2. These compounds did not exhibit any significant protective action against experimental streptococcic infections in mice.

GLENOLDEN, PENNSYLVANIA RECEIVED MAY 16, 1940

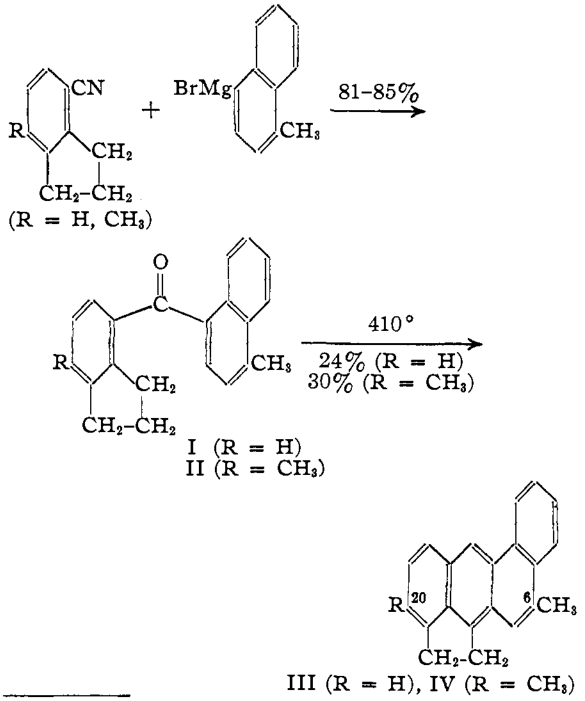
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

New Methyl and Dimethyl Derivatives of Cholanthrene

BY LOUIS F. FIESER AND DOUGLAS M. BOWEN

Information concerning the influence of alkyl substitution on the carcinogenic properties of cholanthrene is available with respect to only three positions.[1] 20-Methylcholanthrene, the only one of the twelve possible monomethyl isomers hitherto known, corresponds closely with the parent hydrocarbon in potency, while the 15,20- and 16,20-dimethyl homologs show diminished activity associated with the presence of the added substituent in the five-membered ring. It is of interest to study the effect of attaching alkyl groups elsewhere in the molecule, particularly for comparison with the results obtained in the 1,2-benzanthracene series where all twelve monomethyl derivatives are now known.

In one series of experiments we investigated the introduction of methyl at position 6 via the Elbs reaction. 4-Methyl-1-naphthylmagnesium bromide condensed smoothly with 4-cyanohydrindene and its 7-methyl derivative and after hydrolysis of the ketimines the ketones I and II were obtained easily in a crystalline condition. Pyrolysis of the monomethyl compound I gave a hydrocarbon mixture probably containing some cholanthrene and affording a pure methyl homolog in low yield only after considerable processing by adsorption and crystallization. 6-Methylcholanthrene (III) has a relatively high melting point (209°), which facilitated its characterization as to purity. Although some cleavage of the methyl group probably occurred, as indicated by the character of the reaction mixture, the retention of the alkyl radical at position 6 was much better than observed with other substituents. The methoxyl group was found to be completely eliminated from this position,[2] and although chlorine was in part retained the yield of 6-chloro compound was only 1.2%.[2] The Elbs reaction proceeded even better in the case of the dimethyl compound II, and 6,20-dimethylcholanthrene (IV) was produced in an easily purified condition and in yield comparable with that of the parent hydrocarbon.[3,4] The methyl group appearing at the 20-position seems to favor the condensation.



(R = H, CH$_3$)

I (R = H)
II (R = CH$_3$)

III (R = H), IV (R = CH$_3$)

A second series of experiments was concerned with substitution at position 22. 6-Methyl-4-cyanohydrindene (X), required as an intermediate for application of the Elbs synthesis, was obtained by the following process starting with acetyl *p*-toluidine (V).

