Summary

Crowfoot's data on X-ray reflections from insulin crystals, as summarized in a set of Patterson–Harker vector maps, are found to correspond in great detail to the C_2 polyhedral structure predicted for the insulin molecule on the basis of the cyclol theory. The features of the insulin molecule confirmed by the X-ray data include: (1) six high density points at the corners of an octahedron of side 29.4 Å., which is the size given by the cyclol theory; (2) low density regions near the centers of the 44 lacunae in the cyclol fabric that are located in definite positions in the edges and faces of the polyhedron; (3) a comparative hollow at the molecular center, *i. e*, a cage structure; (4) three zinc atoms per molecule on lines connecting molecular centers (except along the *z*-axis) and low and high density groups attached to these zinc atoms outside the C_2 structure.

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RECEIVED JULY 30, 1938

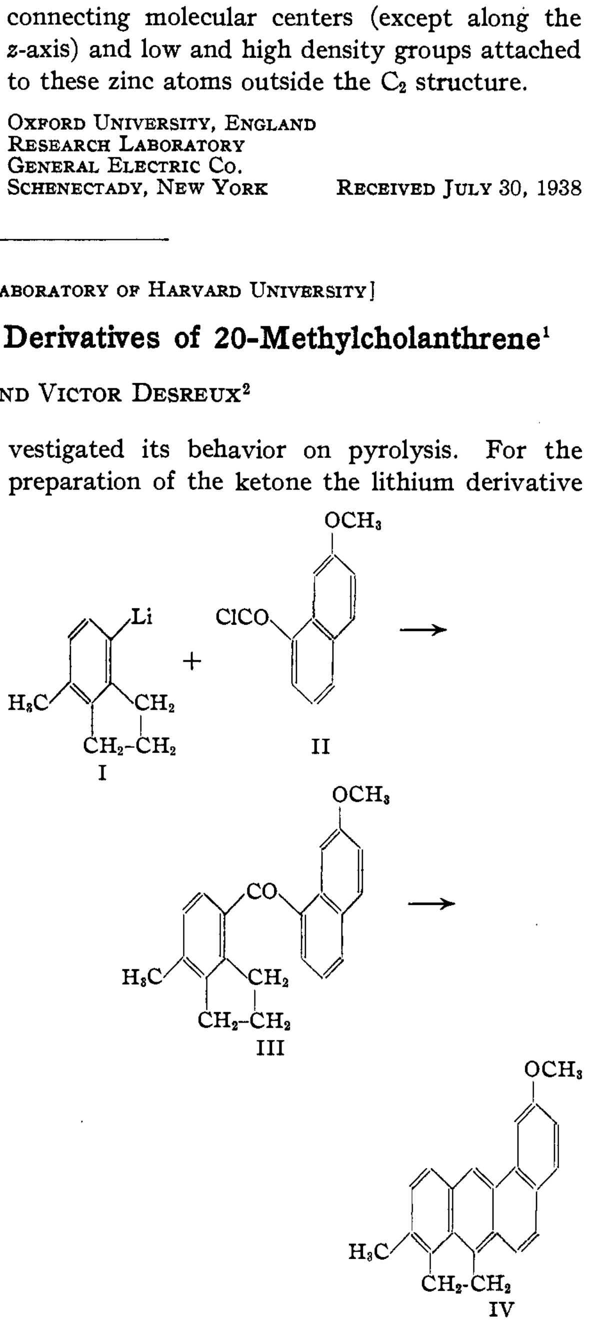
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

The Synthesis of 2- and 6-Substituted Derivatives of 20-Methylcholanthrene[1]

BY LOUIS F. FIESER AND VICTOR DESREUX[2]

Derivatives of carcinogenic hydrocarbons having active functional groups are of interest to the general problem of attempting to correlate structure and biological activity, and if, among such compounds, derivatives can be found which possess marked carcinogenic activity they may be of value in providing a route to the preparation of interesting glycosides or conjugated proteins.

The only functional derivatives of methylcholanthrene previously known are 3-hydroxy-20-methylcholanthrene,[3,4] and its ether and acetate, 3-chloro-,[4] and 3-cyano-20-methylcholanthrene.[4] These were all made available by application of the Fieser–Seligman methylcholanthrene synthesis[5] to suitable methoxy- and chloro-substituted ketones, and the successful outcome of the syntheses shows that these substituent groups are capable of withstanding the pyrolytic conditions of the Elbs reaction when located in a position corresponding to the 3-position of methylcholanthrene. This is a β-position and is located in the terminal angular nucleus at a point rather remote from the site of ring closure, and it seemed likely that the other β-position 2 in this ring also would offer an environment favorable for the retention of an active functional group. Consequently, as a next step in the search for compounds of the type desired we synthesized the ketone III and investigated its behavior on pyrolysis. For the preparation of the ketone the lithium derivative I from 4-methyl-7-chlorohydrindene[5,6] was condensed with the chloride of 7-methoxy-1-naph-



I

II

III

IV

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(1) This investigation was conducted as part of a program of research receiving support from the National Cancer Institute.

(2) Fellow of the Belgian American Foundation; Aspirant du Fonds National de la Recherche Scientifique Belgique.

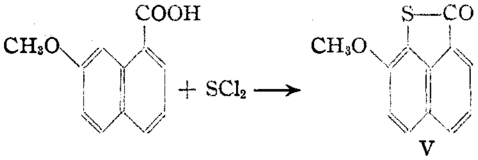
(3) Cook and de Worms, *J. Chem. Soc.*, 1825 (1937).

(4) Fieser and Riegel, THIS JOURNAL, **59**, 2561 (1937).

