimine hydrochloride had completely disappeared (three hours). The acetic acid was found to facilitate the hydrolysis, while the toluene dissolves the ketone as it is formed and also floats the solid material and prevents bumping. The aqueous layer was extracted once with ether and the combined ether–toluene solution was washed with water and submitted to steam distillation from a mixture with dilute alkali. After removal of the solvent the distillation was continued in order to eliminate some naphthalene. The residual oil was dried in ether and distilled at 2 mm., b. p. 211–214°, the yield of light yellow, viscous oil being 194 g. (89%). On one occasion, after evaporating the bulk of the ether prior to the distillation of the crude ketone, the material crystallized to a hard solid on standing for a day or so. After this product had been distilled it remained as a glass when kept for over a week. The analytical sample from the earlier work[2] began to crystallize after about twenty months.

**Methylcholanthrene.**—The pyrolysis of 168.5 g. of the ketone was conducted in three lots and the products were combined for purification. In a 100-cc. flask with a sealed-on receiving bulb a portion of the ketone was warmed over a free flame and then placed in a preheated nitrate bath and heated at 405–410°, uncorr., for forty minutes. A nitrogen atmosphere is unnecessary. Since the true temperature of the bath was not determined, it may be noted that the pyrolysis temperature is sharply defined by brisk bubbling which is hardly noticeable at a temperature 5° lower. The water and hydrocarbon cleavage products collecting in the receiver amounted to 6 g. in a typical 56.5-g. run. At the end of the period of heating the flask was removed from the bath and cooled somewhat with a blast of air. A capillary was inserted, the receiver was rinsed with acetone and the hydrocarbon was distilled at 2–3 mm. pressure. It is convenient to distill the material rather rapidly and to remove traces of entrained tar in a second distillation. There was a fair amount of tarry residue in the first distillation, and the first few drops of the distillate failed to solidify.

The redistilled material from the three pyrolyses consisted of a bright yellow solid weighing 113.3 g. This was dissolved in 400 cc. of benzene, and after cooling slightly 1 liter of ether was added. The bulk of the methylcholanthrene separated in a nearly pure condition as fine yellow needles (72 g.). This was dissolved in 500 cc. of benzene and 300 cc. of ether was added; on cooling, the hydrocarbon separated as beautiful yellow needles of high purity, m. p. 178.5–179.5°; yield 63 g. The mother liquor from this crystallization was concentrated and treated with 12 g. of picric acid, affording 12.5 g. of methylcholanthrene picrate, m. p. 176–177°. The original mother liquor was evaporated and the residual oil was submitted to pyrolysis at 405–410°, uncorr., for thirty-five minutes, but no appreciable amount of water was formed. Vacuum distillation gave an oil which solidified only partially, and on warming this with 100 cc. of ether and cooling, there was obtained in all 14.6 g. of solid, consisting of quite impure methylcholanthrene. Treated with picric acid in benzene solution, this yielded, after suitable recrystallization, 14.5 g. of satisfactory methylcholanthrene picrate, m. p. 178–179°. The total yield of the hydrocarbon, collected as such or as the picrate, amounted to 77.1 g. (49%).

The ethereal mother liquor remaining after the removal of the impure methylcholanthrene left on evaporation 26 g. of a somewhat dark oil which set to a glass on cooling. Only traces of picrate could be obtained from this material, and in earlier experiments it had been found that heating the oil with selenium resulted in no noticeable increase in the quantity of methylcholanthrene still present. To remove this hydrocarbon completely a solution of the oil in about 150 cc. of tetrachloroethane was shaken mechanically with 3-cc. portions of concentrated sulfuric acid, each time decanting the solution as well as possible and washing the acid residue with fresh solvent. The acid liquor at first was colored a dull reddish-black, but after repeating the process a few times it acquired a clear, brilliant, crimson color similar to that given by pure methylcholanthrene under the same conditions. After about ten extractions the material was recovered for inspection and distilled. The product (11 g.) was then treated as before until fresh acid acquired only a light red color (about ten extractions). The decanted solution was then filtered twice through Norite on a sintered glass funnel to remove traces of acid and the nearly colorless filtrate was subjected to steam distillation. The residual oil was dried in ether over calcium chloride and twice distilled in vacuum. The pale yellow distillate (7.4 g.) formed a glass. No picrate could be obtained from the material in either alcohol or benzene. After two careful fractionations the main portion of the oil (5.2 g.) distilled at 221–226° (4 mm.). The analysis is that of 4-methyl-7-(1-naphthylmethyl)-hydrindene.

*Anal.* Calcd. for $C_{21}H_{20}$: C, 92.60; H, 7.41. Found: C, 92.71; H, 7.34.

A sample of the oil was treated in glacial acetic acid with sufficient dichromate for conversion to the ketone VIII, but the recovered product gave no methylcholanthrene on pyrolysis and resembled the starting material. The oily hydrocarbon is attacked only slowly on being heated with dilute nitric acid; after oxidation finally had been accomplished the clear solution was evaporated and the residue sublimed. Phthalic anhydride was identified in the first sublimate and there was then obtained a substance which crystallized from benzene as colorless prisms which became opaque on drying and melted at 189–191° (found: C, 54.27; H, 1.33).