Using the method of Cohen and Raper[5] with some modifications, this was converted into 4-bromo-3-chlorotoluene (VII). Since a preliminary trial of the condensation of a comparable Grignard derivative with the γ-chloropropyl ester of *p*-toluenesulfonic acid gave unpromising results, the desired three-carbon side chain was introduced via the aldehyde. The reaction of 4-methyl-2-chlorophenylmagnesium bromide with ethyl ortho-

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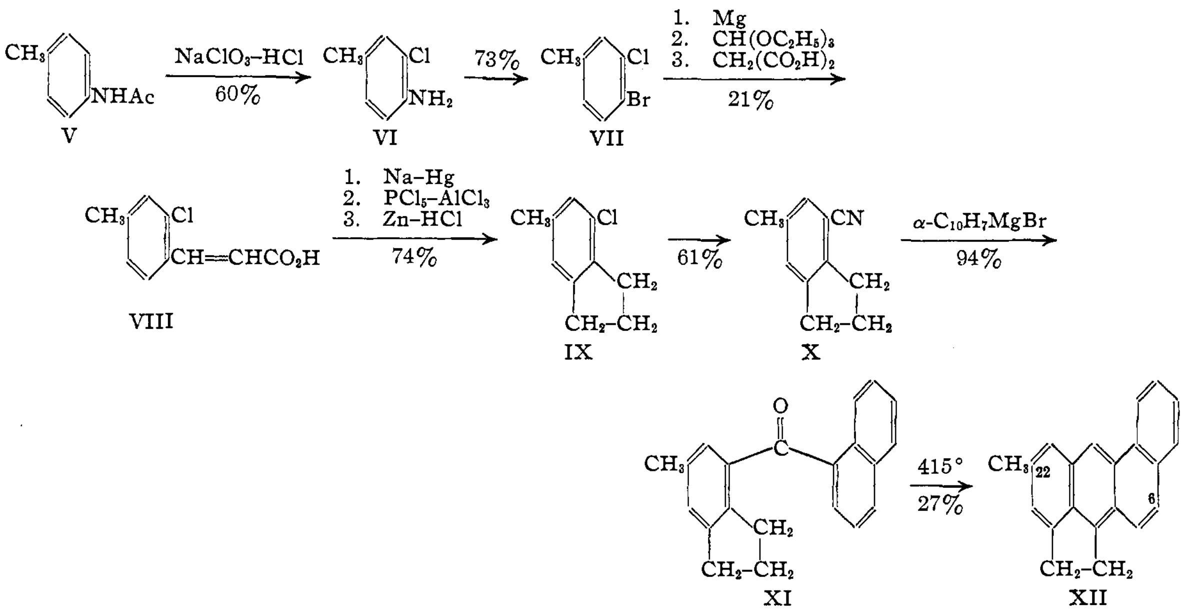
(1) For literature and summary of the biological data, see Fieser, *Am. J. Cancer*, **34**, 37 (1938).

(2) Fieser and Desreux, THIS JOURNAL, **60**, 2255 (1938).

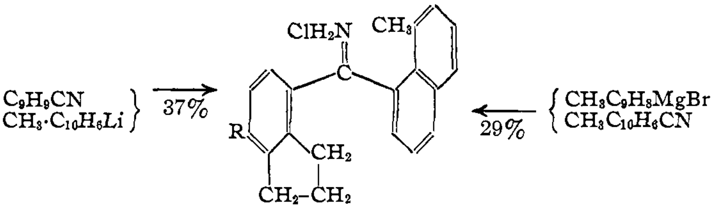
(3) Fieser and Seligman, *ibid.*, **57**, 2174 (1935).

(4) Bachmann, *J. Org. Chem.*, **3**, 434 (1938).

(5) Cohen and Raper, *J. Chem. Soc.*, **85**, 1269 (1904).



formate proceeded very poorly in comparison with the behavior noted with bromobenzene (90%), but the crude aldehyde liberated from the acetal condensed satisfactorily with malonic acid and gave the cinnamic acid derivative VIII in an easily purified form if in low over-all yield. Reduction of the unsaturated acid was effected quantitatively with sodium amalgam, and ring closure, Clemmensen reduction, and conversion to the nitrile X proceeded smoothly by standard methods.



XIII (R = H), XIV (R = CH3)

The condensation of α-naphthylmagnesium bromide with 6-methyl-4-cyanohydrindene gave the ketone XI in excellent yield as an oil which failed to crystallize, and this underwent smooth pyrolysis and afforded pure 22-methylcholanthrene (XII) in good yield. 6,22-Dimethylcholanthrene was also synthesized by employing 4-methyl-1-bromonaphthalene in the Grignard reaction; in this case the product was not as easily purified and the yield was lower (19%).

The present results, coupled with earlier observations,[2,6] show that in the Elbs synthesis of cholanthrenes substituents are more resistant to cleavage when located in either of the two terminal benzenoid rings than when present in the ring involved in the cyclization.

