

data for these products are given in Table I.

For purposes of comparison of physical properties a number of corresponding sulfonamides

were prepared. Data for them are given in Table II.

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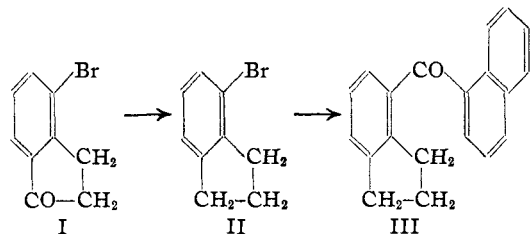
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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

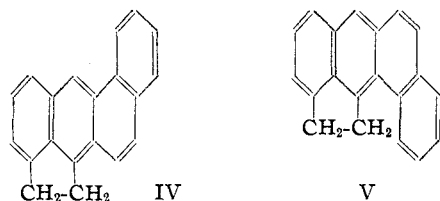
Cholanthrene and Related Hydrocarbons

BY LOUIS F. FIESER AND ARNOLD M. SELIGMAN

The synthesis of cholanthrene by three different methods has been reported recently by Cook and his associates.¹ We have found that the modified Elbs synthesis² provides still another route to this interesting hydrocarbon. The ketone III was prepared from the known 4-bromohydrindone-1 (I)³ as indicated, and on pyrolysis



there was obtained a hydrocarbon corresponding to the description¹ of cholanthrene, IV. From

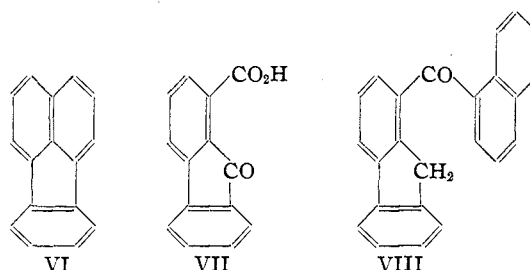


the ketone resulting from the reaction of the Grignard compound of II with β -naphthoyl chloride, the isomeric hydrocarbon V was obtained.

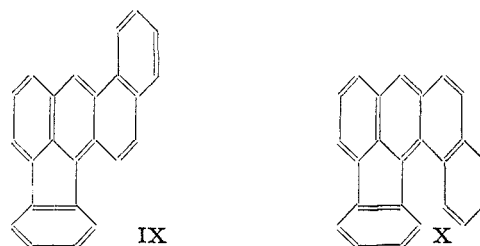
Dr. M. J. Shear has observed that crystalline cholanthrene injected subcutaneously in mice produced effects similar to those obtained with methylcholanthrene and in approximately the same time. The hydrocarbon induced ulcerations beginning with the fortieth day and the first tumor, noted on the sixty-second day, took successfully on transplantation. From these preliminary results it appears that a methyl group at C₂₀ is of less influence in determining the carcinogenic

activity than might have been expected on the basis of the available data.⁴

Another hydrocarbon having the cholanthrene ring system was obtained very easily starting with fluoranthene (VI) from coal tar. By the methods of Fittig and Liepmann,⁵ modified in some details, fluorene-1-carboxylic acid can be prepared in any desired quantity by the oxidation of fluoranthene, followed by the reduction of the resulting keto acid VII. 1-(α -Naphthoyl)-fluorene (VIII) was obtained from α -naphthylmagnesium



bromide and fluorene-1-carboxylic acid chloride, and on pyrolysis it yielded the hydrocarbon IX.



To indicate the relationship to the carcinogenically active parent hydrocarbon, this substance may be called 15,16-benzdehydrocholanthrene.⁶

The Friedel and Crafts reaction of the above acid chloride with naphthalene was investigated, with rather unexpected results. The condensation proceeded poorly in carbon bisulfide, probably because of the sparing solubility of the com-

(1) Cook, Haslewood and Robinson, *J. Chem. Soc.*, 667 (1935); Cook and Haslewood, *ibid.*, 767, 770 (1935).

(2) Fieser and Seligman, *THIS JOURNAL*, **57**, 942 (1935).

(3) Miersch, *Ber.*, **25**, 2110 (1892); Mayer, Phipps, Ruppert and Schmitt, *ibid.*, **61**, 1966 (1928).