**Methylcholanthrene-choleic Acid.**—Conditions have not been found under which the choleic acid crystallizes directly from a solution of the components, and the following process has been employed. Fifteen grams of commercial desoxycholic acid is dissolved in 200 cc. of absolute alcohol, the solution is filtered, 0.4 g. of methylcholanthrene is added, and the mixture is refluxed for a few minutes in order to bring the hydrocarbon into solution. On standing undisturbed overnight the solution deposits a few large clusters of long, fine, rather pale yellow needles of pure methylcholanthrene. This material is collected, and the filtrate is concentrated to a volume of about 125 cc. and allowed to stand overnight without disturbance. Methylcholanthrene-choleic acid separates at this point as small clusters of fine, colorless needles amounting to 0.7–2.1 g. The melting point usually is 196.5–197°, sometimes 197.5–198°. There is some drawing together of the particles a few degrees lower, and some darkening at the melting point. From 0.1 to 0.2 g. of methylcholanthrene, depending on the size of the first crop of the choleic acid, is dissolved in the mother liquor and on slow cooling a further crop of the choleic acid is obtained. This procedure can be repeated about four times, keeping the volume about 125 cc. If the solution darkens, it is clarified with Norite.

## Summary

By a modification of the synthetic method previously described, methylcholanthrene can be prepared rapidly and on a large scale using *p*-chlorotoluene, $\beta$-chloropropionyl chloride, and $\alpha$-bromonaphthalene as the starting materials. The over-all yield in the six-step process is 20%.

CONVERSE MEMORIAL LABORATORY
CAMBRIDGE, MASS. RECEIVED OCTOBER 20, 1936

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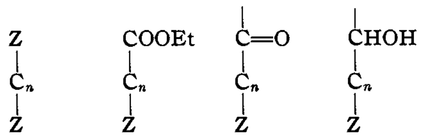
[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

# The Synthesis of Pyrrolidines, Piperidines and Hexahydroazepines[1,2]

BY JOSEPH H. PADEN AND HOMER ADKINS

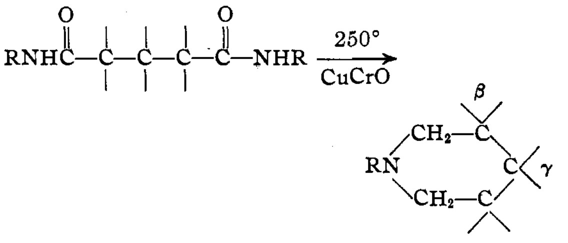
Compounds of the types



$$Z{-}C_n{-}Z \qquad \mathrm{COOEt}{-}C_n{-}Z \qquad \overset{|}{C}{=}O{-}C_n{-}Z \qquad \overset{|}{C}HOH{-}C_n{-}Z$$

where $n$ is 2, 3 or 4 and Z is —CN, —CONH$_2$, —CONHR, $-\overset{|}{\underset{|}{C}}-NH_2$, $-\overset{|}{\underset{|}{C}}-NHR$, $-\overset{|}{\underset{|}{C}}-NO$, $-\overset{|}{\underset{|}{C}}-NO_2$, $-\overset{|}{C}{=}NOH$ or $-\overset{|}{C}{=}N{-}N{=}$ presumably may be converted into cyclic amines by catalytic hydrogenation. The present paper is concerned primarily with the synthesis of such amines from diamides of succinic, glutaric and adipic acids. Attention has been also given to the hydrogenation of imides to cyclic amides over nickel or to cyclic amines over copper–chromium oxide. In addition a new process for the preparation of cyclic amines by the alkylation of amines with glycols has been developed.

**Piperidines from Glutaramides.**—The eight substituted piperidines prepared by ring closure from glutaramides as indicated in Table I have substituents on the nitrogen and (or) in the gamma position.



Presumably piperidines bearing substituents in the beta position could be prepared similarly, while it is obviously impossible to prepare alpha substituted piperidines from glutaramides. Among the piperidines prepared, the group on the nitrogen was *n*-amyl, benzyl or phenethyl, while the substituents on the central carbon were methyl, dimethyl or phenyl. The yield of piperidines was not much modified by the character of the substituent, being approximately 70%, which was also the yield of piperidine obtained from glutaramide itself. The lowest yield (62%) of a piperidine was due to incomplete hydrogenation and becomes the highest (81%) if allowance is made for the recovered amide.

The other products of reaction, isolated in the yields given in Table I, can be accounted for by cleavage at the nitrogen to carbon bond in the amide or the piperidine. The effect of structure upon the extent of this type of reaction will be considered in a subsequent section.

Three dipentamethylene glutaramides of the type

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(1) Azepine is the seven-membered ring containing one nitrogen atom and three double bonds. Hexahydroazepine was suggested by Dr. Austin M. Patterson in preference to the synonymous terms hexamethyleneimine or homopiperidine.

(2) The Wisconsin Alumni Research Foundation allotted funds for a research assistantship held by J. H. P.