In a third series of experiments we attempted to synthesize 1-methyl- and 1,20-dimethylcholanthrene, but without success. The ketimine salt XIII was prepared by condensing 4-cyanohydrindene with the lithium derivative obtained from 1-methyl-8-chloronaphthalene,[7] while the homolog XIV was prepared by converting 1-methyl-8-chloronaphthalene to the nitrile and condensing this with 4-methyl-7-hydrindylmagnesium bromide. The yields were much lower than in comparable cases where the hindering *peri*-methyl group is absent, and the crystalline ketimine hydrochlorides resisted all attempts to effect hydrolysis. While Seligman[7] succeeded in hydrolyzing the analogous *o*-chlorophenyl 8-methyl-1-naphthyl ketimine hydrochloride with formic and sulfuric acids at 150°, this expedient was of no avail in the present case. It appears that the ortho methylene group of XIII and XIV contributes more to the total hindering effect than a chlorine atom in the same position.

The ultraviolet absorption spectra of the four new cholanthrene homologs were determined in alcoholic solution and the positions of the maxima are recorded in Table I. The spectra are almost identical in form with those of cholanthrene and

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

(7) Fieser and Seligman, *ibid.*, **61**, 136 (1939).

TABLE I

MAXIMA IN THE ULTRAVIOLET ABSORPTION SPECTRA OF THE CHOLANTHRENES (λ IN Å.) AND CORRESPONDING INTENSITIES (LOG E_M); SOLVENT, ETHANOL

Derivative of cholanthrene	Absorption data for bands characteristic of 1,2-benzanthracene (A, etc.[a]) and cholanthrene (a, etc.[b])									
	A(a)	B(b)	C(c)	D(d)	E	F(e)	G(f)	H(g)	I(h)	K
6-Methyl	2615	2755	2863	2975	3032	3238	3415	3598	3782	3945
	4.63	4.64	4.83	4.87	4.45	3.71	3.89	3.97	3.83	3.45
22-Methyl	2633	2758	2855	2960	3048	3262	3430	3582	3749	3934
	4.65	4.63	4.82	4.88	4.15	3.69	3.80	3.88	3.78	3.48
6,20-Dimethyl	2610	2768	2868	2983	3044	3255	3430	3605	3800	3953
	4.65	4.65	4.89	4.98	4.52	3.69	3.85	3.92	3.82	3.51
6,22-Dimethyl	2635	2780	2882	2985	3050	3310	3445	3600	3750	3970
	4.64	4.63	4.78	4.82	4.43	3.69	3.80	3.84	3.75	3.44

[a] See Fig. 1, ref. 10. [b] See Fig. 1, ref. 9.

20-methylcholanthrene[8,9] and are of the characteristic 1,2-benzanthracene type.[10] The bathochromic shift of the principal absorption band D of cholanthrene is very nearly the same for the 6-methyl group (25 Å.) as for the 20-methyl group (20 Å.), while a methyl at C_{22} is slightly less effective (10 Å.). The dimethyl compounds show a significantly greater displacement (33–35 Å.). The results confirm the structures assigned to the hydrocarbons.

Experimental Part

6-Methyl Series

Potassium 1-Methylnaphthalene-4-sulfonate.—The hydrocarbon can be sulfonated more effectively with chlorosulfonic acid than with sulfuric acid[7]; the following procedure is an improvement of that of Veselý and Štursa.[11]

A solution of 200 g. of α-methylnaphthalene in 425 cc. of carbon tetrachloride was agitated with a tantalum wire stirrer and kept at −7° to 0° by ice cooling while adding dropwise a total of 169 g. of chlorosulfonic acid. The sulfonic acid produced soon began to separate and toward the end of the addition the mixture became so pasty that it had to be stirred by hand. The supernatant solvent was decanted and the residue treated with 800 cc. of water. The material largely dissolved, and after filtration from a small quantity of yellowish precipitate (sulfone?) a layer of carbon tetrachloride was separated and rejected and the solution was neutralized with potassium hydroxide. The precipitated potassium sulfonate was collected, pressed free of liquor with the use of a rubber dam, and dried at 110° (22 mm.); yield 322 g. (88%). This material was satisfactory for bromination; a once crystallized sample of the *p*-toluidine salt melted at 228–230° (compare 227–229°[12]). The potassium salt can be recrystallized from water with 95% recovery.