(4) Cook and co-workers, *Proc. Roy. Soc. (London)*, **B111**, 455, 454 (1932); **B117**, 318 (1935).

(5) Fittig and Liepmann, *Ann.*, **200**, 1 (1879).

(6) Fieser and Seligman, *THIS JOURNAL*, **57**, 1377 (1935).

plex compounds, and there was obtained a mixture which was not separated, but which was found by pyrolysis experiments to contain a considerable proportion of the α -ketone VIII. Using tetrachloroethane the chief reaction product was the higher melting 1-(β -naphthoyl)-fluorene. The results were about the same with nitrobenzene as the solvent. Pyrolysis of the β -ketone afforded the hydrocarbon X.

Experimental Part⁷

4-Bromohydrindone-1 (I) was prepared from *o*-bromohydrocinnamic acid, using the method of ring-closure described by Hoyer,⁸ but employing more thionyl chloride. In large-scale experiments the yield of pure ketone, m. p. 97°, was only 70% of the theoretical amount, based on the acid.

Various methods of preparing *o*-bromohydrocinnamic acid were investigated, the one found most satisfactory consisting in the catalytic hydrogenation of *o*-bromocinnamic acid prepared from *o*-bromotoluene by the convenient method of Reich and Chaskelis.⁹ The yield reported by these workers (26%) was confirmed. Using material which had been sublimed *in vacuo* the hydrogenation with Adams catalyst proceeded smoothly in absolute alcoholic solution, the acid being largely esterified during the process; yield, 85%. *o*-Bromocinnamic acid was also prepared from *o*-nitrocinnamic acid according to Gabriel,¹⁰ the yields being 89% in the reduction and 67% in the Sandmeyer reaction, but the method requires a much more expensive starting material.

We also investigated the preparation of the desired acid from *o*-bromobenzyl chloride and malonic ester, following the procedure employed previously.² The yields were good but the commercial *o*-bromobenzyl chloride, even after repeated careful fractionation, gave rise to unhomogeneous products at every step. The impure *o*-bromohydrocinnamic acid gave a hydrindone preparation which crystallized well but melted persistently low (88°). 4-Bromohydrindene was obtained in a pure condition by repeated fractionation of the mixture obtained on reduction, but with considerable loss of material.

4-Bromohydrindene was prepared in 77% yield by the Clemmensen reduction of pure 4-bromohydrindone-1 by the usual procedure;² b. p. 118° at 18 mm.

Anal. Calcd. for C₉H₉Br: C, 54.83; H, 4.60. Found: C, 54.55; H, 4.48.

4-(α -Naphthoyl)-hydrindene (III) was obtained in a form (A) suitable for pyrolysis in 50% yield by the Grignard procedure.² On further distillation in vacuum it was obtained as a viscous yellow oil.

Anal. Calcd. for C₂₀H₁₆O: C, 88.20; H, 5.93. Found: C, 87.75; H, 5.90.

4-(β -Naphthoyl)-hydrindene was prepared similarly, using β -naphthoyl chloride, in 46% yield: small colorless needles, m. p. 68–69°, from ether–petroleum ether.

(7) Analyses by Mrs. G. M. Wellwood, Dr. R. G. Larsen and Mr. E. L. Martin.

(8) Hoyer, *J. prakt. Chem.*, **199**, 242 (1934).

(9) Reich and Chaskelis, *Bull. soc. chim.*, [4] **19**, 287 (1916).

(10) Gabriel, *Ber.*, **15**, 2294 (1882).

Anal. Calcd. for C₂₀H₁₆O: C, 88.20; H, 5.93. Found: C, 88.25; H, 6.05.

Cholanthrene (IV).—On pyrolysis of the partially purified ketone III (A) at 400–405° for twenty-five minutes there was obtained, after vacuum distillation and one crystallization from ether–benzene, a pale yellow product melting at 170°; yield, 34%. This material was altered but little on further purification. After passage of a benzene solution through four adsorption towers containing activated alumina, the hydrocarbon was obtained as very faintly yellow plates, m. p. 173–173.5°, corr.