(5) (a) Fieser and Seligman. *ibid.*, **57**, 942 (1935); (b) **58**, 2482 (1936).

(6) If the condensation of such a lithium derivative with a suitable nitrile constitutes a "modification of the original method of Fieser and Seligman," as stated by Cook and de Worms,[3] it may be noted that the modification was introduced not by these workers but by Fieser and Hershberg, *ibid.*, **59**, 394 (1937).

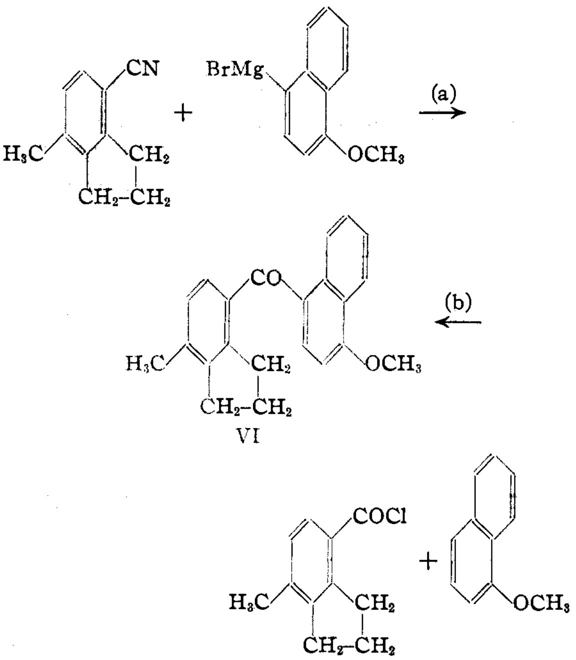
thoic acid, prepared by the synthesis described by Fieser and Holmes.[7] The 7-methoxy-1-naphthoyl chloride was prepared satisfactorily with the use of phosphorus pentachloride, but an unexpected difficulty was encountered on employing a commercial lot of thionyl chloride which, being colorless, had not been further purified. The acid chloride in this case was contaminated with a persistent yellow impurity, and when this was isolated it was found to contain sulfur and to have the properties of a lactone (insoluble in cold alkali, slowly dissolved by alcoholic alkali). From the analyses and properties it is probable that the yellow substance has the structure V and that it arises from the condensation of sulfur dichloride, present in the commercial thionyl chloride, into the activated 8(α)-position of the acid or acid chloride, with subsequent ring closure.



V

The pyrolysis of the ketone III proceeded satisfactorily and pure 2-methoxy-02-methylcholanthrene (IV) was obtained in 40% yield, which is practically the same as that obtained in this Laboratory[4] in the preparation of the isomeric 3-methoxy compound. The hydrolysis, however, presented special difficulties, for the 2-ether is unusually resistant to acid cleavage and the free hydroxy compound is very sensitive and decomposes extensively under the influence of acids or bases, or when heated in the presence of oxygen. The hydrolysis consequently could not be carried to completion without destruction of all of the product formed and it was necessary to work with mixtures. It was found, however, that after acetylation of the crude mixture the more stable acetate can be separated from the ether and purified satisfactorily, and careful saponification of the pure acetate afforded the hydroxy compound in such a condition that it could be purified.

The synthesis of the 2- and 3-methoxy compounds having been accomplished successfully by the Elbs reaction, we investigated the possibility of preparing 6-methoxy-20-methylcholanthrene by the pyrolysis of the ketone VI. As indicated in the formulas, this was synthesized by two different methods, the first of which fully establishes the structure of the ketone. The 4-bromo-1-naphthol required for this synthesis (a) was prepared by the bromination of α-naphthol with iodine bromide according to Militzer,[8] but the purification was very tedious and the yield of satisfactory material was only 23%. The Friedel and Crafts synthesis (b) was therefore investigated and found to give the identical ketone in excellent yield. The 4-methylhydrindene-7-carboxylic acid required was prepared conveniently by heating the corresponding 7-chloro compound with cuprous cyanide, pyridine, and water at 210°; this gave some acid and some amide, and the latter was easily converted into acid by alkaline hydrolysis.



VI

Since the methoxyl group of the ketone VI is in an α-position of a ring involved in the cyclization, there is more opportunity here than with the previously investigated compounds for disturbance of the substituent in the course of the Elbs reaction conducted at a temperature above 400°. Such disturbance evidently occurred, for in several experiments the only product that could be isolated was methylcholanthrene, and when the total crude product was submitted to acid hydrolysis no trace of a phenolic substance was obtained. We are not prepared to say that conditions cannot be found permitting retention of the methoxyl group, but record merely that under the conditions found most satisfactory for the pyroly-

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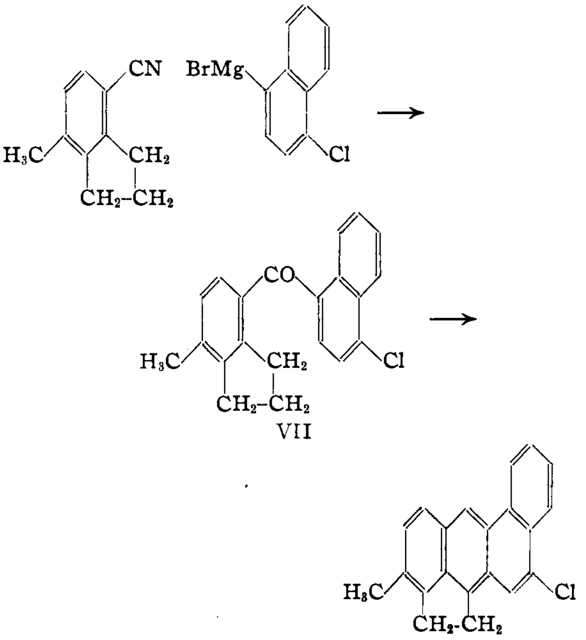
[7] Fieser and Holmes, THIS JOURNAL, **58**, 2319 (1936).