1-Methyl-4-bromonaphthalene.—A further study of the method of Fieser and Seligman[7] indicated that precautions to avoid the formation of a dibromide are unnecessary. In a typical experiment 170 g. of crude potassium 1-methylnaphthalene-4-sulfonate in 1830 cc. of water was treated at 50° with 123 g. of bromine and 178 g. of sodium bromide in 570 cc. of water and after one-half minute the excess bromine was reduced with sodium bisulfite and the mixture was cooled and extracted with ether. The yield of purified methylbromonaphthalene was 98 g. (68%). Another run made with the moist sulfonate from 200 g. of α-methylnaphthalene gave 175.5 g. of once distilled bromide (over-all yield 56.5%). On redistillation through a 1-m. Podbielniak column the recovery was 172 g.

4-(4′-Methyl-1′-naphthoyl)-hydrindene (I).—The preparation of the Grignard reagent[7] from 4.4 g. of magnesium and 40.6 g. of 1-methyl-4-bromonaphthalene in 120 cc. of ether was complete after refluxing under nitrogen for fifteen hours. Benzene (50 cc.) was added and the ether was distilled until a b. p. of 55° had been reached; 17.9 g. of 4-cyanohydrindene[13] was then added in 50 cc. of benzene. After a first brisk reaction the mixture was refluxed and stirred for three days and decomposed with 300 g. of ice and 150 cc. of concentrated hydrochloric acid. After evaporating the benzene, with stirring, the solid ketimine hydrochloride was collected and refluxed overnight with 160 cc. of water, 100 cc. of concentrated hydrochloric acid, 100 cc. of acetic acid, and 100 cc. of toluene.[14] The collected product when distilled at about 215° at 1.5 mm. from a large flask (frothing) afforded 30.5 g. (85%) of satisfactory ketone as a slightly reddish-yellow, viscous oil. This crystallized readily on standing or treatment with solvent (m. p. 77–80°) and on repeated crystallization from ether-petroleum ether was obtained as fine white needles, m. p. 84.6–85.1° corr.

Anal. Calcd. for $C_{21}H_{18}O$: C, 88.07; H, 6.34. Found: C, 87.92; H, 6.38.

6-Methylcholanthrene (III).—For pyrolysis 10.2 g. of crystallized ketone was heated in a bath initially at 400° and the temperature was slowly raised to 410°, when a brisk reaction set in. After forty minutes at this temperature, when the boiling had become practically negligible, the material was distilled in vacuum. Preliminary tests had indicated that further distillation is attended with losses, that direct crystallization gives material of inferior

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(8) Mayneord and Roe, *Proc. Roy. Soc.* (London), **A152**, 299 (1935); **A158**, 634 (1937).

(9) Fieser and Hershberg, THIS JOURNAL, **60**, 940 (1938).

(10) Jones, *ibid.*, **62**, 148 (1940).

(11) Veselý and Štursa, *Coll. Czech. Chem. Commun.*, **3**, 328 (1931).

(12) Sample of Fieser and Bradsher, THIS JOURNAL, **61**, 417 (1939); m. p. 232–233°, corr.

(13) Prepared according to Fieser and Hershberg, *ibid.*, **59**, 394 (1937), with comparable yields throughout, and starting with as much as 212 g. of *o*-chlorobenzaldehyde.

(14) Fieser and Seligman, *ibid.*, **58**, 2482 (1936).

quality (m. p. 200–202° after three crystallizations from benzene–ether), and that little separation is effected by repeated crystallization of the picrate (best material, m. p. 174–177°). The once distilled crude material was therefore dissolved in benzene and passed through an adsorption tower packed with alumina and diatomaceous earth. A very dark layer was strongly adsorbed at the top and the filtrate was light yellow and fluorescent. After evaporating this to a small volume and adding an equal volume of ether, 2 g. of hydrocarbon separated as yellow needles and rhombic prisms. In subsequent crystallizations from benzene–ether the substance separated in either or both of these interconvertible crystal forms, which have the same m. p. and mixed m. p. After recrystallization to constant m. p. the best material formed very pale yellow needles or cubes, m. p. 204.2–205.2° (208.4–209° cor.). The yield was 1.37 g. (12.8%), and recovery from the mother liquors of material m. p. 203–204.8° brought the yield to 24%.

Anal.[15] Calcd. for $C_{21}H_{16}$: C, 93.98; H, 6.01. Found: C, 94.19; H, 6.05.