Anal. Calcd. for C₂₀H₁₄: C, 94.45; H, 5.55. Found: C, 94.51; H, 5.65.

The *picrate* crystallized from benzene as small, reddish-purple needles, m. p. 169–170°, corr.

Anal. Calcd. for C₂₆H₁₇O₇N₃: N, 8.69. Found: N, 8.75.

8,9-Dimethylene-1,2-benzanthracene (V) was prepared similarly, the melting point at various stages of purification being as follows: one crystallization, 172°; chromatographic purification, 173°; treatment with sulfuric acid in benzene solution, very faintly yellow plates from benzene–ether, m. p. 174° (176.5–177°, corr.).

Anal. Calcd. for C₂₀H₁₄: C, 94.45; H, 5.55. Found: C, 94.48; H, 5.65.

The *picrate* forms purple-black needles from benzene, m. p. 158–159°, corr.

Anal. Calcd. for C₂₆H₁₇O₇N₃: N, 8.69. Found: N, 8.86, 8.98.

Fluorenone-1-carboxylic acid⁶ was prepared by adding slowly a solution of 340 g. of chromic anhydride in 300 cc. of water and 200 cc. of glacial acetic acid to a solution of 100 g. of fluoranthene in 2.5 liters of glacial acetic acid, keeping the mixture just below the boiling point. After standing for several hours the solution was heated to the boiling point for one hour and then diluted with about 15 liters of water. The crude acid was collected and extracted with cold alkali, precipitated, and heated with an aqueous suspension of barium carbonate until no further material could be extracted. On acidifying the filtrate, 56 g. (48%) of orange, crystalline material, m. p. 191–193°, was obtained. For reduction to *fluorene-1-carboxylic acid*, 60 g. of the keto acid was added in portions to a mixture of 1920 g. of 4% sodium amalgam and 2 l. of water, heated on the steam-bath. The solution was kept near the neutral point by the frequent addition of hydrochloric acid, a fresh portion of keto acid being introduced only after the precipitate which formed on acidification was nearly colorless. The mixture was heated for two hours after the addition was complete, when it was cooled and filtered. The crude acid which precipitated on acidification was extracted as the barium salt, from which it was recovered in a colorless condition; yield 47.5 g. (84%). After sublimation *in vacuo* the acid (m. p. 245°) was refluxed with a large excess of thionyl chloride for two hours, the excess reagent was removed and the acid chloride was distilled at diminished pressure; yield, 83%.

1-(α -Naphthoyl)-fluorene (VIII).—A solution of the Grignard reagent from 15 g. of α -bromonaphthalene in 70 cc. of ether was added slowly to 26.5 g. of fluorene-1-car-

boxylic acid chloride in 250 cc. of dry benzene and 50 cc. of ether at 0°. The mixture was slowly brought to 35–40° and kept at that temperature overnight. The crude ketone was subjected to thorough steam distillation from an alkaline medium and then extracted with ether–benzene, distilled at the oil pump, and crystallized from ether–petroleum ether; colorless needles, m. p. 108–110°; 12.3 g. (56% yield, 10 g. of fluorene-1-carboxylic acid being recovered from the alkaline solution).

The ketone is very readily soluble in benzene, moderately soluble in ether, and sparingly soluble in alcohol. Recrystallized from benzene–ether it formed slender needles, m. p. 113–114°.

Anal. Calcd. for C₂₄H₁₆O: C, 89.97; H, 5.04. Found: C, 90.02; H, 5.15.

15,16-Benz-dehydrocholanthrene (IX).—Four grams of the above ketone was heated for twenty-five minutes at 415° under nitrogen and the product was distilled in vacuum and crystallized once from benzene; yield, 2.25 g. (60%) of orange-red material, m. p. 177°. Purification by chromatographic adsorption was more tedious and wasteful than with sulfuric acid and gave no better material. On shaking a dilute benzene solution of the hydrocarbon with small portions of sulfuric acid until the acid acquired only a yellow color, the extraneous red material was removed with little loss of product. The purified hydrocarbon crystallized from benzene, in which it is only moderately soluble, as bright yellow, cottony needles, m. p. 181–181.3° corr.

Anal. Calcd. for C₂₄H₁₄: C, 95.33; H, 4.67. Found: C, 95.23; H, 4.98.