[8] Militzer, *ibid.*, **60**, 256 (1938).

sis of related ketones the methoxy group in this position is easily eliminated.

It was of interest to learn whether a chlorine atom in the same position would suffer a similar fate, and for this purpose we required 5-methyl-7-(4′-chloro-1′-naphthoyl)-hydrindene (VII). The synthesis was accomplished by the Grignard reaction indicated in the chart, the 1-bromo-4-chloronaphthalene being prepared conveniently in a very pure form from the known[9] acetyl-4-bromo-1-naphthylamine.

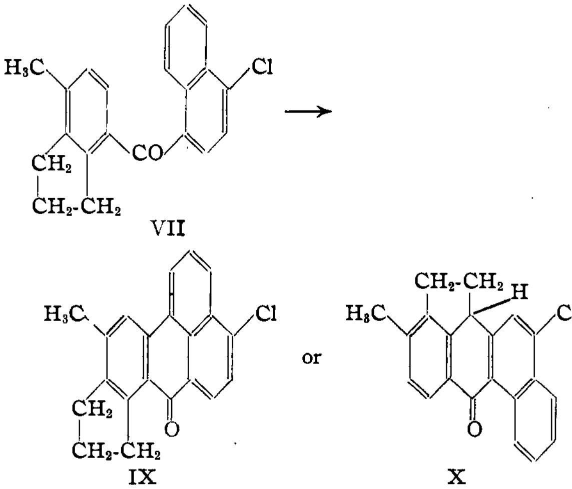


VII

VIII

The direct bromination of α-chloronaphthalene was also tried but gave a mixture from which the desired isomer was isolated in only very poor yield. When the chloro ketone VII is heated no change occurs until a critical temperature of about 410° is reached and at that point a vigorous reaction sets in with loss of water and evolution of hydrogen chloride. The reaction is exothermic, and if the external temperature is not decreased the product is largely destroyed. By quickly lowering the bath temperature as soon as the reaction had started, it was possible to conduct the pyrolysis with sufficient success to permit the isolation of 6-chloro-20-methylcholanthrene (VIII) in a pure condition, if in only 1.2% yield. The reaction mixture contained in addition a considerable quantity of methylcholanthrene, but the sparing solubility of the chloro compound made possible its isolation in a condition believed to be free from contamination with the carcinogenic hydrocarbon. The chloro compound is rather sensitive and decomposes when heated at the melting point in the presence of air, but it is nevertheless transformed very smoothly into the nitrile when heated with cuprous cyanide in pyridine. The nitrile is very resistant to hydrolysis, and in a few trial experiments we did not succeed in preparing the corresponding acid. 6-Chloro- and 6-cyano-10-methylcholanthrene are of particular interest because the position of substitution corresponds to that of 3-substituted 1,2-benzanthracenes, some of which have been found to possess carcinogenic activity.[10]

An interesting observation was made in the course of a preliminary attempt to prepare the chloro ketone VII by the Friedel and Crafts reaction between 4-methylhydrindene-7-carboxylic acid chloride and α-chloronaphthalene. Little reaction took place at −10°, but at room temperature in tetrachloroethane solution there was produced a yellow substance having two hydrogen atoms less than the expected ketone VII. After the latter compound had been made available by the Grignard synthesis it was found that the same yellow condensation product can be obtained by the action of aluminum chloride on the ketone in tetrachloroethane solution at 25°. From the composition of the condensation product and the structure of the intermediate from which it can be obtained, it would seem that the substance is probably either a benzanthrone derivative IX or the cholanthrone X.



VII

IX

X

While conclusive evidence of the structure cannot

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[9] Meldola, *Ber.*, **11**, 1904 (1878).

[10] Fieser, Hershberg, Long, Jr., and Newman, THIS JOURNAL, **59**, 475 (1937).

be given, the following observations appear to be significant. If the substance were a cholanthrone, it would be expected to yield a cholanthranol acetate on treatment with acetic anhydride in pyridine, but the yellow compound failed to react under these conditions and was recovered unchanged. The alternate structure IX, on the other hand, is consistent with the behavior of the substance in a qualitative test with zinc dust, sodium acetate and acetic anhydride. It has been observed recently in this Laboratory that benzanthrones can be converted by this method of reductive acetylation into easily hydrolyzed dihydrobenzanthrone-enol acetates,[11] and the compound in question gave evidence of reacting in this manner, although the product proved to be quite unstable and was not isolated in a pure condition. The structure therefore is probably that of formula IX, and the observations suggest that the α-benzoylnaphthalene derivative VII undergoes the Scholl peri-condensation under the influence of aluminum chloride in tetrachloroethane solution at a temperature lower than is required to produce benzanthrones by the usual process using aluminum chloride alone or sodium aluminum chloride.

In connection with the attempt to synthesize the ketone VII by the Friedel and Crafts reaction, we investigated the action of aluminum chloride on α-chloronaphthalene in tetrachloroethane at room temperature and found that a part of the material was isomerized to β-chloronaphthalene. This isomerization was observed some time ago by Roux,[12] but at a considerably higher temperature. There was also a higher boiling fraction probably similar to that obtained by Weitzenböck and Seer[13] at a higher temperature and found to contain perylene and dinaphthyl derivatives.