The **picrate** crystallized from benzene–ligroin as black, rhombic crystals, m. p. 208.4–209° cor.

Anal. Calcd. for $C_{26}H_{29}O_7N_3$: C, 65.19; H, 3.85. Found: C, 64.87; H, 3.71.

7-Methyl-4-(4′-methyl-1′-naphthoyl)-hydrindene (II).—The Grignard reagent from 21.1 g. of 1-methyl-4-bromonaphthalene was prepared as above except that benzene was added as required to keep the Grignard reagent in solution; the reaction was much faster and the magnesium was largely consumed in two hours. Ten grams of 4-methyl-7-cyanohydrindene was added in benzene, when the precipitate dissolved, and the mixture was refluxed for twenty-two hours. On working up the reaction mixture as above there was obtained 15.3 g. (81%) of ketone as a light yellow oil, b. p. 230° (1 mm.), which solidified on cooling. One crystallization from ether–petroleum ether gave small, colorless cubes, m. p. 130.2–131.2° cor., unchanged by further crystallizations.

Anal. Calcd. for $C_{22}H_{20}O$: C, 87.96; H, 6.67. Found: C, 87.84; H, 6.71.

6,20-Dimethylcholanthrene (IV).—The pyrolysis of 12.2 g. of purified ketone at 410°, followed by one distillation, passage of a benzene solution through an adsorption tower, and crystallization from benzene–ether gave 4.6 g. of crude hydrocarbon, m. p. 169–171.5°. Three recrystallizations gave 3.1 g. (27%) of material of constant m. p., and 0.3 g. (2.6%) of nearly pure product was recovered from the mother liquors. The hydrocarbon forms pale yellow, fluffy needles, m. p. 175.8–176.5° cor.

Anal.[14] Calcd. for $C_{22}H_{18}$: C, 93.58; H, 6.42. Found: C, 93.45; H, 6.44.

The picrate formed purple needles, m. p. 199.8–200.2° cor.

Anal. Calcd. for $C_{28}H_{21}O_7N_8$: C, 65.74; H, 4.14. Found: C, 65.55; H, 4.23.

22-Methyl Series

4-Amino-3-chlorotoluene (VI) was prepared according to Cohen and Raper[5] from 200 g. of acetyl-*p*-toluidine in 400 cc. of acetic acid and 600 cc. of concentrated hydrochloric acid, treated slowly with stirring at 5° with 60 g. of sodium chlorate in 70 cc. of water. After stirring for one-half hour and adding 400 cc. more hydrochloric acid the mixture was refluxed for two hours and steam distilled to remove oily material and most of the acetic acid. The amine was liberated with alkali, steam distilled, extracted with ether after saturation of the distillate with salt, and distilled. The yield of colorless amine, b. p. 220–225°, was 225 g. (60%). This material was found to contain small amounts of *p*-toluidine and dichloro-*p*-toluidine; for the purpose at hand it is best to convert the substance to the bromide before effecting a further purification.

4-Bromo-3-chlorotoluene.[5]—The above crude amine (117 g.) was stirred into a mixture prepared from 162 g. of concentrated sulfuric acid and 660 g. of ice and the amine sulfate was dissolved by heating and the solution cooled rapidly to give fine crystals. While the mixture was kept below 15°, 57.9 g. of sodium nitrite in 103 cc. of water was added during fifteen minutes, followed by 213 g. of sodium bromide. The mixture was kept iced and added in small portions through a dropping funnel to a solution of 65 g. of cuprous bromide and 102 g. of constant boiling hydrobromic acid in 800 cc. of water through which steam was being passed. The addition was done as rapidly as the foaming permitted and was completed in about forty minutes. The product distilled as an almost colorless oil; after separating the main portion the rest was collected by benzene extraction. Washed with concentrated sulfuric acid (slight color) and with alkali, the material distilled as a colorless liquid, b. p. 115–120° at 25 mm.; yield 133 g. On distillation through a 1-m. Podbielniak column there was a fore-run of solid *p*-bromotoluene (5 g.) and a residue of solid dibromochlorotoluene (5 g.), while the 4-bromo-3-chlorotoluene (123 g., 73%) distilled at 115–116° at 25 mm.