The *picrate* crystallizes from benzene as small, brick-red needles, m. p. 174.5–175.5°, corr.

Anal. Calcd. for C₃₀H₁₇O₇N₃: N, 7.91. Found: N, 8.22.

1-(β-Naphthoyl)-fluorene was the chief product of the reaction of 14.5 g. of fluorene-1-carboxylic acid chloride with 9 g. of naphthalene, and 9.2 g. of aluminum chloride in 300 cc. of tetrachloroethane, the mixture being initially at 5–10°, then at room temperature. The crude ketone was heated with acetone and alkali in order to hydrolyze unchanged acid chloride, 3.9 g. of acid being recovered after distilling the solvent and extracting the ketone with ether–benzene. After distillation *in vacuo*, one crystallization from benzene–ligroin gave 8 g. of the nearly pure β-ketone, m. p. 145–150°; total yield, 12.5 g. (84%). After several crystallizations of the first crop from benzene–ether the substance formed clusters of pale yellow needles, m. p. 159–162°. The compound is considerably less soluble than the α-isomer.

Anal. Calcd. for C₂₄H₁₆O: C, 89.97; H, 5.04. Found: C, 89.97; H, 5.25.

1',2'-Naphtho-1,2-fluoranthene (X).—The pyrolysis of the above ketone proceeded as in the case of the α-isomer, but the hydrocarbon, which is considerably more soluble than IX, is best purified with the use of an adsorption tower. It crystallized from benzene–ether in the form of flat, golden yellow needles, m. p. 178–179°, corr.

Anal. Calcd. for C₂₄H₁₄: C, 95.33; H, 4.67. Found: C, 95.25; H, 5.04.

The *picrate* crystallizes from benzene in the form of crimson needles melting at 181–182° corr.

Anal. Calcd. for C₃₀H₁₇O₇N₃: N, 7.91. Found: N, 8.16.

Summary

Cholanthrene and three additional hydrocarbons of the 1,2-benzanthracene series have been prepared by the modified Elbs synthesis.

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[CONTRIBUTION FROM KEDZIE CHEMICAL LABORATORY, MICHIGAN STATE COLLEGE]

Halogenation of Phenolsulfonic Acids in Nitrobenzene

BY RALPH C. HUSTON AND ARTHUR H. NEELEY¹

The replacement of sulfonic acid groups of phenols with nitro groups or halogen takes place with rapidity in the presence of aqueous acid.^{2,3} If, however, the reaction is carried on in alkaline solution this group is rendered stable and serves as an effective blocking agent.^{4,5}

Fuming sulfuric acid has been used with more or less success in the preparation of 2-nitroresor-

cinol⁶ and to protect the four and six positions of *m*-cresol during nitration.^{7,8} Good yields of 2-bromo-*m*-cresol⁹ and 2-chloro-*m*-cresol¹⁰ were obtained in this Laboratory by brominating or chlorinating *m*-cresol directly with one mole of halogen in four volumes of fuming sulfuric acid and then removing the sulfonic acid groups by hydrolysis with superheated steam at 180–200°.

Numerous attempts to adapt this method to the preparation of 2,6-dibromophenol and 2-

(1) Presented in partial fulfillment of the requirements for the Ph.D. degree.

(2) Datta and Bhoumik, *THIS JOURNAL*, **43**, 303 (1921).

(3) Datta and Mitter, *ibid.*, **41**, 2033 (1919).

(4) Tanaki and Kutani, *J. Pharm. Soc. Japan*, **541**, 196 (1927); *C. A.*, **21**, 2255 (1927).

(5) Huston and Ballard, "Organic Syntheses," John Wiley and Sons, Inc., 440 Fourth Ave., New York City, 1934.

(6) Kaufman and DePay, *Ber.*, **37**, 725 (1904).

(7) Gibson, *J. Chem. Soc.*, **123**, 1269 (1923).

(8) Hodgson and Beard, *ibid.*, **127**, 498 (1925).

(9) Huston and Peterson, *THIS JOURNAL*, **55**, 3880 (1933).

(10) Huston and Chen, *ibid.*, **55**, 4214 (1933).