Experimental Part[14]

2-Hydroxymethylcholanthrene

Preparation of Starting Materials.—In the preparation of **β-(4-methoxybenzoyl)-propionic acid** by the procedure of Fieser and Hershberg[15] it was found unnecessary to keep the mixture at 0–5° after adding the aluminum chloride; we allowed the mixture to stand at room temperature for three days and obtained purified acid, m. p. 146.5–147°, in 90% yield. Reduction (Martin[16]) gave **γ-(4-methoxyphenyl)-butyric acid,** m. p. 60.5°, in 90% yield, and the ethyl ester (96% yield) boiled at 176.5–177° (15 mm.). **α-Keto-δ-(4-methoxyphenyl)-valeric acid** was prepared by condensing the ester and ethyl oxalate with the use of sodium ethylate following the procedure of Fieser and Holmes,[7] but our observations indicated that the time specified for the condensation is insufficient for complete conversion. Probably a longer period should be allowed also for effecting decarboxylation. The following method of purification gave a better product than that previously described and made possible the recovery of starting material. After decarboxylation, the crude keto acid was treated with dimethyl sulfate in warm alkali and after clarifying the solution with Norite the sodium salt of the keto acid was allowed to crystallize. After this purification through the crystalline salt, the liberated acid was obtained directly in a very pure condition and melted sharply at 76–77°. The material failing to crystallize as the sodium salt was refluxed again with 15% sulfuric acid (five hours) and put through the above process, but as the product seemed to be a mixture it was esterified and distilled. The main fraction (b. p. about 160° at 2 mm.) after saponification was found to consist chiefly of γ-(4-methoxyphenyl)-butyric acid, while the fraction boiling at 190–200° (2 mm.) was a mixture of the ester of this acid and the keto ester. A separation was accomplished easily by taking advantage of the greater ease of saponification of the keto ester, and by purifying the keto acid as sodium salt. In all 444 g. of ethyl γ-(4-methoxyphenyl)-butyrate gave 223 g. (50%) of very pure keto acid and 110 g. (25%) of recovered starting material.

7-Methoxy-Δ'-dihydro-1-naphthoic acid was prepared as described[7] except that the acid was used for cyclization rather than the ester. The crude material was remethylated in alkali and the solution was clarified and acidified. Acetone proved unsatisfactory as a solvent for crystallization and this was done from water, giving pure acid, m. p. 117.5°, in 65% yield. **7-Methoxy-1-naphthoic acid** was prepared as described[7] and purified by remethylation of the sodium salt; m. p. 169–170°, yield 87%.

In preparing **4-methyl-7-chlorohydrindene**[5b] it was found convenient, after cyclizing the β-chloropropionyl derivatives, to take up the ketone mixture in benzene and wash the solution with saturated sodium chloride solution at 50–60°. Decantation was then easily accomplished and after removing the solvent the product was distilled quickly; yield 60%. No other changes were made in the procedure and the yields agreed closely with those reported.

Action of Thionyl Chloride on 7-Methoxy-1-naphthoic Acid.—The acid was treated with 3–4 equivalents of commercial thionyl chloride (Fraenkel and Landau, colorless), and after it had dissolved the solution was warmed for about one-half hour longer. The excess reagent was removed in vacuum and the product was distilled at 2 mm. (liberation of hydrogen chloride noted). The distillate was a yellow, unhomogeneous solid, m. p. 75–85°, and as trial crystallizations were not promising the material was saponified with a hot sodium hydroxide–acetone mixture. Distillation of the acidic material gave a yellow solid, m. p. 158–168°, and on crystallization from dilute acetone this yielded a product melting at 167° and giving no de-

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[11] Fieser and Hershberg, unpublished observation.

[12] Roux, *Ann. chim.*, [6], **12**, 349 (1887).

[13] Weitzenböck and Seer, *Ber.*, **46**, 1994 (1913).

[14] All melting points are corrected. Analyses by Mrs. Verna R. Keevil, Dr. C. Fitz and the Arlington Laboratories.

[15] Fieser and Hershberg, THIS JOURNAL, **58**, 2314 (1936).

[16] Martin, *ibid.*, **58**, 1438 (1936).

pression when mixed with methoxynaphthoic acid. The material was still yellow, however, and it was noted that it dissolved with difficulty in alkali, and only on warming, and that it contained sulfur. Six crystallizations from benzene served to remove the impurity and gave pure white methoxynaphthoic acid, m. p. 170° (neut. equiv. 200; calcd. 202). The yellow benzene mother liquors were extracted three times with 10% alkali to remove the remaining acid, and on concentrating the benzene solution the by-product was obtained in a nicely crystalline condition. Purified further for analysis, the **sulfur compound** (V?) formed bright yellow needles melting constantly at 143.5–144°. The substance is attacked only very slowly by boiling aqueous alkali; it dissolves in hot alcoholic alkali with almost complete loss of color and precipitates in the original condition on acidification of the diluted solution.

Anal. Calcd. for $C_{12}H_8O_2S$: C, 66.63; H, 3.73; S, 14.83; mol. wt., 216. Found: C, 66.87; H, 3.82; S, 14.76; mol. wt. (micro Rast), 221, 231.

7-Methoxy-1-naphthoyl Chloride.—A mixture of 10 g. of the acid and 12 g. of phosphorus pentachloride was warmed at 50° until solution was complete and the phosphorus oxychloride was removed in vacuum at 50°. As the clear mixture was found to darken rapidly even at this temperature it seemed inadvisable to attempt to distil the acid chloride, and the mixture therefore was cooled and extracted with 150 cc. of dry petroleum ether (b. p. 30–60°). Evaporation gave 8 g. (73%) of pale yellow crystalline product, m. p. 65–75°, and titration with alkali indicated the presence of 90% of the desired acid chloride. When prepared immediately before use, this material was satisfactory for the Grignard reaction, but it is subject to ready hydrolysis and does not keep well. It dissolves readily in warm alkali, but not in the cold. A recrystallized sample melted at 78.5°.