4-Methyl-2-chlorocinnamic Acid.—The reaction between 4-bromo-3-chlorotoluene (41.1 g.) and magnesium (4.86 g.) in ether started readily and was complete in about three hours, when 29.6 g. of ethyl orthoformate was added. After refluxing and stirring for twelve hours, during which time a white precipitate separated, the mixture was decomposed with hydrochloric acid and the product extracted with ether. Evaporation of the ether left the crude acetal as a reddish oil; this was mixed with 100 cc. of 12% sulfuric acid and steam distilled as long as any aldehyde passed over (colorless oil). The oil was collected by ether extraction and heated for six hours with 25 g. of malonic acid and 4 cc. of pyridine on the steam-bath. The cinnamic acid, which partially crystallized during the heating, was collected by adding water and extracting with a large volume of ether and extracting the ether with soda solution. Acidification produced a white precipitate, and one crystallization gave 8 g. (21%) of acid satisfactory for reduction in the form of heavy needles, m. p. 218–219°. Further purification raised the m. p. only slightly and the best sample melted at 223.7–224°, cor.

Anal. Calcd. for $C_{10}H_9O_2Cl$: C, 61.08; H, 4.61. Found: C, 61.02; H, 4.63.

4-Methyl-2-chlorohydrocinnamic Acid.—A solution of 3.38 g. of the cinnamic acid and 1.07 g. of sodium hydroxide in 25 cc. of water was added to 57.4 g. of 2% sodium

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(15) Microanalysis by Herbert S. Wight.

amalgam in a separatory funnel and the mixture was shaken for about twenty minutes, the amalgam at once liquefying and much heat being evolved. The mercury was separated and the solution was filtered and made strongly acidic with hydrochloric acid. The precipitated acid weighed 3.4 g. (quantitative), m. p. 94–96°. A sample repeatedly crystallized from dilute alcohol formed small, colorless needles, m. p. 96.6–97.4°, cor.

Anal. Calcd. for $C_{10}H_{11}O_2Cl$: C, 60.46; H, 5.58. Found: C, 60.39; H, 5.64.

4-Chloro-6-methylhydrindone-1.—A suspension of 2.5 g. of the above acid in 5 cc. of benzene was treated cautiously with 2.7 g. of phosphorus pentachloride and when the vigorous reaction was over the benzene and phosphorus oxychloride were evaporated in vacuum. The acid chloride in 12 cc. of carbon bisulfide was treated at 0° with 2.8 g. of aluminum chloride, and after five minutes the partially solid mixture was allowed to come to room temperature, allowed to stand at 30° for one-half hour, and treated with ice and acid. The solvent was evaporated on the steam-bath and the solidified ketone was digested with ammonia solution and collected, the yield of material suitable for the next step being 1.93 g. (85%). In a run employing 34.5 g. of acid the cyclization was incomplete and the recovered acid was consequently put through the process again, allowing one hour for the Friedel and Crafts reaction. The total yield of ketone was 30 g. (95%). Recrystallized for analysis from alcohol, the ketone formed small white cubes, m. p. 104–104.5° cor.

Anal. Calcd. for $C_{10}H_9OCl$: C, 66.49; H, 5.02. Found: C, 66.51; H, 4.98.

4-Chloro-6-methylhydrindene.—The Clemmensen reduction of the above ketone (30 g., crude) was conducted exactly as described by Fieser and Seligman[14] for the 7-methyl isomer except that the alcoholic solution of the ketone was added in very small portions over a period of four hours. This seemed to decrease the amount of polymeric reduction product and the yield of the hydrindene, distilling as a colorless oil at 128–132° at 27 mm., was 21.5 g. (78%). As a check for purity the analysis was performed on a portion of the entire sample.

Anal. Calcd. for $C_{10}H_{11}Cl$: C, 72.09; H, 6.66. Found: C, 72.59; H, 6.66.

6-Methyl-4-cyanohydrindene (X) was prepared in the usual manner[14] from 21.5 g. of the chloro compound, 12.2 g. of cuprous cyanide, 17.5 cc. of pyridine, and 2 cc. of acetonitrile, shaken well and heated at 240–250° for twenty hours. The temperature probably was too high, for the yield of nitrile, b. p. 138–139° at 10 mm., was only 12.5 g. (61%) and there was much tarry residue. The product was a colorless liquid which froze at 10°. A sample was redistilled for analysis.

Anal. Calcd. for $C_{11}H_{11}N$: C, 84.01; H, 7.06. Found: C, 83.76; H, 7.19.