4-Methyl-7-(7′-methoxy-1′-naphthoyl)-hydrindene (III).—A three-necked flask provided with a stirrer, condenser and funnel was charged under nitrogen with 1 g. of lithium (cut under dry ether into small pieces), 10 cc. of ether and 1 g. of 4-methyl-7-chlorohydrindene. The reaction started after warming and stirring for about ten minutes, and in the course of three hours 7 g. more of the chloro compound in 90 cc. of ether was introduced, adding benzene as required to keep the lithium compound in solution. After twenty hours the reaction was complete; the solution was then forced under nitrogen pressure into a stirred benzene solution of 9 g. of 7-methoxy-1-naphthoyl chloride, while cooling to 0°. The mixture was eventually brought to boiling, the ether was allowed to distil and refluxing was continued for two hours. After the careful addition of dilute acid, the mixture was neutralized and steam distilled in the presence of soda. The solid residue, after being dried in ether, distilled at 260–270° (3 mm.), but in order to remove traces of acid or acid chloride the distillate was taken into an acetone-alkali mixture and boiled for two hours. A second distillation, followed by crystallization from ether–petroleum ether, gave colorless prisms melting at 91.4–91.6°; yield 7 g. (48%).

Anal. Calcd. for $C_{22}H_{20}O_2$: C, 83.51; H, 6.37. Found: C, 83.60; H, 6.27.

2-Methoxy-20-methylcholanthrene (IV).—One gram of the above ketone was heated in a bath kept at 405° for fifteen minutes and the temperature was then rapidly raised to 420°. Once this temperature had been reached the mixture was cooled and distilled at 3 mm. The distillate was taken into benzene and the solution filtered through a tower of activated alumina and concentrated. Satisfactory crystalline material was in this way obtained without difficulty in total yield of 40%. When the ketone (2 g.) was heated in the presence of zinc dust (0.5 g.) loss of water occurred at exactly the same temperature as above and the total yield was 36%.

The methoxy compound on recrystallization from benzene–ether formed yellow prisms melting constantly at 163–163.4°. Like the 3-methoxy isomer,[4] the substance exists in two crystalline forms, for on standing in contact with the mother liquor the prisms are slowly transformed into needles; both forms have the same melting point.

Anal. Calcd. for $C_{22}H_{18}O$: C, 88.56; H, 6.08. Found: C, 88.43; H, 5.95.

The picrate crystallizes from alcohol as brown-black needles, m. p. 185.5–186°.

Anal. Calcd. for $C_{22}H_{18}O \cdot C_6H_4O_7N_3$: N, 7.97. Found: N, 7.72.

2-Acetoxy-20-methylcholanthrene.—Because of the great resistance of the methoxy derivative to hydrolysis and the sensitivity of the hydroxy compound to acid, alkali, and oxidation, the isolation of the hydrolysis product could only be accomplished by way of the acetate. In the first successful method found the conditions were similar to those employed by Cook and de Worms[3] for the 3-isomer, but somewhat more drastic. A suspension of 95 mg. of the ether in 3 cc. of glacial acetic acid and 0.5 cc. of constant boiling hydrobromic acid was sealed in a tube in an atmosphere of nitrogen and heated at 140° for three hours. The product was precipitated with water, collected and dried, and treated directly with acetic anhydride and sodium acetate under nitrogen. Dried in ether and fractionally crystallized from ethyl acetate, the product yielded in all 26 mg. (25%) of pure acetate. Some unchanged methoxy compound was still present but the acetate can be separated from this without difficulty by fractional crystallization. The pure acetate forms yellow micro prisms melting, when sealed into an evacuated capillary tube and introduced at a bath temperature of 210°, at 218–219°. When heated in the presence of air the sample turns black at about 210°.

Anal. Calcd. for $C_{23}H_{18}O_2$: C, 84.63; H, 5.56. Found: C, 84.59; H, 5.72.

In an attempt to increase the yield the methoxy compound (500 mg.) was warmed in a sealed tube on the steam-bath with 13 cc. of glacial acetic acid and 5 cc. of hydrobromic acid solution under nitrogen for fifteen hours. The solution became highly colored, but unchanged ether was still present. After acetylating the crude product, purification by fractional crystallization and sublimation in high vacuum at 210° gave 130 mg. (23.5%) of pure acetate.

In other trials it was found that demethylation does not occur at either 25 or 40° on shaking for several days. At higher temperatures decomposition to dark products invariably occurred and some ether always escaped hydrolysis. Attempts to isolate the hydroxy compound by chromatographic adsorption on alumina and elution of a pale blue fluorescent zone with benzene–alcohol gave no crystalline product, and separation with alkali led to extensive oxidation. Demethylation with aluminum chloride was tried without success.

2-Hydroxy-20-methylcholanthrene.—For hydrolysis a mixture of 200 mg. of the acetate, 35 cc. of alcohol and 2 cc. of 50% aqueous sodium hydroxide solution was sealed in a tube under nitrogen and heated at 40°. In about five minutes the acetate dissolved, and the deep orange-red solution was then diluted and acidified. The crude precipitated material was dried and sublimed in high vacuum, giving 120 mg. of crystalline yellow material, but this was still impure. A product of constant melting point was obtained by fractional crystallization from benzene, in which the hydroxy compound is sparingly soluble, but the yield of pure product was only 49 mg. (28%). The substance forms fine yellow needles which, when heated in an evacuated capillary in a bath preheated to 220°, melt at 225.5–226°. In concentrated sulfuric acid the substance gives an orange color turning blue on heating.