6-Methylhydrindene-4-carboxylic Acid.—For hydrolysis the nitrile (1 g.) was heated with concentrated hydrochloric acid for ten hours at 180–200°. The dark, crystalline product was extracted from ether with carbonate (colorless extract) and precipitated as a white powder, m. p. 155–156.5° (90% yield). Crystallization from alcohol gave needles, m. p. 158.6–159.3°, cor.

Anal. Calcd. for $C_{11}H_{12}O_2$: C, 74.93; H, 6.92. Found: C, 74.93; H, 7.02.

6-Methyl-4-(α-naphthoyl)-hydrindene (XI) was prepared from 2 g. of 6-methyl-4-cyanohydrindene and 3.41 g. of α-bromonaphthalene by the procedure outlined above, using a twelve-hour reaction period. After hydrolysis of the ketimine salt, which was complete in the short time of two hours, the ketone was obtained as a yellowish oil which failed to crystallize; b. p. 205–210° at 1.5 mm., yield 3.4 g. (94%). A random sample was used for analysis.

Anal. Calcd. for $C_{21}H_{18}O$: C, 88.07; H, 6.34. Found: C, 88.40; H, 6.39.

22-Methylcholanthrene (XII).—Pyrolysis of XI (2.95 g.) was conducted at 410–415° and the product was distilled once and passed in benzene through alumina–diatomaceous earth. Since much dark material was eliminated, the absorption step was repeated; the filtrate, concentrated to about 10 cc. and diluted with 15 cc. of ether, deposited 0.9 g. of yellow plates of the hydrocarbon, m. p. 151.5–153.5°. One more crystallization gave 0.7 g. (27%) of pale yellow 22-methylcholanthrene, m. p. 153–154°, and repeated crystallization gave only slightly purer material. m. p. 154.5–155° cor.

Anal. Calcd. for $C_{21}H_{16}$: C, 93.98; H, 6.01. Found: C, 93.99; H, 6.15.

The **picrate** crystallized from benzene–ligroin in dark purple needles, m. p. 173.6–174°, cor.

Anal. Calcd. for $C_{27}H_{19}O_7N_3$: C, 65.19; H, 3.85. Found: C, 65.14; H, 3.87.

6-Methyl-4-(4′-methyl-1′-naphthoyl)-hydrindene was obtained as described for IV in 89% yield as a golden oil, b. p. 230° at 1.5 mm. A sample collected for analysis from a middle fraction solidified on standing.

Anal. Calcd. for $C_{20}H_{20}O$: C, 87.96; H, 6.67. Found: C. 87.95; H, 6.80.

6,22-Dimethylcholanthrene.—Pyrolysis of 3.05 g. of the ketone and recovery as described for XII gave a first crystallizate of 1.05 g., m. p. 156–157.5°. Three further crystallizations from ether–benzene were required to give satisfactory material, m. p. 159.5–160.2°; yield 0.65 g. (23%). One more crystallization narrowed the melting range, and the m. p. remained constant at 161.7–162.4°, cor. on further crystallization. The substance formed golden-yellow plates.

Anal. Calcd. for $C_{22}H_{18}$: C, 93.58; H, 6.42. Found: C, 93.74; H, 6.51.

The **picrate** formed black cubes from benzene–ligroin, m. p. 185.6–186° cor.

Anal. Calcd. for $C_{28}H_{21}O_7N_3$: C, 65.74; H, 4.14. Found: C, 65.46; H, 3.95.

Approach to the 1-Methyl Series

1-Chloro-8-nitronaphthalene was prepared and reduced to the amine as described by Fieser and Seligman[7] and with the same yields. In preparing **8-chloro-1-bromonaphthalene,** the procedure[7] was modified to advantage by adding the nitrite solution in the course of twenty minutes and stirring the suspension for two hours to complete the diazotization. After addition to the cuprous bromide solution the mixture was allowed to stand for eight hours before being heated. Two distillations of the product from 165 g. of amine gave 124.5 g. of the desired fraction and the foreruns afforded 9 g. more of pure material; total yield 59.5% (compare 49%[7]). **1-Methyl-8-chloronaphthalene** was obtained in better yield (76%) than before[7] by essentially the same procedure except that all reagents were specially purified and the ether solution of the halide was added very slowly (two hours) with stirring to the magnesium.