Anal. Calcd. for $C_{21}H_{16}O$: C, 88.70; H, 5.67. Found: C, 88.63; H, 5.55.

The picrate forms brown needles from benzene and melts, under the above conditions, at 204°.

Anal. Calcd. for $C_{21}H_{16}O{\cdot}C_6H_4O_7N_3$: N, 8.19. Found: N, 8.04.

Synthesis and Pyrolysis of 4-Methyl-7-(4′-methoxy-1′-naphthoyl)-hydrindene

Preparation of Starting Materials.—For the preparation of **4-bromo-1-naphthol** the procedure of Militzer[8] was modified in the following respects. The solution of bromine and iodine in acetic acid was added dropwise to a vigorously stirred solution of α-naphthol in an atmosphere of nitrogen at 10°, and at the end of the reaction the solution was added by drops to the sulfite solution under mechanical stirring, which avoids occlusion of iodine by the precipitate. After complete precipitation with sodium bicarbonate the washed and dried product was crystallized once from chloroform and several times from aqueous alcohol. The purification is very tedious and the yield of pure material, m. p. 120° (constant), was only 23%. **4-Bromo-1-methoxynaphthalene,** prepared with the use of excess dimethyl sulfate, was obtained in 60% yield as an oil, b. p. 182° (15 mm.).

4-Methyl-7-cyanohydrindene was prepared as described by Fieser and Seligman[5b] (E. B. H. procedure) except that a few cc. of acetonitrile was added to take up traces of water and the heating was conducted at 240–245°. It was found advisable to use very pure chloro compound. The yield in several experiments was close to 90%. **4-Methylhydrindene-7-carboxylic acid**[5b] was most conveniently prepared directly from the chloro compound. A mixture of 12.5 g. of 4-methyl-7-chlorohydrindene, 7 g. of anhydrous cuprous cyanide, 10 cc. of pyridine and 2 cc. of water was heated in a sealed tube at 200–210° for twenty hours (probably a longer period would be better). The mixture was treated with aqueous ammonia, the solid material was collected and extracted with benzene and the ammoniacal filtrate was extracted with the same solvent. The ammonia solution was evaporated until copper oxide precipitated, and on acidifying the filtered solution methylhydrindene-carboxylic acid precipitated (1.6 g.). The combined benzene extracts, after being washed with bicarbonate solution and dried, afforded 8 g. of the corresponding amide on concentration, and the amide was transformed into acid by refluxing with 20% sodium hydroxide solution, the total over-all yield of acid being 75%. The Rosenmund reaction[17] was tried without success, no acid being found on acidification. **4-Methylhydrindene-7-carboxylic acid chloride** was obtained without difficulty from the acid (4.5 g.) and phosphorus pentachloride (5.2 g.) at 40–50° (ten minutes), distilling the product (low melting solid) in vacuum; yield 4 g. (80%).

Grignard Synthesis.—The reaction between 4-bromo-1-methoxynaphthalene (12.5 g. in 60 cc. of ether) and magnesium (1.5 g.) started very easily and was complete in three hours, some benzene being added to keep the complex in solution. The Grignard solution was cooled in ice and 8.5 g. of 4-methyl-7-cyanohydrindene was added in benzene; after distilling the ether the mixture was refluxed for three hours and allowed to stand overnight. After adding water and acid the benzene was removed by distillation, and hydrolysis of the ketimine was accomplished by adding toluene, acetic acid and concentrated hydrochloric acid and refluxing for four hours. The toluene solution was dried and distilled, the ketone boiling at about 262° (2 mm.). Crystallized from ether, **4-methyl-7-(4′-methoxy-1′-naphthoyl)-hydrindene** formed colorless prisms, m. p. 121.5–122°; yield, 11 g. (66%).

Anal. Calcd. for $C_{22}H_{20}O_2$: C, 83.51; H, 6.37. Found: C, 83.26; H, 6.30.

Friedel and Crafts Synthesis.—A mixture of 4 g. of the chloride of 4-methylhydrindene-7-carboxylic acid, 30 cc. of purified tetrachloroethane and 4 g. of 1-methoxynaphthalene was stirred at 0° and 6.5 g. of aluminum chloride was added in portions over six hours. After standing overnight at room temperature, the mixture was decomposed with acid, steam distilled, and the product distilled in vacuum. To remove traces of acid, the distillate was heated with acetone–alkali and the recovered material melted at 118.5°; yield, 5.2 g. (82%). Crystallized from ether, the substance melted at 121.5° and did not depress the melting point of the above sample.

Pyrolysis.—In a typical experiment 2 g. of the ketone was heated at 405° for fifteen minutes and the product then was distilled in vacuum. A solution of the distillate in benzene was filtered through a tower of alumina, and after many crystallizations there was obtained a crystalline yellow substance melting at 174.5° and giving no depression when mixed with a sample of methylcholanthrene, m. p. 175.5°. No other substance was encountered, and the following observation indicates that the desired methoxy compound was not present. The material (150 mg.) obtained from a pyrolysis similar to that described and purified by passage through an adsorption tower was boiled with 10 cc. of glacial acetic acid and 1 cc. of hydrobromic acid for two hours, the solution was diluted and extracted with benzene. On extraction with dilute alkali there was no coloration in the alkali layer and no precipitate on acidification.

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(17) Rosenmund and Struck, *Ber.*, **52**, 1749 (1919).

Pyrolysis in the presence of zinc dust gave the same results.

6-Chloro-20-methylcholanthrene

1-Bromo-4-chloronaphthalene. (a) By Direct Bromination.—As no mention of this possible method was found in the literature, a trial was made in which 50 cc. of bromine was added in twenty-four hours to a stirred solution of 162 g. of carefully fractionated (1-meter column) α-chloronaphthalene in 1 liter of carbon tetrachloride at 50–60°. After refluxing overnight the solvent was removed with steam and the residue was treated with steam in the presence of alkali, fractionated at 3 mm. and crystallized from acetic acid. After six crystallizations the 1-bromo-4-chloro compound was obtained in a pure condition, m. p. 67° (compare 66.5–67°[18]), but the yield was only 6.5 g.

(b) **From Acetyl-α-naphthylamine.**—The acetyl compound (200 g.) was brominated in glacial acetic acid solution with vigorous stirring at about 10° according to Meldola,[9] and the crystallized product was hydrolyzed[19] by refluxing with 3 liters of alcohol and 300 cc. of concentrated hydrochloric acid for three hours. Most of the resulting amine hydrochloride crystallized on cooling in a very pure form, and a further crop was obtained on concentrating the solution. The total yield was 215 g. (overall yield, 77%). The amine liberated from the salt melted at 102.5° (compare[19] 102°).

For diazotization 35 g. of 4-bromo-1-naphthylamine hydrochloride in 650 cc. of water and 65 cc. of concentrated hydrochloric acid was stirred at 0° and treated with a cold aqueous solution of 20 g. of sodium nitrite. After one hour a cold aqueous solution of 10 g. of urea was added and after forty-five minutes the solution was added slowly to a stirred solution of 33 g. of cuprous chloride in 350 cc. of concentrated hydrochloric acid at 5–10°. The mixture was allowed to come to room temperature, with continued stirring, and at 15–20° there was a color change and decomposition of the complex occurred. After heating on the steam-bath until the reaction product melted, the mixture was cooled and extracted with benzene. On distillation the product boiled at 159–160° (3 mm.) and melted at 65–66°. One crystallization gave very pure 1-bromo-4-chloronaphthalene, m. p. 67.5°, and the yield was 82–84% in several experiments.

When copper powder was used as catalyst in the Sandmeyer reaction the yield was the same and the only difference noted was that there was a shorter induction period before evolution of nitrogen commenced, although the decomposition occurred at the same temperature.

4-Methyl-7-(4′-chloro-1′-naphthoyl)-hydrindene (VII).—The reaction of 1-bromo-4-chloronaphthalene (6.5 g.) in ether (60 cc.) and magnesium (0.7 g.) started very easily and was complete in two hours, some benzene being added to keep the complex dissolved. The solution was cooled in ice and 4.2 g. of 4-methyl-7-cyanohydrindene in benzene solution was added with stirring. After removing the ether and refluxing for three hours, the product was decomposed with dilute acid and the ketimine hydrolyzed by refluxing with toluene, acetic and hydrochloric acids, as above. The hydrolysis proceeded very slowly and sometimes refluxing had to be continued for fifteen hours. The toluene layer was washed with water and with bicarbonate solution and the aqueous layer was extracted with ether. The material from the toluene–ether solutions was distilled at 3 mm. and the product crystallized from benzene–ether. The yield of very satisfactory ketone was 6.2 g. (72%), and the purest sample formed prisms, m. p. 144.5–145°.

Anal. Calcd. for $C_{21}H_{17}OCl$: C, 78.62; H, 5.34. Found: C, 78.62; H, 5.47.

In one experiment the ketimine hydrochloride was collected before hydrolysis, and in this case the distilled ketone was directly pure (m. p. 144.5–145°) and required no crystallization; the yield, however, was slightly lower (65%).

6-Chloro-20-methylcholanthrene (VIII).—The Elbs reaction with the above ketone proceeds very poorly, and in order to obtain any of the desired chloro-hydrocarbon it is necessary to control the temperature very carefully. Otherwise the sole product that can be isolated is methylcholanthrene. A critical temperature must be reached before loss of water begins and at this temperature considerable hydrogen chloride is evolved and the reaction proceeds exothermally with extensive decomposition.

In the most successful experiment 80 g. of ketone was pyrolyzed in two lots as follows. The bath was heated to 410° and as soon as the reaction started the temperature was decreased to 360–370°. Evolution of water continued to occur at this temperature for about ten minutes, after which the bath was again heated to 410°. The very dark, tarry mixture was then distilled at 3 mm. pressure and a solution of the distillate was passed through an adsorption tower of alumina. Concentration of the solution afforded a clean, crystalline product, but this proved to be a mixture which was separated only by a tedious process of fractional crystallization. Chloromethylcholanthrene is but sparingly soluble in benzene and was obtained as the top fraction, the yield of thoroughly purified material, m. p. 233.5–233.8° (see below), being 940 mg. (1.2%). There was a second fraction of nearly pure material (140 mg.), m. p. 230°, and 450 mg. of a mixture of the chloro compound and the hydrocarbon. From the residue there were isolated 1.7 g. of nearly pure methylcholanthrene and 8 g. of very impure hydrocarbon picrate.

After very careful purification to remove traces of the hydrocarbon, 6-chloro-20-methylcholanthrene formed glistening, pale yellow needles, m. p. 233.5–233.8° (evacuated capillary, preheated bath).

Anal. Calcd. for $C_{21}H_{15}Cl$: C, 83.29; H, 4.99; Cl, 11.71. Found: C, 83.28; H, 5.18; Cl, 11.77.