8-Methyl-1-cyanonaphthalene was prepared by mixing 19.5 g. of solid 8-methyl-1-chloronaphthalene with 12 g. of cuprous cyanide, 2 cc. of acetonitrile, and 10 cc. of pyridine (heat effect) in a flask with a ground-glass condenser. The mixture was heated for twenty-four hours in a metal bath at 240° and the nitrile was isolated in the usual manner and obtained as a colorless solid, b. p. 175° at 7 mm.; yield 14.5 g. (79%). A sample crystallized from alcohol formed colorless cubes, m. p. 95–95.5°, cor.

Anal. Calcd. for $C_{12}H_9N$: C, 86.18; H, 5.43. Found: C, 86.22; H, 5.63.

8-Methyl-1-naphthoamide.—Attempted acid hydrolysis of the nitrile gave only tarry products. Saponification was effected by heating 0.5 g. of the nitrile with 33 cc. of alcohol and 40 cc. of water containing 5 g. of potassium hydroxide for fifteen hours on the steam-bath. The solution was evaporated, with repeated addition of water, until the alcohol had distilled and the product had separated as a solid. There was no acidic material in the filtrate and the yield of crude amide was quantitative. The substance formed colorless needles from dilute alcohol, m. p. 208.7–209.4° cor. The amide (0.15 g.) was largely recovered unchanged after being refluxed for one hour with 3 cc. of acetic acid, 1.7 cc. of water and 3 cc. of concentrated sulfuric acid.

Anal. Calcd. for $C_{12}H_{11}ON$: C, 77.81; H, 5.99. Found: C, 77.71; H, 6.13.

In preparing **4-methyl-7-bromohydrindene** according to Fieser and Seligman[16] it was found that the yield in the Blanc reaction drops to 41% when the amount of trioxymethylene is increased to 95% of the theoretical. The mixture of malonic esters was obtained in the yield reported; hydrolysis was effected more conveniently by refluxing 100 g. of the ester for two hours with 75 cc. of alcohol and 350 cc. of water containing 67 g. of potassium hydroxide. After distilling most of the alcohol the solution was acidified and the oily mixture refluxed for four hours, cooled and extracted with ether. The propionic acid mixture distilled at 2 mm. as a colorless oil; yield 65 g. (92%). The remainder of the process was conducted as described. It was observed that although freshly distilled, colorless 4-methyl-7-bromohydrindene formed a Grignard reagent readily and without delay, a sample which had stood for over a month had acquired a pale yellow color and could not be caused to react with magnesium. On redistillation this gave satisfactory material which formed the Grignard derivative, but a significant amount of tar was left as a residue.

Preparation of the Ketimines.—The reagent from 8.1 g. of 4-methyl-7-bromohydrindene and 1.03 g. of magnesium in 40 cc. of ether, after being refluxed overnight to complete the reaction, was treated with 6.1 g. of 8-methyl-1-cyanonaphthalene in 40 cc. of benzene. Most of the ether was removed and refluxing was continued for three days. After adding ice and concentrated hydrochloric acid (100 cc.), the benzene was evaporated and the sticky red mass produced was refluxed for three days with water (40 cc.), hydrochloric acid (20 cc.), acetic acid (20 cc.) and toluene (25 cc.). No ketone was found in the toluene layer or on extraction with ether, and the aqueous layer deposited 4.6 g. (29%) of orange-yellow crystals of **7-methyl-4-hydrindyl 8′-methyl-1′-naphthyl ketimine hydrochloride** (XIV). Recrystallization from water with the addition of hydrochloric acid gave small orange-yellow cubes.

Anal. Calcd. for $C_{22}H_{22}NCl$: C, 78.65; H, 6.60. Found: C, 78.32; H, 6.52.

The condensation of the lithium derivative from 1-methyl-8-chloronaphthalene (13.9 g.) with 4-cyanohydrindene was conducted in an entirely analogous manner and gave 8.32 g. (37%) of the ketimine hydrochloride XIII as dark yellow cubes. All attempts to hydrolyze the two substances failed, including the formic–sulfuric acid method of Fieser and Seligman.[7]

Summary

Syntheses utilizing the Elbs reaction have been developed for the preparation of 6- and 22-methylcholanthrene and of the 6,20- and 6,22-dimethyl homologs, and the hydrocarbons are being tested for carcinogenic activity. The attempt to produce cholanthrenes with a methyl group at the 1-position reached a stopping point at the stage of the intermediate ketimines, which resisted hydrolysis.

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[16] Fieser and Seligman, THIS JOURNAL, **57**, 942 (1935).