A pure picrate could not be obtained from the chloro compound, possibly because of the low solubility of the substance in the usual solvents The separation of the pyrolysis mixture through the picrate was tried but found unsatisfactory.

We tried carrying out the Elbs reaction by distilling the ketone through a glass coil heated at 520° in a nitrate bath but little pyrolysis occurred under these conditions.

6-Chano-10-methylcholanthrene.—A mixture of 120 mg. of the pure chloro compound, 50 mg. of cuprous cyanide, 0.2 cc. of pyridine and a trace of acetonitrile was heated in a sealed tube at 230–240° for twenty hours. The

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[18] Beattie and Whitmore, *J. Chem. Soc.*, 50 (1934).

[19] Gomberg and Blicke, THIS JOURNAL, **45**, 1765 (1923).

cooled mixture, which was very clean and partly crystalline, was washed out with water and ammonia and the precipitated cyano compound was collected, washed with ammonia water and dried. It was crystallized from glacial acetic acid (sparingly soluble) and from pyridine-benzene and obtained in the form of long yellow needles m. p. 268-268.5° (evacuated capillary, preheated bath). The yield was 75 mg. (66%).

Anal. Calcd. for $C_{22}H_{15}N$: C, 90.07; H, 5.15. Found: C, 89.87; H, 5.29.

The nitrile is very resistant to hydrolysis and was recovered unchanged after being heated with concentrated hydrochloric acid in a tube at 118° for one day. On attempting to convert the chloro compound (140 mg.) directly into the acid with cuprous cyanide, pyridine and water at 230° (twenty hours), the chief product appeared to be the amide (insoluble in dilute ammonia, decomposes when heated above 300°) and only 10 mg. of an acidic product was obtained.

Condensation Product, Probably 2-Chloro-7-methyl-5,6-cyclopenteno-1,9-benzanthrone-10 (IX). (a) By the Friedel and Crafts Reaction.—In a first attempt to condense the chloride of 4-methylhydrindene-4-carboxylic acid with α-chloronaphthalene in the presence of aluminum chloride, the chloro compound was taken in excess and no other solvent was employed. No condensation was observed. In another experiment a mixture of 3.5 g. of the acid chloride, 30 cc. of α-chloronaphthalene and 10 cc. of tetrachloroethane was stirred in ice and 6 g. of aluminum chloride was added during six hours. After standing for several hours at room temperature the mixture was decomposed and the product distilled at 3 mm. By careful distillation it was possible to obtain a certain amount of a crystalline yellow product (b. p. 260°, m. p. 210°, dec.), although the substance is very sensitive to heat and much of the material present was destroyed. Crystallization from benzene (moderate solubility) gave 150 mg. of the pure substance. This forms yellow needles melting at 215° (evacuated capillary, preheated bath). It is insoluble in hot alkali and gives a positive test for chlorine. Decomposition occurred in an attempted molecular weight determination in camphor.

Anal. Calcd. for $C_{21}H_{15}OCl$: C, 79.11; H, 4.74. Found: C, 79.02; H, 4.84.

It may be noted that the Friedel and Crafts reaction is complicated by the sensitivity of α-chloronaphthalene to aluminum chloride. A solution of the substance (5 g.) in tetrachloroethane (40 cc.) was treated at 0° with aluminum chloride (7 g.), and after standing overnight at room temperature the product was recovered and distilled. From the first fraction there was isolated a solid product melting, after crystallization, at 56.5° and identified by mixed melting point determinations as β-chloronaphthalene. There was also considerable high boiling material present, but this appeared to be a mixture and pure components were not isolated.

(b) **From the Ketone VII.**—The action of aluminum chloride (4 g.) on the ketone (5 g.) in tetrachloroethane (40 cc.) was tried at −10°, but most of the ketone was recovered unchanged. In a second experiment (3.5 g. of ketone) the aluminum chloride was added at 5° and the solution was then allowed to stand overnight at room temperature. On working up the mixture and distilling the product as above, there was obtained 150 mg. of the yellow condensation product melting at 213° (as above, 215° when further purified) and giving no depression when mixed with the first sample. Another fraction (500 mg.) proved to be a mixture of the yellow substance and the original ketone.

On attempted acetylation by boiling the yellow product in pyridine with acetic anhydride for five minutes, the starting material was recovered quantitatively in an unchanged condition. On treatment of the yellow compound (80 mg.) with acetic anhydride, sodium acetate and zinc dust a reaction occurred even on moderate heating and a practically colorless solution was obtained. The addition of water precipitated an amorphous product which became more and more yellow as attempts were made to purify it by crystallization, and no satisfactory product could be obtained.

Summary

The general cholanthrene synthesis developed in this Laboratory has been extended to the preparation of 2-methoxy-20-methylcholanthrene. The Elbs reaction proceeded satisfactorily and the corresponding hydroxy compound was obtained, if with some difficulty, on hydrolysis. In an attempt to synthesize 6-methoxy-20-methylcholanthrene by the same method the methoxyl group was completely eliminated. A similar lability of the substituent was noted with the corresponding chloro ketone, but 6-chloro-20-methylcholanthrene was isolated in a pure condition if in poor yield. This was transformed in good yield into the 6-nitrile by reaction with cuprous cyanide in pyridine.

It was noted that 4-methyl-7-(4′-chloro-1′-naphthoyl)-hydrindene suffers dehydrogenation in the presence of aluminum chloride in solution at room temperature and is converted into a yellow substance which probably is a benzanthrone derivative.

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RECEIVED JULY 7, 1938